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Drug development for noncastrate prostate cancer in a changed therapeutic landscape

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Abstract

The unprecedented progress in the treatment of metastatic castration-resistant prostate cancer is only beginning to be realized in patients with noncastrate disease. This slow progress in part reflects the use of trial objectives focused on time-to-event end points, such as time to metastasis and overall survival, which require long follow-up durations and large sample sizes, and has been further delayed by the use of approved therapies that are effective at the time of progression. Our central hypotheses are that progress can be accelerated, and that outcomes can be improved by shifting trial objectives to response measures occurring early that solely reflect the effects of the treatment. To test these hypotheses, a continuously enrolling multi-arm, multi-stage randomized trial design, analogous to that used in the STAMPEDE trial, has been developed. Eligibility is focused on patients with incurable disease or those with a high risk of death with any form of monotherapy alone. The primary objective is to eliminate all disease using a multimodality treatment strategy. End points include pathological complete response and an undetectable level of serum prostate-specific antigen, with recovery of serum testosterone levels. Both are binary, objective, and provide an early, quantitative indication of efficacy.

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Author contributions

All authors contributed to all aspects of the preparation of this manuscript.

Competing interests

H.I.S. declares that he is a member of the board of directors of Asterias Biotherapeutics, has served as a compensated consultant of Blue Earth Diagnostics, Sanofi Aventis, and WCG Oncology, and has served as an uncompensated consultant of Ferring Pharmaceuticals, Janssen Research & Development, LLC and Medivation. M.Y.T., M.J.O., S.M.M. and H.A.V. declare no competing interests.

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The unprecedented progress in the treatment of metastatic castration-resistant prostate cancer (mCRPC) in the past 7 years is only beginning to be realized in the treatment of patients with early stage, noncastrate disease. The traditional approach to developing drugs for prostate cancer has followed a paradigm in which therapies that are effective in patients with mCRPC are then studied in patients with prostate cancer of different non- castrate states, including 'high risk' localized disease in the neoadjuvant and/or adjuvant setting, biochemical recurrence after local therapy, or in noncastrate metastatic disease, using time-to-event outcome measures that include prostate-specific antigen (PSA)-defined recurrence, PSA-defined progression, radiographic progression, or death. These trials take years to complete and often provide inconclusive results owing to the long natural history and the limited number and clinical significance of the failure events on which conclusions are based. Moreover, with six life-prolonging treatments for patients with prostate cancer currently approved by the FDA[1–7], a seventh designated as a breakthrough therapy for which an accelerated approval is anticipated[8], and many more in development, simply too many possible combination therapies exist to study all of them with the available resources. If six to eight agents are available, the number of possible two-drug combination, for example, ranges from 15 to 28. Furtherrmore, the ongoing de-lineation of a molecularly defined disease taxonomy[9,10], and the approval and ongoing clinical testing of a variety of targeted agents further highlights the need to design and complete informative trials in a more timely manner.

A new strategy that provides a more rapid and definitive readout of treatment success or failure is urgently needed, so that only the most promising therapeutic approaches are investigated further. In this Review, we describe how this can be achieved using a multimodality clinical trial platform that involves the enrolment of patients with noncastrate disease across a continuum of risk, and shifts the objectives from time-to-event outcomes, for which therapy is given to delay or prevent outcomes that occur late in the course of disease, to response indicators that solely indicate the effects of treatment that occur early and reflect 'no evidence of disease' or a 'complete elimination of disease' state[11]. Each response indicator, approached in a biomarker context, should be reproducibly and reliably measurable and, in itself, clinically meaningful as an indicator of treatment efficacy.

Limitations of traditional measures

The difficulties in evaluating drugs in patients with prostate cancer have long been recognized. These difficulties are in part caused by the fact that the traditional measures of response used to assess the effects of drugs in other tumour types, such as the RECIST criteria, do not apply to changes in serum PSA levels or osseous metastases, which are the most-common manifestations of the disease. Measurable disease, for which changes in size can be quantitated objectively, is infrequent. To address this challenge, a group of clinical investigators came together to form the Prostate Cancer Working Group 2 (PCWG2), in order to focus on aspects of drug development related to the treatment of patients with mCRPC[11]. Among the group's recommendations were: to consider each disease manifestation — such as serum PSA level, the primary tumour, lymph nodes, bone, or visceral metastases, and other symptoms — independently; to avoid the grouped categorizations of different disease manifestations into broad overall response

categorizations, such as complete response, partial response or stable disease; to separate treatment outcomes into early measures of response, classified as the control, relief, or elimination of each disease manifestation present at the start of therapy, and later time-to-event measures of progression, such as the delay or prevention of future manifestations[11].

The indications for use of currently approved drugs for mCRPC align with the PCWG2 outcomes paradigm, although none were approved based on an early indicator of a response, such as a decline in serum PSA level or tumour shrinkage. To date, the combination of mitoxantrone and prednisone remains the only drug regimen approved based on an early response end point: the relief or palliation of pain[12]. All of the other approved drugs were licensed based on their demonstrated ability to delay the onset of disease manifestations such as skeletal-related events, symptomatic skeletal events, or death. Progression-free survival (PFS) has not, by itself, been an end point on which approval decisions have been made. However, with the development of an analytically valid bone-scan-based assay, which has shown strong correlation with overall survival outcomes, radiographic PFS based on this validated assay and RECIST 1.1 criteria for soft-tissue disease, when present, is now included as a regulatory end point to support approval decisions[13,14].

High-risk localized disease.

The clinical activity of androgen-deprivation therapy (ADT) in patients with advanced-stage localized and/or metastatic disease was first described in 1944 (REF. 15), when the ability to assess the extent of disease using imaging was virtually nonexistent and trial design methodologies were in their infancy. Considerable resources have since been invested in trials in the neoadjuvant and/or adjuvant setting that enrolled patients with tumours classified as locally advanced or high-risk. These trials are costly, both in terms of the large number of patients needed to show the protocol-defined level of benefit and the time required to do so. The conclusions of a critical review show that the majority of trials that have influenced clinical practice demonstrated a survival benefit (delaying or preventing all-cause or prostate-cancer-specific mortality)[16]. Unfortunately, before 2014, few treatments had been demonstrated to have this level of efficacy (TABLE 1).

As an example, the results of two international multicentre trials[17,18] collectively showed a statistically significant, clinically meaningful improvement in disease-specific and overall survival outcomes for the combination of localized radiotherapy and ADT, relative to ADT or radiotherapy alone. Both results were practice-changing[17,18], and while each study was sufficiently powered to answer the clinical question asked, a total of 2,080 patients and 6–12 years of follow-up monitoring were needed to do so.

The findings of these trials contrast with the outcomes of trials addressing the question of whether the addition of docetaxel to ADT, which was originally reported to be effective in patients with mCRPC in 1999 (REFs. 19,20), would improve outcomes relative to ADT alone in patients with high-risk localized disease. GETUG-12, a trial involving men with high-risk localized disease, was launched in 2002, and was designed to determine whether neoadjuvant docetaxel in combination with ADT would lead to a 54% reduction in risk of relapse relative to ADT alone in men who had undergone radical prostatectomy[21]. The study adopted a composite definition of relapse, which included biochemical recurrence, the

development of metastatic disease, or symptoms of metastatic disease. However, 2 years later, when the findings of two definitive phase III trials — TAX-327 (REF. 1) and SWOG-9916 (REF. 22) — indicated the survival benefit of docetaxel plus prednisone versus mitoxantrone plus prednisone, which lead to FDA approval of docetaxel for mCRPC, the true efficacy of docetaxel was found to have been overestimated in GETUG-12. The planned statistical analysis was subsequently modified to increase both the sample size and follow-up duration in order that a sufficient number of relapse events could be captured. Ultimately, 13 years after trial activation, an absolute 12% difference in relapse-free survival was found. A close inspection of the data also revealed that most of the relapse events were PSA-defined recurrences that, ultimately, were not necessarily clinically significant[21]. Furthermore, at the time of reporting, no survival advantage was detected, which was postulated to reflect a low number of deaths observed during follow-up monitoring. Also of note was the observation that 46% of the patients in the control arm never had any disease recurrence. Docetaxel would, therefore, have been an unnecessary overtreatment of these patients that could not have improved their outcomes[21]. The authors concluded that “longer follow-up will be needed to establish whether this benefit translates into improved metastasis-free, and ultimately, overall survival” (REF. 21); however, the real question is how long can patients continue to wait.

Another example is provided by RTOG-0521 (REF. 23), a trial of similar design to GETUG-12 (REF. 21), which used radiotherapy as the definitive treatment of the primary tumour, seeking to show a 7% absolute 4-year survival benefit with a planned enrolment of 600 patients, with 78 death events projected to occur over 5 years of accrual and 4 years of additional follow-up monitoring. The final results, reported 10 years after enrolment of the first patient, revealed a modest 4% improvement in overall survival from 89% to 93%, which was only statistically significant with a one-sided *P* value; owing to the low number of death events among patients in the control arm (59 in total, of which only 23 were attributed to prostate cancer), this finding is unlikely to change clinical practice.

The findings of SWOG-9921, a study comparing the efficacy of ADT alone to that of ADT plus mitoxantrone in the adjuvant setting, which started in 1999, were reported at the 2017 ASCO Genitourinary Cancers Symposium[24]. This trial was stopped by the data safety monitoring committee after three incidences of leukaemia were documented among patients in the mitoxantrone arm. In the final analysis, >900 patients were enrolled over a 7-year period and monitored for an additional 10 years, only to demonstrate that the addition of mitoxantrone to ADT did not improve overall survival[24].

The long disease trajectories and low event rates inherent in trials involving patients with noncastrate prostate cancer have now made overall survival a challenging end point at best. This problem is further compounded by the increasing availability of therapies that are effective when disease progression occurs on protocol, particularly when given to patients in the control arms of these trials, which can blunt the effects of the experimental regimen on survival outcomes. The use of serum PSA-based surrogate end points has been proposed[25], but is not currently accepted, in part owing to uncertainty as to the source of the PSA increase, such as a local recurrence that might still be cured using additional therapy delivered to the primary site, compared with a nonlocalized recurrence that might not reflect

the presence of lethal disease. To further address this need, the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group was established in order to identify potential surrogate markers of overall survival by pooling raw data from 28,905 individual patients with localized prostate cancer from 43 ongoing or completed clinical trials. The analysis demonstrated a strong association between metastasis-free survival and overall survival[26,27], and this surrogate will likely be accepted as a clinical trial end point for accelerated or potentially full regulatory approvals. The results of the ICECaP analysis provide a major step forward, but still fail to address the likelihood that metastasis-free survival, as an end point, will be affected by patients receiving treatment at the time of biochemical (PSA) recurrence that invariably occurs before the development of detectable meta stases, once again blunting the potential effects of treatment on the primary outcome.

Biochemical recurrence and metastasis-free survival.

Concerns similar to those surrounding studies involving patients with high-risk localized disease also apply to trials enrolling patients with biochemical recurrence after definitive localized therapy. Overall, around 15% of localized prostate cancers recur following treatment[28], with the frequency varying as a function of disease aggressiveness and extent at the time of diagnosis — ranging from 50% to 80% in patients with highrisk disease[29]. In this scenario, the first objective is to identify patients in whom an increase in serum PSA level is solely a result of localized disease recurrence, who might therefore still be curable with additional therapy applied directly to the prostate bed following radical prostatectomy or to the prostate itself following primary radiation therapy. To do so, a range of predictive nomograms have been developed that incorporate features of the disease at diagnosis, time to recurrence, serum PSA kinetics, and/or newer biologically-based disease profiles[30–33]. However, many of these nomograms were based on data from small retrospective series, all of which involve slightly different patient populations, and have not been prospectively and externally validated.

Trials in this context also use time-to-metastasis and overall survival as end points, and although the required follow-up durations are shorter, the influence of additional systemic treatment given at the time of bio chemical relapse (be it approved or investigational, such as the addition of short-term ADT to salvage radio therapy in the RTOG-9601 (REF. 34) and GETUG-16 (REF. 35)), before either of these end points is achieved, can obviate the ability to determine whether intervention has had a favourable influence on patient outcomes.

Noncastrate metastatic disease.

Trials designed to improve the outcomes of patients presenting with metastatic disease began in the pre-PSA era with end points that were also primarily time-to-event based. Most trials used overall survival as the primary end point and asked the question regarding whether or not the addition of a first-generation anti-androgen to standard ADT was superior, in terms of efficacy, to ADT alone[36,37]. At the time, metastatic disease was largely detected using plain radiography and radionuclide bone scans. The results varied; some trials demonstrated superiority of the combination therapy and others not[36,37].

Ultimately, the findings of a large meta-analysis that included data from a total of 27 trials and 8,257 patients revealed a statistically insignificant 1.8% absolute difference in overall survival at 5 years[38], an observation supported by other meta-analyses that differed in terms of the studies included and agents examined[38–43]. Here again, the lack of an intermediate end point of efficacy and the sobering final results have reduced enthusiasm for the development of treatments of metastatic non castrate disease.

Renewed interest in trials involving patients with noncastrate disease began with the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED)[44–46], and the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE)[47] studies, which were launched in 2005 and 2006, respectively. Both trials were designed to investigate whether the addition of docetaxel to ADT would be superior to ADT alone; however, ADT was given continuously in CHAARTED[44–46], and for a minimum of 2 years in STAMPEDE[47]. CHAARTED, with results presented publicly in 2014 (REF. 44) and published in 2015 (REF. 45), revealed a significant delay in time to progression and an improvement in overall survival for patients who received the chemohormonal combination (HR for death 0.61, 95% CI 0.47–0.80; P <0.001).

The CHAARTED study[44–46] achieved its stated primary end point; however, the observed effect was only statistically significant in patients with high-volume meta static disease (defined as ≥4 lesions detected on bone scan or the presence of visceral disease). In the initial report, the point estimate in subgroup analyses of groups of patients with low-volume disease appeared comparable to that of patients in the high-volume disease cohort and to that of the entire cohort, despite not reaching statistical significance[45]. With longer follow-up monitoring and a higher number of recorded deaths, as reported at ESMO 2016 (REF. 46), the trend towards potential benefit from docetaxel was lost, with an HR of 1.04. Similar results were seen in the STAMPEDE trial, which were first presented in 2015 (REF. 47) and published in 2016 (REF. 48), and also showed a significant improvement in overall survival following chemo hormonal combination therapy in patients with castration-sensitive prostate cancer, ranging from high-risk, localized, advanced-stage disease (stage T3 or T4, Gleason score 8–10 and serum PSA >40 ng/ml) to meta static or relapsed disease with high-risk features (HR for death 0.78, versus ADT alone, 95% CI 0.66–0.93; P = 0.006). A notable improvement in failure-free and overall survival outcomes was observed across the trial population, with no evidence of the treatment having a heterogeneous effect in patients with metastatic disease[47].

A third trial designed to investigate the same question in patients with metastatic noncastrate prostate cancer, GETUG-15 (REF. 49), enrolled patients with a more-favourable risk profile than that of those enrolled in CHAARTED[44–46], and showed no difference in out-comes, despite the trial design allowing up to 50% more chemotherapy to be administered (9 cycles versus 6 cycles in both STAMPEDE[48] and CHAARTED[44–46]). At present, the variations in the results from the subgroups of patients with high-volume and lower-volume disease are an area of active debate. To the STAMPEDE investigators[48], the survival benefit for both groups is clear, given that the trial was designed for the cohort as a whole and the primary end point was met. By contrast, the position of ASCO is that the question of benefit for

patients in the low-volume disease subgroup remains open (Michael Morris, personal communication).

Both CHAARTED[44–46] and STAMPEDE[48] are landmark trials with results that dramatically changed clinical practice, although they required 9 years from initiation to the first public presentation of the results, and 10 years to the first peer-reviewed publication. For GETUG-15, 4 years were required to accrue sufficient follow-up data, and 9 years passed before the first report was published[49], with an additional 2 years for an update that included a reclassification of disease burden in accordance with the definitions used in CHAARTED[50]. Such timelines are simply too long in the current therapeutic landscape. A similar survival benefit was reported for patients in the abiraterone plus ADT and prednisone arm (versus placebo plus ADT and prednisone) of the LATITUDE trial[51], which included patients with metastatic noncastrate prostate cancer and in STAMPEDE[48,52], which included patients with both metastatic and non-metastatic disease. These findings raise the new question as to which patients are most likely to benefit from either treatment approach, and under what circumstances should the combination approach be considered standard.

A focus on early measures of response

Shifting the primary trial objective from time-to-event measures that occur late in the course of disease to response measures that occur early and that solely reflect the effects of the treatments is central to achieving the goal of more rapid and informative drug develop ment in noncastrate disease states. To achieve this goal, we applied the same control/relieve/eliminate paradigm developed in PCWG2 (REF. 11) to individual disease manifestations that occur across non castrate disease states including the primary tumour and, separately, to sites of metastatic spread such as the pelvic lymph nodes, retro peritoneal lymph nodes, and bone. Our central hypo thesis is that the demonstrated level of efficacy of currently available and approved systemic therapies, used as part of a multimodality therapeutic approach, is sufficient to begin to systematically ask the question as to whether all disease can be completely eliminated in patients who present with tumours that range from locally advanced, high-risk disease to low-volume metastatic disease. This approach is not only an informative method for identifying successful strategies for further investigation in larger cohorts of patients, but is also a necessary prerequisite to the establishment of a paradigm for cure.

The feasibility of achieving this objective is based on the demonstration that rigorously defined patho logical complete responses (pCRs) are now being achieved in men with locally advanced prostate cancer who are treated with next-generation inhibitors of androgen signalling, such as abiraterone, in the neoadjuvant setting[53]. In our own experience, an undetectable serum PSA level following recovery of serum testosterone levels can be achieved using a planned multimodality approach in selected patients with low-volume metastatic disease that is incurable with any single therapeutic modality[54]. Such multimodality approaches are not only the standard-of-care treatment for many types of cancer including urothelial[55] and germ-cell tumours[56,57], but have also been shown to cure a proportion of patients with these tumours who present with metastatic disease. Effective systemic therapies used earlier in the natural history of a disease, when required to treat

micro metastases or visible metastatic disease in order to improve a patient's outcome, can also lower the risks of morbidity and/or disease-specific mortality by reducing the risk of progression to mCRPC.

All trials designed to evaluate the efficacy of drugs and/or different therapeutic approaches in patients with detectable disease in any location, be it local, regional, biochemically recurrent, or metastatic, incorporate out-come measures to assess the effects of treatment. Each measure, regardless of how it is defined, is a biomarker of a response, or a change from baseline as a result of treatment. The challenge in patients with prostate cancer is to show that each defined response indicator can be measured reproducibly and quantitatively, and that the observed change from baseline following treatment is clinically meaningful, providing the justification to continue the development of the drug and/or overall therapeutic approach, and ultimately, to show that the response indicator does reflect a clinical benefit to the patient or patient group. If researchers are able to test and reject the null hypothesis that low-volume metastatic disease cannot be completely eliminated by treatment, the clinical benefit of various experimental approaches can then be truly established.

pCR and minimal residual disease in patients with advanced-stage and/or high-risk localized disease.

The efficacy of ADT has been studied extensively in the neoadjuvant setting using a range of early outcome measures. In some trials, the primary end point was a pCR, representing the complete elimination of disease, although the definition of pCR and how it was determined varied between trials, or was not explicitly defined. Furthermore, most trials that reported pCR did not have a central pathology review by expert genitourinary pathologists. Overall, however, pCRs in these trials have been rare (TABLE 2). Other reported outcome measures that have been used in trials include tumour regression (assessed clinically or using MRI), surgical margin rates, and findings of the post-therapy pathological analysis of tumour specimens, but were notable for a lack of standardization in how the end points were defined, assessed, and reported. Equally important, however, was that the systemic therapies available at the time had limited efficacy in terms of elimination of the primary tumour. A renewed level of interest in the concept of pCR has emerged with the potential as a surrogate for clinical outcomes, as demonstrated in patients with breast cancer[58,59], as well as the introduction of more-efficacious second-generation inhibitors of androgen-receptor signalling. These agents include abiraterone, which suppresses circulating androgen levels to an order of magnitude lower than those routinely obtained using conventional ADT[60], and enzalutamide, which has demonstrably superior activity against bicalutamide-resistant cell lines[61] and in patients[62,63], compared with first-generation ADT. Both agents have been shown to prolong overall survival when used either before or after chemotherapy in patients with mCRPC, and both are approved by the FDA for these indications[4–7].

In the past 3 years, investigators at the Dana-Farber Cancer Institute applied an approach used in a series of neoadjuvant trials involving patients with breast cancer[65] to develop and later report on the performance of two rigorously defined pathological end points for use in a series of single-arm and randomized phase II neo adjuvant trials involving patients with high-risk localized prostate cancer. The end points were pCR, reflecting the complete

elimination of all disease in the gland, and minimal residual disease (MRD), defined either as a residual cancer burden (RCB; a calculation of tumour volume corrected for cellularity) of ≤0.25 cm^3 of tumour, or 1–5 mm of viable tumour. In the first proof-of- concept trial[53], patients were randomly assigned to receive either leuprolide alone or leuprolide plus abiraterone for 12 weeks, followed by another 12 weeks of combination therapy for all patients. The number of patients in each of the arms ranged from 28–30 with a higher pCR rate of 10% versus 4% following 24 weeks versus 12 weeks of treatment with abiraterone[53]. In a subsequent study that is currently ongoing, researchers evaluated the efficacy of more-extensive suppression of androgen levels with enzalutamide, abiraterone, and ADT, with a pCR rate approaching 12% (Mary-Ellen Taplin, personal communication). An additional 30% of patients met the MRD end point. Long-term follow-up monitoring is needed to evaluate the association between pathological response in the gland and subsequent outcomes, such as serum PSA recurrence, metastasis, and survival.

Biochemical recurrence.

The end point of an un-detectable serum PSA level with serum testosterone levels similar to pretreatment levels can be regarded as an equivalent to a ‘no-evidence-of-disease’ status and has long been used as an early surrogate for ‘cure’ after radical prostatectomy for localized disease. Notably, such an out-come is rarely achieved with ADT alone, whether given on an intermittent basis (shown to be equivalent to continuous therapy) for patients with biochemically recurrent disease[66] or to those with visible metastases observed on imaging[67]. We have long explored the value of this end point in trials involving patients with biochemically recurrent disease with a rapid (≤9 month) serum PSA doubling time. These patients require therapy based on their proven risk of developing detectable metastases and ultimately dying of prostate cancer. Completed studies involving this end point include our phase II study of the efficacy of docetaxel, ADT, and rapid androgen cycling[68]. Other studies include the phase III TAX3503 trial (), which is currently in the follow-up period and was designed to compare the efficacy of ADT for 18 months, with or without six cycles of docetaxel[69], and the phase II AbiCure trial, in which patients were randomized to receive either degarelix alone, abiraterone acetate plus prednisone alone, or the combination of degarelix and abiraterone acetate plus prednisone (). The cohort size in each study accounts for the fact that serum testosterone levels do not return to noncastrate levels in 10–15% of patients, thus rendering these patients unable to meet the primary end point. In these single-modality studies, approximately 5–20% of patients had no evidence of disease at 18 months[68,69], which demonstrates the feasibility of biochemical recurrence as an end point in trials involving patients with rising PSA levels alone, or with overt metastatic disease, although few of the responses were durable.

Metastatic noncastrate prostate cancer.

ADT, as a standard of care, results in median failure-free and overall survival durations of 11 months and 42 months, respectively, with sites of metastatic disease and initial Gleason scores remaining statistically significant prognostic indicators of both progression-free and overall survival[70]. Baseline serum PSA levels are strongly associated with failure-free survival[70], while in the SWOG-9346 trial[71] patients who achieved a PSA nadir of ≤4 ng/ml had longer survival durations than those with a serum PSA nadir >4 ng/ml. As discussed

earlier, the added efficacy provided by addition of docetaxel to ADT has been definitively established in patients with high-volume disease[45], but is debatable for patients with lower-volume disease, with similar results seen with abiraterone plus prednisone in LATITUDE[51] and STAMPEDE[48].

Definitive management of the primary lesion in the prostate has not been regarded as the standard of care for patients with metastatic disease; however, emerging data indicate that radical prostatectomy in this setting is feasible and safe[72,73], and that both radical prostatectomy and radiotherapy to the prostate might even confer a survival benefit[74–76]. In a small study cohort, patients with low-volume metastatic disease who underwent radical prostatectomy had a significantly longer time to development of castration resistance and clinical progression compared with those who did not undergo radical prostatectomy, in addition to extended cancer-specific, but not overall, survival[72]. Furthermore, a contemporary analysis of the National Cancer Database indicates that the overall survival outcomes of men with metastatic prostate cancer treated with radiotherapy plus ADT are superior to those of patients treated with ADT alone[76], even after adjusting for age, year, ethnicity, comorbidity score, serum PSA level, Gleason score, T stage, N stage, previous chemotherapy, treating facility, and insurance status. Collectively, a large body of retrospective evidence indicates a survival benefit following radical management of the primary tumour, even in the metastatic setting; this principle is currently being actively explored and validated in a number of clinical trials[77] (TABLE 3).

Similarly, radiotherapy delivered to bone metastases in patients with low-volume disease is not an established standard of care, although data from several centres[78] highlight the potential benefits of effective control of individual osseous lesions in patients with low-volume disease. Such control is achieved most frequently with stereotactic body radiotherapy (SBRT), defined by the American Society for Radiation Oncology (ASTRO) as “external beam radiotherapy used to deliver a high dose of radiation very precisely to an extracranial target within the body, as a single dose or a small number of fractions” (REF. 79). Local control rates obtainable with this approach are high: in one series of patients with prostate cancer and 1–2 bone metastases receiving single-fraction SBRT, the 12-month local control rate (defined as a lack of progression on follow-up imaging) was 95.5%, with follow-up durations of 6–77 months[80]. Repeat SBRT has also been used in patients with minimal bone and/or lymph-node only recurrences in an effort to delay the need to start ADT. The results of these studies are some-what difficult to interpret owing to differences in trial design, outcomes, and the triggers used to indicate a need for systemic therapy[81]. More importantly, the efficacy of SBRT is currently being evaluated further in a number of ongoing trials (TABLE 3).

Multimodality therapy.

In 2016, we reported the out-comes of a pilot experience of multimodality treatment in patients with low-volume metastatic disease, defined as <10 bone metastases, based on ^{99m}Tc radionuclide bone scans and/or nonregional lymph-node involvement[54]. Patients were treated for 6–12 months with ADT followed by radical prostatectomy with lymph-node dissection of all gross nodal disease and SBRT to bone metastases. The report included a

total of 20 patients, of whom four (20%) met the primary end point of a PSA response (serum PSA <0.05 ng/ml) with noncastrate serum testosterone levels at 20 months after the initiation of treatment. In two of these patients, serum PSA remained undetectable at 27 months and 46 months, respectively[54]. This pilot experience established the feasibility and safety of the multimodality approach and provides an approximate baseline response rate for the design of future trials. The most-important finding was that each treatment modality was required and contributed to the outcome; indeed, the frequency at which an undetectable serum PSA level was achieved increased as each modality was applied, ultimately leading to 95% of patients having undetectable serum PSA levels during the course of treatment (FIG. 1).

A new approach to drug development

To test the hypothesis that a multimodality treatment strategy that includes systemic therapy, radiotherapy to visible metastases and radical surgery can eliminate disease, MetaCURE, a continuously enrolling Multi-Arm Multi-Stage (MAMS) randomized trial design has been developed, analogous to that used in the STAMPEDE trial[82], which enables the efficacy of several approaches to be studied in parallel, and new treatment arms to be added at any time without the need for a new protocol (BOX 1, FIG. 2). Both trials are predominantly enrolling patients with newly diagnosed disease across a range of noncastrate clinical states.

The designs of both trials involve a prespecified intermediate activity analysis to determine whether or not a given approach is worthy of further investigation[83–85]. Differences between our platform and that of STAMPEDE[82] include the intermediate activity end point used (early response indicators that are binary and occur early, as opposed to time-to-event measures that occur later), and the sample sizes enrolled to inform the decision to proceed (30–40 per arm for MetaCURE, in contrast to STAMPEDE[82], which incorporates three to four efficacy stages that require >100 events to be observed in the control arm for the first stage of comparative analysis). An additional difference is that the next step for a successful initial experimental arm in MetaCURE is validation in an independent phase III trial, while STAMPEDE[48] enables the seamless continuation of enrolment until the phase III question is answered, without the need to design a new trial.

A randomized design is used to avoid imbalances in treatment assignment as a result of the rapidly changing diagnostic and therapeutic landscape. Two binary end points are used: pCR and MRD in the prostate for patients with the primary tumour *in situ* at the start of therapy, and undetectable serum PSA levels with physiological levels of serum testosterone after completion of treatment for those with metastatic disease who are effectively incurable with any single-modality approach. Both end points are objective, occur early, result solely from treatment, and provide an early quantitative readout of efficacy, thus enabling the results obtained with each treatment approach to be viewed in the context of others and prioritized for additional investigation.

In MetaCURE, new treatments will be entered over time, and treatment cohorts that have completed accrual are monitored as outlined in the statistical plan. For each new treatment, the same end points, patient accrual goals, and efficacy boundaries will be retained. The

benefit of integrating new treatments is that the existing treatments can be used as concurrent controls, thus ensuring that stage migration has not occurred over time. A fundamental difference with STAMPEDE[85], is that, although patients are randomized to different treatments, the response rates between randomized groups will not be formally tested.

Eligibility.

We propose to include patients with prostate cancer of different clinical states, ranging from very-high-risk localized disease (defined as a minimum of four tumour-positive biopsy cores with Gleason score 8–10 disease, or Gleason 4 + 3 disease with either serum PSA levels >20 ng/ml or evidence of stage T3 disease on MRI), with or without regional lymph-node involvement in the pelvis, to those with a limited number of detect able extrapelvic metastases in the retro peritoneum and/or bone. The lower and upper limits of this continuum have been defined with recognition of the uncertainty in the accuracy of clinical staging using standard imaging modalities, such as CT and radionuclide bone scans. However, the accuracy of staging is anticipated to improve with increasing use of commercially available assays that enable profiling of the primary tumour. We particularly use the term ‘low-volume metastatic’ as opposed to ‘oligometastatic’ to describe those with a limited number of metastases because, as PET tracers become increasingly available, patients who were previously considered to have oligometastatic disease, with three or fewer sites detectable on imaging, will likely be found to harbour more metastases and will no longer meet the current criteria.

Issues addressed by MetaCURE

Differences in eligibility for the ‘same’ named popu lation.

The limitations of the TNM staging classification in determining risk in patients with clinically localized disease have resulted in a range of risk stratification schema based on parameters that reflect the extent of disease, including: T-stage using digital rectal examination; number of tumour-positive biopsy cores, and the percentage of cancer present within each core; in addition to measures of tumour aggressiveness, such as Gleason score and baseline serum PSA level. The reported criteria for classification of high-risk and very-high-risk localized disease overlap considerably, without a definite consensus among guidelines provided by different groups, such as the AUA, EAU, and NCCN (TABLE 4). Some guidelines describe dichotomized variables while others are nomogram-based and include continuous variables, all of which have been combined to generate a final score. These variations lead to substantial heterogeneity in 5-year PFS rates ranging from 50% to 80%, depending on the guidelines used[29]. This recognition of the range of outcomes led to efforts, such as that of the International Society of Urological Pathology, to revise the Gleason scoring system into grade groups that reflect the distinction in prognosis between men with high-risk Gleason score 8 disease relative to that of those with Gleason score 9–10 disease[86].

Genomic testing is also becoming widely adopted. Examples include the RNA-based Decipher genomic classifier[87], which revealed a strong correlation between genomics-based risk score and the presence of high-risk pathological features; the Oncotype Genomic

Prostate Score[88], which is designed to identify patients at risk of biochemical recurrence or disease progression; or the PAM50 classifier[89], which enables the identification of luminal subtypes among patients with early stage prostate cancer with varying risks of biochemical recurrence. Several of these genomic classifiers have been demonstrated to provide prognostic information beyond what can be obtained using clinical or pathological investigations alone[90–92].

Imaging extraprostatic disease.

The specific imaging modalities used to determine the extent of primary disease and to detect metastases varies widely between centres. This variability in part reflects the availability of specific PET imaging tracers, differences in image interpretation, and in how they are reported once the images have been analysed. The preoperative identification and localization of pelvic nodal disease is important from both a prognostic and therapeutic perspective[93]. Detection of pelvic nodal disease using conventional CT and/or MRI has limited sensitivity and specificity[94,95]. However, this situation is changing rapidly with the increasing availability of ^{11}C-choline PET, ^{18}F-fluciclovine, and prostate-specific membrane antigen (PSMA)-directed tracers labelled with ^{18}F or ^{68}Ga. These tracers are currently the most frequently used among patients with biochemically recurrent disease in order to determine the source and location of the PSA, and to better inform the decision to recommend the delivery of salvage therapy to the prostate or prostate bed and/or systemic therapy. The role of PET in the detection of nodal disease remains an active area of investigation[96].

Radionuclide-based bone imaging remains the standard imaging approach for determining the extent of osseous metastases, despite limited levels of sensitivity. A key limitation of this technique is that the radio nuclides only localize to areas of bone formation that occur in response to the tumour and not to the tumour itself, in addition to poor specificity owing to accumulation of radionuclides in degenerative, traumatic, and/or inflammatory lesions. ^{18}F-sodium fluoride PET imaging generally enables more lesions to be detected, relative to conventional bone scintigraphy, but is also similarly limited by nonspecific uptake in nontumour involved areas[97]. CT is useful in determining the morphological changes that distinguish between lytic, blastic, and mixed lesions but is not advisable for routine detection of bone metastases[98]. Contrast-enhanced whole-body MRI is proving to be a sensitive detection method that not only enables secondary changes in bone structure to be detected, but also changes in the bone marrow, in the absence of a discernible change in the patient's bone structure[99]. Detection rates associated with contemporary PET imaging agents vary as a function of the tracer selected, and the serum PSA thresholds at which imaging is performed. Choline is currently considered the least-sensitive imaging agent and, at the Advanced Prostate Cancer Consensus Conference in March 2017, PSMA–PET and whole- body MRI were considered to provide comparable levels of perfromance[100].

Interventions

The multimodal approach includes a period of induction with systemic therapy followed by surgery, and SBRT to any detectable osseous metastases, potentially followed by adjuvant radiotherapy to the prostate bed and regional lymph nodes according to pathological findings

during surgery. This approach is based on a previous pilot experience demonstrating that each treatment modality contributes to the 'no-evidence-of-disease' state[54]. ADT and a second-generation androgen receptor signalling pathway inhibitor, such as abiraterone, enzalutamide, or apalutamide, will serve as the systemic therapy backbone, to which additional agents, either those that target androgen receptor signalling or alternative pathways, can be added to future arms. The choice of the systemic backbone agent is supported by the results of both LATITUDE[51] and STAMPEDE[48] showing that more-complete inhibition of the androgen-receptor signalling axis prolongs survival, relative to ADT alone. Systemic therapy is discontinued after 8–12 months in patients with undetectable serum PSA levels, and patients' serum testosterone levels are then monitored until testosterone levels return to noncastrate levels. The first stage of the protocol will begin with examinations of the role of intensification of androgen suppression, with future arms focusing on tumours with deficient DNA-damage repair mechanisms.

Surgery.

In the proposed meta CURE platform, all patients will undergo radical prostatectomy with a thorough pelvic and, if applicable, retroperitoneal lymph-node dissection after 6–8 months of systemic therapy, building on the safety and feasibility demonstrated in research by our group[54] and others[72,73]. Clinically, this approach offers the potential to eliminate disease that, in patients in whom systemic therapy does not result in a pCR in the primary tumour, could be a persistent source of metastases[101] or localized disease symptoms. The removal of any residual primary disease is also necessary in order to best assess the neuroendocrine differentiation end point that might be achieved with combinations of systemic therapy. Finally, this protocol will provide ample amounts of both primary tumour and lymph-node tissue samples, thus enabling molecular interrogation of predictors of responses, which might help to identify those who are most likely to benefit from surgery and enable the antineoplastic activity of drug combinations to be evaluated.

Radiotherapy.

Radiotherapy will have multiple roles in our proposed study paradigm. Firstly, SBRT will be used to treat any radiographically evident, minimally osseous disease, with the caveat that such disease must be safely encompassed within three radiation isocentres — to balance between maximizing treatable metastatic lesions versus minimizing the risk of overexposing patients to radiation. Radiotherapy will be delivered in 1–5 fractions. Secondly, conventionally fractionated radiotherapy delivered to the prostate bed and/or pelvic nodal basins will be given as an adjuvant therapy in patients with pathological features suggestive of high-risk disease following prostatectomy (such as positive margins or pelvic nodes), or as part of salvage therapy in patients with biochemically recurrent disease owing to the established role of salvage radiotherapy in providing durable local disease control in the majority of these patients[102,103].

Outcomes.

Two binary end points are used in Meta CURE: a common end point of pCR in the prostate for all patients undergoing radical prostatectomy, and undetectable serum PSA levels following recovery of serum testosterone levels, reflecting the complete elimination of all

macroscopic and microscopic disease present at the start of treatment. Both binary end points are unequivocal, can be reached early in the course of treatment, and result solely from treatment. Taken together, the use of such end points eliminates the uncertainty associated with trying to interpret changes in serum PSA levels and tumour regression at unmeasurable disease sites, in addition to that surrounding the clinical significance of the reported outcomes of many time-to-event based studies, and the effects of the available and approved post-protocol therapies that can dilute the influence of a treatment on overall survival outcomes. Both end points also provide a quantitative measure that enables the performance of competing strategies to be ranked and prioritized for further study in trials with larger cohorts of patients. We will also be able to prospectively explore the clinical and/or prognostic value of MRD in the prostate, as observed previously in other disease types, such as breast cancer[104].

Conclusions

The advantages of a platform that functions as a master trial, in which additional treatment arms can be added without the need to develop a new protocol, are manifold. The continuous control arm enables a higher percentage of enrolled patients to undergo treatment using an experimental approach — that is, to receive treatment regimens that are likely to meet the criteria for superiority to become the new standard approach without the need for a new trial[82,85]. Another advantage is the inclusion of patients with low-volume disease of a wide range of stages and using a common end point for an effect of treatment: such a control arm also eliminates the uncertainties associated with differences in stage classification based on the various imaging modalities and criteria used to assess both the primary tumour and the presence or absence of metastatic disease.

As a platform to enhance scientific understanding of prostate cancer biology, Meta CURE will provide a standardized clinical framework that enables the prospective investigation of different imaging-related and biomarker-related questions; with the use of an acquisition algorithm designed to promote consistent and standardized collection of tissue and blood samples, biological questions can be prioritized and examined using retrospective and/or prospective designs that enable clinical validation timelines to be shortened. The inclusion of patients with a wider range of clinical characteristics enables trials directed at biologically defined subsets of patients that, comparatively, will be completed more rapidly, at a time when the disease is less heterogeneous and more likely to be sensitive to targeted agents. Molecular profiles of prostate cancers of different disease states show the increasing level of complexity and tumour heterogeneity acquired as their disease progresses and is exposed to a wider range of systemic therapies (FIG. 3). The frequency of genomic alterations in the clinically localized tumours examined as part of The Cancer Genome Atlas cohort[9] was approximately 27% versus 90% in the SU2C dataset[105] which involved prospective whole-exome and transcriptome sequencing of bone or soft-tissue tumour biopsy samples from patients with mCRPC, although these two series are not directly comparable. In the MSK–IMPACT series, in which tumours across different clinical states were examined, a markedly lower rate of alterations in androgen receptor signalling pathways was observed in both the localized and noncastrate metastatic states[9,10], potentially predicting increased sensitivity to therapies targeting androgen receptor signalling. In addition to interrogation of the baseline

molecular features of these cancers, the MetaCure platform will facilitate a systemic and prospective study of MRD in prostatectomy specimens to enable further understanding of the mechanisms of disease and treatment resistance.

Using binary end points that occur early in the course of disease and solely reflect the effects of treatment provides a more-rapid readout of success or failure, thus enabling the results of different treatment strategies to be placed in the context of others. Such an approach also provides an objective platform to prioritize areas for investigation in large-scale trials. Use of binary end points also substantially reduces the time and number of patients needed to show benefit, thus eliminating the uncertainty and lack of clinical significance often associated with time-to-event outcome-based studies. Importantly, the confounding effects of the post-protocol choice of therapy on patient outcomes will also be eliminated. If a relationship between achieving a pCR or MRD in the primary tumour and improved long-term disease-free survival outcomes can be demonstrated, this approach will set the stage for the development of trials designed to establish these outcomes as end points for registration, analogous to what has been established from the neoadjuvant studies conducted in patients with breast cancer, which showed such outcomes to be reliable surrogate indicators of overall survival[104] that can lead to accelerated approval[106]. Most importantly, the approach to trial design presented herein provides an opportunity to capitalize on the latest advances in drug development, molecular and diagnostic taxonomy, and imaging to accelerate the identification of the optimal therapeutic strategies for men with noncastrate prostate cancer.

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Box 1 |

MetaCure: advantages and future directions

Eligibility

- The broad range of eligibility, along with a randomized design reduces the uncertainties associated with clinical staging based on the specific imaging modalities used to assess both the primary tumour and the presence or absence of metastatic disease
- The inclusion of a wider range of disease states enhances accrual, and trials can be directed at biologically defined subsets of patients, and be completed more rapidly

Treatment

- The ability to add new experimental arms on a continuous basis eliminates the need for new trials, thus enabling promising new approaches to be evaluated earlier and reducing the amount of resources required to conduct a clinical trial

Results

- Early readouts of success or failure using a binary end point that solely reflects the effects of treatment
- Reduces the number of patients needed to show benefit, and reduces the uncertainty associated with time-to-event measures and confounding the effects of post-protocol therapy on outcomes
- Enables the results of competing treatments to be placed into the context of other findings

Secondary/exploratory

- Provides a standardized clinical framework to prospectively ask questions regarding the performance of imaging and molecular biomarkers with an appropriate level of statistical power
- The standardized trial framework, including acquisition and storage of clinical samples, enables specific biological questions to be prioritized and investigated using retrospective and/or prospective studies, thus substantially shortening the time required for validation
- Provides an objective platform enabling the prioritization of approaches and biomarkers for investigation in larger clinical trial cohorts

Key points

- The increasing number of both approved and experimental therapies available mandates the use of new trial designs for patients with noncastrate prostate cancer, which provide expedited readouts of efficacy
- Trials based on time-to-event end points, such as progression to metastatic disease and overall survival, require large numbers of patients with long follow-up durations, and might provide inconclusive results owing to use of post-protocol interventions
- To accelerate progress, a multi-arm, multistage, multimodality trial platform involving delivery of systemic therapy, radiotherapy to detectable metastases, and radical surgery was developed that enables new arms to be added at any time
- The objective is to eliminate all disease using binary quantitative end points that occur early and solely reflect the effects of treatment, such as pathological complete response and undetectable serum prostate-specific antigen levels after testosterone recovery

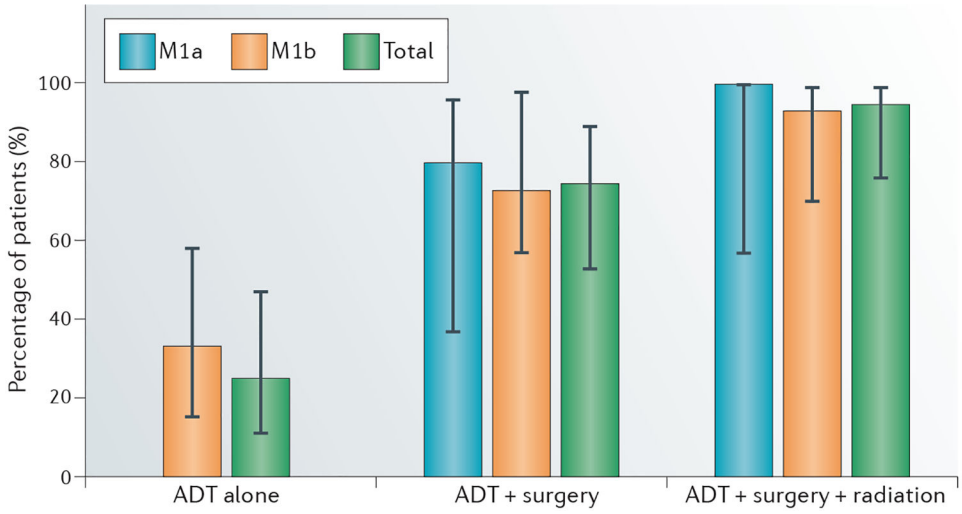

Figure 1 |. Percentage of patients with an undetectable serum PSA level following multimodality therapy.

The percentage of patients with an undetectable serum prostate-specific antigen (PSA) level during the treatment phase increased with the addition of each component of multimodality therapy[54]. Patients responses to treatment were assessed using measurements of serum PSA levels; the frequency of patients in whom serum PSA levels were undetectable after androgen-deprivation therapy (ADT) alone, ADT plus surgery, and/or ADT plus surgery plus radiotherapy is shown. M1a, extrapelvic nodal disease; M1b, bone metastasis. Reproduced with permission obtained from Elsevier © O'Shaughnessy, M. J. *et al.* A pilot study of a multimodal treatment paradigm to accelerate drug evaluations in early stage metastatic prostate cancer. *Urology* 102, 164–172 (2017).

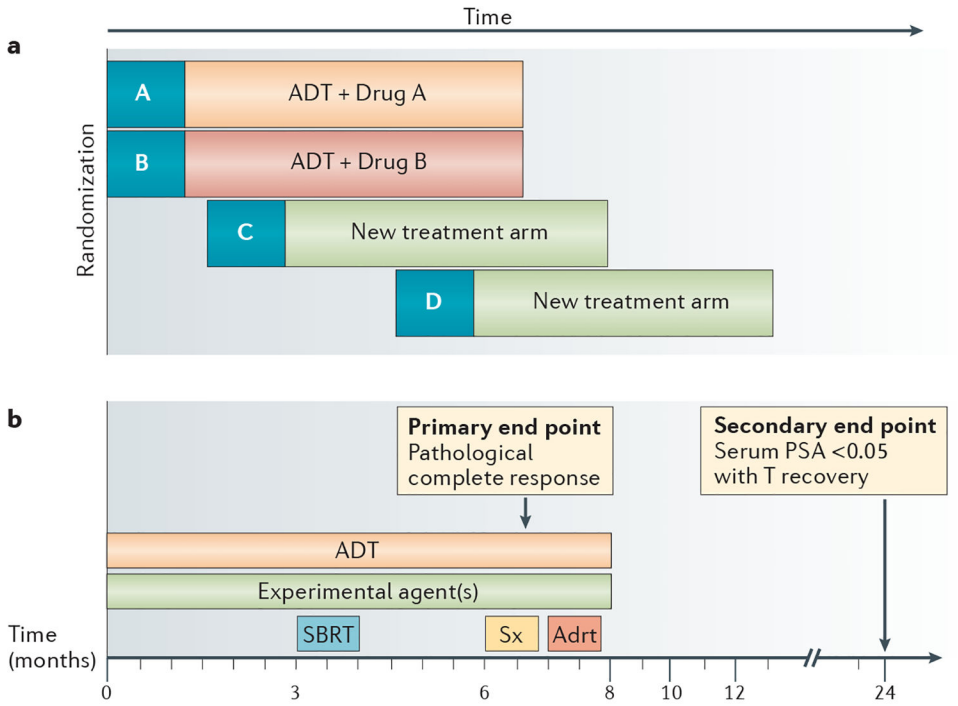

Figure 2 |. Multimodality treatment schema for multiarm, multistage trials in patients with advanced-stage prostate cancer.

a | General study schematic, in which treatment arms can be added in the future, with existing arms serving as a contemporary control. **b** | Binary trial end points include pathological complete response for patients with prostate cancer *in situ* and undetectable serum prostate-specific antigen (PSA) levels following testosterone recovery; these end points are measured at 6 and 24 months after randomization, respectively. Failure to achieve an undetectable serum PSA level with testosterone recovery at the conclusion of active treatment will be used as a futility end point. ADT, androgen-deprivation therapy; adrt, adjuvant radiotherapy to prostate bed; SBRT, stereotactic body radiation therapy; Sx, surgery (radical prostatectomy plus pelvic lymph node dissection with or without retroperitoneal lymph node dissection).

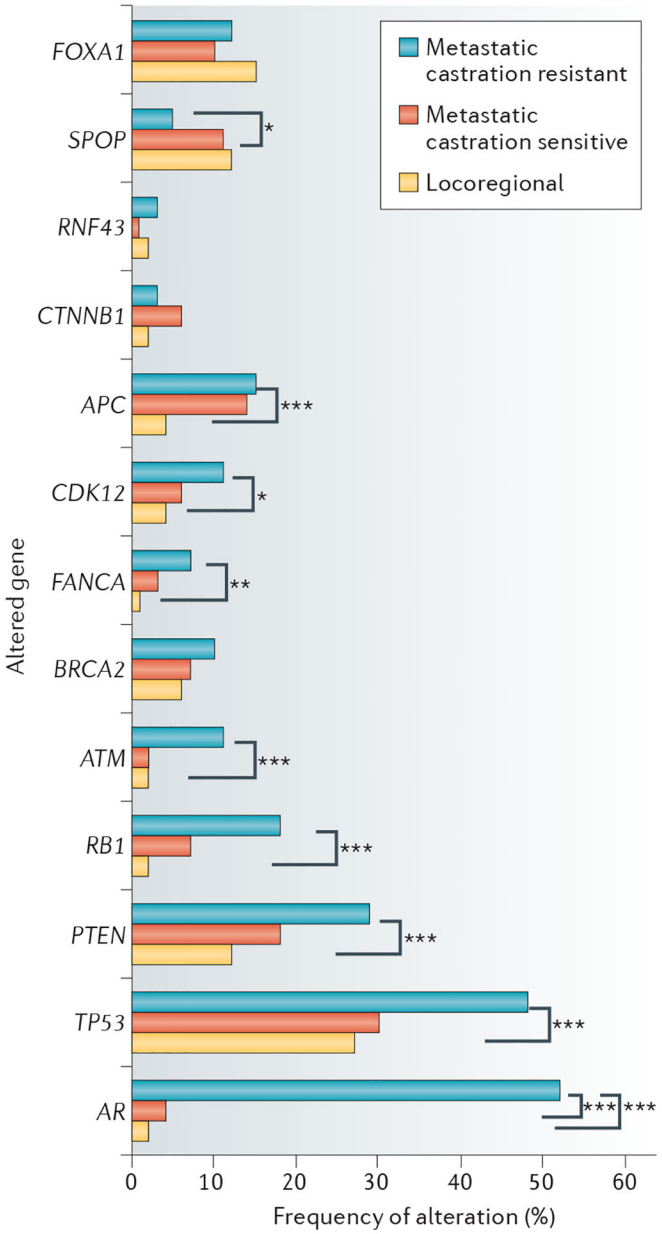

Figure 3 |. Frequency of genetic alterations in different disease states.

Locoregional and metastatic castration-sensitive prostate cancers (CSPCs) have a similar genomic landscape, in contrast to CSPCs, which have a higher rate of genomic alterations. This figure illustrates the frequencies of alterations in selected genes across different disease states in the MSK–IMPACT dataset[107]. P values are represented (Fisher's exact test).

Table 1 |

Cohort sizes and time to publication, and clinical implications of selected phase III trials

Treatment approach	Number of patients*	Number of centres	Start of accrual	Accrual duration (months)	Months from start of accrual to publication	Supported changes in clinical practice?‡	Ref.
High-risk localized disease							
RTOG 0521 (RTfollowed by ADT ± docetaxel)	282 vs 281	12§	December 2005	43.6	113.1	No	23
GETUG12 (ADT ± docetaxel + estramustine followed by RP/RTfollowed by ADT)	207 vs 206	26	November 2002	48.8	149.2	No	21
TAX - 3501(RP followed by ADT ± docetaxel)	70 vs 68	108	December 2005	20.8	91.6	No	69
SWOG S9921 (RP followed by ADT ± mitoxantrone)	480 vs 481	NR	October 1999	86.2	206.3	No	24
Locally-advanced disease							
RT ± GnRH	987 vs 992	212	October 1994	77.4	199.8	Yes	108
ADT ± RT	603 vs 602	78	March 1995	124.0	189.8	Yes	109
ADT ± RT	436 vs 439	47	February 1996	81.3	153.2	Yes	18
Biochemically recurrent disease							
Salvage RT ± anti-androgen	384 vs 376	19§	March 1998	59.5	225.2	Yes	34
Metastatic castration-sensitive disease							
Intergroup (intermittent versus continuous ADT)	770 vs 765	18§	May 1995	158.7	213.3	No	66
Bilateral orchiectomytflutamide (Ml)	667 vs 669	9§	December 1989	56.5	105.4	No	37
GETUG 15 (ADT ± docetaxel)	192 vs 193	29§	October 2004	50.0	97.9	No	49,50
CHAARTED (ADT ± docetaxel)	397 vs 393	15§	July 2006	76.4	108.7	Yes	44–46
STAMPEDE (ADT ± docetaxel)	727 vs 1,090	125	October 2005	89.1	121.5	Yes	47,48
LATITUDE (ADT ± abiraterone)	597 vs 602	235	February 2013	21.8	31.2	Yes	51
STAMPEDE (ADT ± abiraterone)	500 vs 502	116	November 2011	25.9	66.1	Yes	52

ADT, androgen deprivation therapy; GnRH, gonadotrophin-releasing hormone; NR, not reported; RP, radical prostatectomy; RT, radiotherapy.

*First number represents the number of patients assigned to the experimental arm, followed by the number assigned to the control arm.

‡Refers to study results that lead to incorporation within National Comprehensive Cancer Network guidelines.

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§Estimated, based upon number of investigators.

Table 2 |

Selected clinical trials involving neoadjuvant ADT with pCR rates reported

Study	n	Predefined study entry criteria in manuscript					Treatment arm(s)	pCR rate	MRD (≤ 5 mm)	MRD (<0.25 cm^3)	pCR defined?	MRD defined?
		T-stage	Gleason score	Number of cores	Baseline PSA	Imaging criteria						
Labrie *et al.* (1997)[110]	161	Yes	No	No	No	No	Leuprolide + flutamide for 3 months	7%	NA	NA	No	No
Van Der Kwast *et al.*(1999)[111]	47	No	No	No	No	No	Leuprolide + flutamide for 3 months	0%	NA	NA	No	No
							Leuprolide + flutamide for 6 months	9%				
G leave *et al.* (2001)[112]	547	No *	No	No	No	No	Leuprolide + flutamide for 3 months	5%	NA	NA	Yes	No
							Leuprolide + flutamide for 8 months	9%				
Klotz *et al.* (2003)[113]	213	Yes	No	No	Yes	No	Cyproterone for 3 months	0%	NA	NA	No	No
TAPS (2014)[114]	35	Yes	Yes	No	No	No	Goserelin + dutasteride for 3 months	0%	NR	17% ≠	No	Yes
							Goserelin + bicalutamide + dutasteride for 3 months	10%	NR	20% ≠		
							Goserelin + bicalutamie + dutasteride + ketoconazole for 3 months	8%	NR	23% ≠		
NeoAbi (2014)[53]	56	Yes	Yes	No	Yes	No	LHRH agonist for 6 months + abiraterone for 3 months	4%	0%	44%	No	Yes
							LHRH agonist for 6 months + abiraterone for 6 months	10%	14%	52%		
NeoEnza (2015)[115]	48	Yes	Yes	Yes	Yes	No	Enzalutamide for 6 months	0%	0%	36%	Yes	Yes
							Enzalutamide + dutasteride + leuprolide for 6 months	4%	13%	74%		
MDACC (2016)[116] §	65	Yes	Yes	No	Yes	No	Abiraterone + enzalutmide + LHRH agonist for 6 months	2%	NR	NR	No	Yes
							Abiraterone + LHRH agonists for 6 months	5%				
	30	Yes	Yes	Yes	Yes	Yes	Leuprolide + enzalutamide	10%	55%	NR	NA	NA
							Leuprolide + enzalutamide + abiraterone	15%	50%			

ADT, androgen-derpivation therapy; LHRH, luteinizing-hormone releasing hormone; NA, not available; NR, not reported; pCR, pathological complete response; PSA, prostate specific antigen

* Patients were stratified for Gleason score and baseline serum PSA level

≠ MRD defined as <0.2 cm^3 in this study

§ Full study not reported, data were obtained from abstract.

Table 3 |

Selected ongoing studies in metastatic noncastrate prostate cancer

Study	Study arms	Phase	Estimated cohort size	Identifier	Primary end point
Systemic therapy in mCSPC					
ARCHES	ADT + enzalutamide versus ADT + NSAA	III	1,100		Radiographic PFS
MRC STAMPEDE (Arm J)	ADT + abiraterone + enzalutamide versus ADT	III	1,800		OS
TITAN	ADT + apalutamide versus ADT	III	1,000		OS and radiographic PFS
ARASENS	ADT+docetaxel + ODM-201 versus ADT + docetaxel	III	1,300		OS
Treatment of the primary lesion in mCSPC					
PEACE1	ADT ± docetaxel ± localized radiotherapytabiraterone	III	916		OS and PFS
MDACC	Best systemic therapytsurgery/radiotherapy	II	180		PFS
JHU	ADT + NSAA + docetaxel + radiotherapy+surgery	II	33		Safety
MRC STAMPEDE (Arm H)	ADT + radiotherapy versus ADT	III	1,250		OS
Treatment ofmetastatic lesions in mCSPC					
Ghent	Observation versus radiotherapy to metastatic sites (≤ 3 sites)	II	54		ADT-free survival
University of Florida	SBRT or stereotactic hypofractionated radiotherapy	II	48		PFS

ADT, androgen-deprivation therapy; mCSPC, metastatic castration-sensitive prostate cancer; NSAA, non-steroidal anti-androgen; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

Table 4 |

Classifications and definitions of high-risk localized prostate cancer

Source	Serum PSA >20ng/ml	Gleason 8–10	Gleason pattern 5	≥5 cores with Gleason score 8–10	≥cT2	cT3a	cT3-cT4	cN+	Other
NCCN guidelines (high risk)[117]	X	X	-	-	-	X	-	-	-
NCCN guidelines (very high risk)[117]	-	-	X	X	-		X	-	-
AUA (high risk)[118]	X	X	-	-	X(T2c)	-	-	-	-
EAU-ESTRO-SIOG[119]	X	X	-	-	X(T2c)	-	-	-	Any serum PSA level, any Gleason score, cT3b -T4orcN + - locally advanced
RTOG/NRG (groups 1 – 4)[120]	-	X	-	-	-	-	X	X	On the basis of patients enrolled in RTOG phase III trials
JHU (very high risk)[121–122]	-	-	X	X	-	-	-	-	Or multiple NCCN-defined high-risk features
EMPaCT(high risk)[123]	X	X	-	-	-	-	X	-	Patients with high-risk disease are substratified into three subgroups *
UCSF-CAPRA[124]	-	-	-	-	-	-	-	-	On the basis of serum PSA, Gleason score,T-stage, percentage positive biopsy and age ≠
MSKCCNomogram[125]	-	-	-	-	-	-	-	-	On the basis of Gleason score, clinicalT stage and serum PSA level ≠
Decipher[87]	-	-	-	-	-	-	-	-	RNA-based classifier
OncoType GenomeProstate Score[88]	-	-	-	-	-	-	-	-	17-gene qRT-PCR based assay

AUA, American Urological Association; CAPRA, Cancer of the Prostate Risk Assessment; EAU, European Urological Association; EMPaCT, European Multicenter Prostate Cancer Clinical and Translational Research Group; ESTRO, European Society for Radiotherapy and Oncology; JHU, Johns Hopkins University; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; qRT-PCR, quantitative reverse-transcriptase polymerase chain reaction; RTOG, Radiation Therapy Oncology Group; SIOG, International Society of Geriatric Oncology; UCSF, University of California, San Francisco.

*Patients with high-risk disease are substratified into three subgroups: a good prognosis subgroup (characterized by a single high-risk factor); an intermediate-prognosis subgroup (serum PSA>20 ng/ml and stage cT3–4 disease); and a poor-prognosis subgroup (Gleason score 8–10 in combination with at least one other high-risk factor).

≠On the basis of a nomogram.