

# Should androgen deprivation therapy and other systemic treatments be used in men with prostate cancer and a rising PSA post-local treatments?

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**Abstract:** Biochemical recurrence is an evolving space in prostate cancer, with increasing multidisciplinary involvement. Androgen deprivation therapy has shown proof of its value in complementing salvage radiotherapy in high-risk biochemical relapsing patients; ongoing trials aim to further refine this treatment combination. As systemic treatments, and notably next-generation androgen receptor targeted agents, have moved towards early hormone-sensitive and non-metastatic stages, the prostate specific antigen (PSA)-relapse disease stage will be undoubtedly challenged by future evidence from such ongoing clinical trials. With the use of modern imaging and newer molecular technologies, including integration of tumoral genomic profiling and liquid biopsies in risk stratification, a path towards a precision oncology-focused approach will become a reality to guide in the future decisions for patients with a diagnosis of biochemical recurrence.

**Keywords:** androgen deprivation therapy, biochemical recurrence, prostate cancer, PSA relapse, systemic treatment

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## The notion and relevance of biochemical recurrence (BCR)

### Definition and clinical outcomes

In contrast to other malignancies, prostate cancer (PC) is characterized by a lower mortality and the majority of patients living with PC have a prognosis of many years. Globally, PC accounts for 7.3% of the overall number of new cancer cases (14.1% for males), and 3.8% of deaths, with an all-stage 10-year survival rate at 98%.<sup>1,2</sup>

Except when it isn't. Most patients with prostate cancer are diagnosed at a localized or locoregional stage, which explains the better survival rates. However, for men diagnosed with metastatic PC, the 5-year survival rate is estimated to be 31%; patients diagnosed with upfront metastatic disease contribute to half of PC deaths.<sup>3</sup> In the US, owing to the high incidence of the disease (first in

males, 21% of all new cancer cases), mortality from metastatic PC ends up being the second highest cause in males (10% of deaths).<sup>4</sup>

The critical moment that often points towards a less optimistic prognosis is the failure of primary treatment, be it radical prostatectomy (RP), radiotherapy (RT), brachytherapy, high-intensity focused ultrasound (HIFU), cryosurgery, or other focal therapy options. This failure will most frequently be in the form of a rising prostate-specific antigen (PSA), without macroscopically detectable disease in the first instance, i.e., a biochemical recurrence (BCR). The definition of BCR depends on the type of prior definitive therapy. In patients who have undergone RP, the European Association of Urology (EAU) 2020 guidelines propose that a rising serum PSA level should be considered a BCR.<sup>5</sup> Ultrasensitive PSA levels >0.01 ng/ml, in combination with clinical

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characteristics such as the International Society of Urological Pathology (ISUP) grade and surgical margin status, may be predictive of PSA progression after RP. In patients treated with RT, the RTOG-ASTRO Phoenix Criteria define BCR as a rise in PSA level of 2 ng/ml or more above the nadir, regardless of androgen deprivation therapy (ADT) use or of the nadir value.<sup>6</sup>

Several nomograms have been created for the estimation of BCR risk, such as the CAPRA-S, the MSKCC, and the Walz nomograms.<sup>7–9</sup> A recent update of the latter seems to provide an elegant estimates BCR risk at 12 and 24 months post-RP based on PSA, Gleason score (GS), pT stage, surgical margin, and lymph node status.<sup>10</sup>

The rate of BCR within 10 years following definite treatment is 20–40% after radical prostatectomy (RP)<sup>11–13</sup> and 30–50% following radiotherapy (RT).<sup>14,15</sup> BCR represents a true progression: it is associated with a 24–34% risk of developing metastasis,<sup>10,16</sup> with a PSA of 0.4 ng/ml a better predictor of this. The median time from RP to PSA failure is reported to be between 2 years<sup>13</sup> (Freedland *et al.*) and 3 years,<sup>17</sup> with a median metastasis-free survival (MFS) reported at 8–10 years.<sup>11,17</sup> After RT, PSA-doubling time (PSA-DT) correlates with the site of recurrence. While patients with local recurrence have a PSA-DT of 13 months, those with a PSA-DT of 3 months present with distant metastases.<sup>18</sup> EAU guidelines utilize PSA-DT (cut-off: 1 year) and GS (cut-off: 8) to define low and high-risk BCR post-RP, and interval to primary therapy (cut-off: 18 months) and GS (cut-off: 8) to define the respective BCR groups post-RP.<sup>19,20</sup>

Does MFS translate into PC-specific mortality? Overall, in unselected patients, the median time from metastasis to death was historically reported as 5 years.<sup>11</sup> However, this data was validated before the recent therapeutic advances in metastatic castration-sensitive (mCSPC) and castration-resistant (mCRPC) prostate cancer. In a cardinal mCRPC study, at a median follow-up (FU) of 6 years (rather limited for such purposes), the 5-, 10-, and 15-year cause-specific survival from the respective time of biochemical recurrence was 93% [95% confidence interval (CI), 90–96%], 73% (95% CI, 66–79%), and 55% (95% CI, 41–67%), but varied widely between the highest and lowest risk subgroups.<sup>13</sup> PSA-DT (especially if less than 3.0 months), pathological GS (8–10), and time from surgery to biochemical

recurrence ( $\leq 3$  years) are strong predictors of metastasis and PC-specific mortality,<sup>11–13</sup> although the latter factor has not been retained in more recent analyses.<sup>17</sup> These factors stratify patients at distinct risk groups, with a median MFS ranging from 1.0 year in the highest risk group to 15.0 years in the lowest risk group.<sup>17</sup> For example, the median MFS is 15 years and PC-specific survival is approximately 90% in patients with a PSA-DT of  $\geq 15$  months, whereas these are approximately 1 year and 20% respectively for patients with a PSA-DT of  $< 3$  months.<sup>13,17</sup> The EAU BCR risk stratification has been externally validated post-RP and found to be significantly predictive of 5-year MFS [hazard ratio (HR): 3.46;  $p < 0.001$ ] and PC-specific mortality (HR 5.12;  $p < 0.001$ ).<sup>19</sup>

*Biology of disease recurrence.* The identification of the earliest alterations in PC can give important insights into the relationships among primary and metastatic sites. Across cancer types, metastases have been reported to originate from single clones in the primary tumour (monoclonal seeding), or multiple clones (polyclonal seeding), however the distribution of these patterns across specific tumour types is not fully known.<sup>21</sup> This polyclonal seeding is a frequent event in prostate cancer and has also been found to be associated with oncogenic alterations of ADT resistance, such as MYC amplification or pathogenic AR substitution, suggesting that the tumour cell populations with a significant survival advantage are not confined within the boundaries of an organ site but can successfully spread to and reseed other sites.<sup>22</sup> In fact, in metastatic PC, multiple metastases were found to be more closely related to each other than any of them were to the primary prostate tumour, with sharing of sub clonal alterations by different metastases, indicating possible inter clonal cooperativity or re modelling of metastatic niches by initial colonizing prostate cancer clones, making them attractive habitats that other clones can colonise.<sup>22</sup> Multiple sub-clones achieve a metastatic potential through early alterations, such as tumour protein 53 (TP53) or phosphatase and tensin homolog (PTEN). TP53 mutations, in particular, appear to be strongly implicated in metastatic spread and can be easily detected with a liquid biopsy even before the appearance of metastatic lesions.<sup>23</sup> Secondary lesions appear to develop in the form of spread between distant sites, rather than single waves coming from the primary tumour. AR alterations are rarely present in the primary

tumour but seem to develop in the CRPC setting. AR aberrations are found to be heterogeneous and involve multiple events at different sites.

If such findings are further exploited and confirmed, primary tumour sequencing and liquid biopsies might prove helpful in detecting occult clones even before they become clinically visible. Importantly, the better understanding of the complex patterns of sub clonal differentiation between different metastases from distinct anatomical sites, with individual subclones able to seed polyclonally from one metastasis to another, support the rationale for an approach combining the local control of the primary with ablation of all oligometastatic tumour deposits.<sup>22–25</sup> Implementation of metastasis-directed therapies (MDT), together with systemic therapies, therefore represents an interesting therapeutic option to potentially eliminate sources for metastatic spread and improve oncological outcome in patients with relapsing prostate cancer (see discussion below).

#### *Impact of novel imaging technologies*

The notion of BCR is recently challenged by technological advances. Molecular and functional imaging shrink the space of PSA-only relapse by increasing the abilities of detecting and localizing sites of otherwise occult recurrent disease. The most sensitive positron emission tomography (PET) tracers currently available are the class of prostate-specific membrane antigen (PSMA)-targeted radiotracers. Its comparative detection sensitivity in the BCR setting has been assessed against a previous-generation tracer, choline, demonstrating the superiority of Ga-PSMA in terms of detection rates at any PSA level,<sup>26–28</sup> and has now been included as a recommendation in this setting in international guidelines.<sup>29</sup>

At the usually low PSA levels BCR features, even with PSMA-PET and more so with conventional imaging, the eventual identification of macroscopic disease is invariably limited to an oligo-recurrence context. Other than enlarging this space as it shrinks the true BCR space, the availability of such imaging has also shifted the treatment paradigm towards metastasis-directed treatment, both in the CSPC and the CRPC setting. This has shown clinically meaningful benefit such as ADT-free survival, CRPC-free survival, or time to treatment escalation.<sup>30–34</sup>

#### *Precision medicine and molecular strategies for risk stratification*

DNA-repair pathway alterations have gained significance in the therapeutic arena of advanced prostate cancer. The prognostic significance of such mutations, notably for the BRCA2 gene, was noted in the last decade, with identified association with poor survival outcomes, including metastatic relapse and cancer-specific survival post local treatment.<sup>35,36</sup> In a relevant meta-analysis, BRCA2 mutations have been shown to predict poor survival outcomes in prostate cancer patients in terms of cancer-specific survival and overall survival (OS), with pooled HRs of 2.53 (95% CI: 2.10–3.06,  $p < 0.001$ ) and 2.21 (95% CI: 1.64–2.99,  $p < 0.001$ ), respectively.<sup>37</sup>

Specifically, in BCR, overexpression of BRCA1/2 in prostatectomy specimens seems to be independently predictive of biochemical recurrence.<sup>38</sup> No information exists on specific phenotype-genotype prognostic correlations for the BRCA or other DNA repair pathway genes.

Multigene panels, such as the 17-gene Oncotype Dx,<sup>39</sup> the 31-gene Prolaris,<sup>40</sup> and the 22-gene Decipher<sup>41</sup> assess BCR risk at the time of diagnosis or post-RP. Although independently validated, these panels have not yet entirely revolutionized localized and loco-regional prostate cancer management for two main reasons. Firstly, their predictive ability is not uniform across the spectrum; for example, Oncotype DX does not significantly predict BCR in certain subgroups such as patients less than 56 years old, nor are all its components individually predictive. In addition, the impact of such tests in treatment decision-making and on PC mortality is unclear, as is their cost-effectiveness and their influence of BCR surveillance post-definite treatment. The Decipher genomic classifier<sup>41</sup> attempts to predict distant metastasis following RP, as a result assessing PC-specific mortality.<sup>42,43</sup> Its predictive ability seems to improve if combined with CAPRA-S.<sup>44</sup> In a prospective evaluation of its clinical utility (PRO-IMPACT trial), the use of Decipher test influenced treatment decisions regarding the choice between adjuvant and salvage treatment, and reduced levels of PC-related anxiety.<sup>45,46</sup>

An interesting classifier is the 15-gene SigMuc1NW signature, which exploits the biomarker potential of tumour-associated antigens (TAAs) such as mucin 1 (MUC1) and opa interacting protein 5 (OIP5). The signature was

validated to strongly predict BCR (HR, 2.44; 95% CI, 1.53–3.87;  $p=1.62e-4$ ) after adjusting for clinico-pathological factors such as GS, surgical margin status, age, and stage.<sup>47</sup> These TAAs, although previously investigated in other cancer types, are relatively novel PC-associated TAAs. Despite this, the signature has not been independently validated on other large databases.

In our era of large data and bioinformatics, attempts have been made to assess the predictive, biomarker potential of other signatures involving miRNAs or lncRNAs; however, these are as yet immature for PC.<sup>48–52</sup>

Finally, although checkpoint inhibition has not yet proven of meaningful benefit in metastatic prostate cancer, there is some recent limited evidence that increased programmed death-ligand 1 (PD-L1) expression is associated with biochemical recurrence.<sup>53,54</sup>

Liquid biopsy technology has further enhanced the detection possibilities related to PC recurrence, using more sophisticated techniques compared to measurements of PSA levels, upon which the conventional notion of BCR is based. Such methods include targets such as circulating tumour cells (CTCs), cell-free nucleic acids (such as mRNA), and extracellular vesicles, detected on readily accessible body fluids such as blood, semen, or urine.<sup>55</sup> An example of success in PC is the detection of the androgen receptor (AR) splice variants, such as AR-V7, in CRPC, predicting resistance to systemic treatments such as enzalutamide or abiraterone acetate. This new modality is slowly entering the space of PC diagnostics and accurate distinction from benign conditions.<sup>56</sup> Circulating mRNA technologies and second-generation CTC technologies have also entered the BCR space, with positive retrospective associations with a higher risk for biochemical recurrence following RP, even in the context of negative PSA.<sup>56–58</sup> Although it is still very early for such technologies to translate into clinical practice and guide treatment decisions, also due to the low abundance of circulating biomarkers in localized or early-recurring PC, it nevertheless incites strong interest for the future.

## Hormonal therapy

### *Immediate versus deferred ADT*

Androgen-deprivation therapy, as the mainstay for macroscopically recurrent disease, is an

obvious option for the management of BCR. Given that the volume of not yet macroscopic disease in BCR is low, the obvious question is whether such management would be beneficial in a BCR setting. Similarly, it is necessary to estimate the potential benefit and optimal timing of any intervention need to be in order for it to be clinically meaningful.

Initial evidence was obtained from two large retrospective studies. The CaPSURE trial (2096 patients with BCR post-RP or RT) demonstrated no significant advantage to immediate ADT *versus* deferred (at metastatic disease or  $\geq 2$  years after BCR) (HR for mortality: 0.91, 95% CI, 0.52–1.60) at a median FU of 54 months. The estimated 5-year OS (95% CI) was 85.7% *versus* 87.7%, the 10-year OS was 69.8.1% *versus* 69.3%.<sup>59</sup> In a larger retrospective study (5804 men), salvage ADT was associated with OS or PC-specific mortality in both the post-RP (HR: 0.35 and HR: 0.43 respectively) or the post-RT cohort (HR: 0.62 and HR: 0.65 respectively) in patients with PSA-DT < 9 months.<sup>60</sup>

The prospective phase III TOAD (TROAG 03.06) trial questioned the optimal timing of ADT in patients with rising PSA.<sup>61</sup> Interestingly, however, the trial was not strictly homogeneous in regard with the eligibility criteria; in addition to the pure PSA relapse patients (post-RT or post-RP with or without post-operative RT), the study also included patients with a *de novo* incurable disease (due to age, comorbidities, or locally advanced disease), the latter amounting to 11% of the total cohort. The study assessed an immediate *versus* deferred ADT; although the scheduled delay for the trial was at least 2 years, 52% of patients started ADT within 2 years, and patients with poor risk features (such as short PSA-DT) at the time of relapse started with a median delay of 12.3 months. Immediate ADT borderline improved 5-year OS (91.2% *versus* 86.4%, log-rank  $p=0.047$ ; unadjusted HR: 0.55,  $p=0.05$ ; adjusted HR: 0.54,  $p=0.047$ ;  $n=293$ ). Survival curves seem to start to separate after 5 years, with 6-year and 7-year survivals estimated at 76.4% *versus* 85.6% and 65.5% *versus* 81% respectively. However, this was not maintained in the PSA relapse only cohort, despite more patients in this group (5-year OS 78.2% *versus* 83.4%, log-rank  $p=0.10$ ; unadjusted HR: 0.58,  $p=0.10$ ; adjusted HR: 0.59,  $p=0.19$ ;  $n=261$ ). The time to local progression was significantly in favor of the immediate ADT arm (adjusted HR: 0.51,  $p=0.001$ ),



while time to a PC complication did not differ (adjusted HR: 0.78,  $p=0.16$ ). No significance could be demonstrated for PC-specific mortality, as the number of events was low. Intriguingly, the time to development of castration resistance from treatment start differed significantly between the two arms in favor of immediate ADT (HR: 0.30,  $p<0.001$ ). As the use of continuous *versus* intermittent ADT was similar between the two arms, this seems to be a true effect. The authors suggest that this may reflect the development of clonal resistance in the untreated patient as the disease progresses, with a reduction of treatment responsiveness and effectiveness in overt metastatic disease.<sup>61</sup> A biological explanation for this reduction in the risk of CRPC development with the use of immediate ADT *versus* referred observed by Duchesne *et al.*<sup>61</sup> might be related to the fact that the timing of ADT corresponds to a state of early *versus* more advanced disease; evidence from mHSPC indicates that disease volume is a predictive factor for progression to CRPC,<sup>62</sup> and in the same direction there seems to be differentiation towards a more 'drug resistant' disease in late advanced metachronous disease, often driven by the use of systemic treatment in the localized disease stage.<sup>21</sup> Finally, the higher percentage of high and very high-risk cancers in the delayed ADT arm (42% *versus* 33% in the immediate ADT arm) could also partly account for the observed shorted time to CRPC in this arm.<sup>61</sup> At the molecular level, an explanation could be that advanced disease has a much higher level of phosphoinositide 3-kinase (PI3K) pathway alterations/PTEN loss, compared to early disease, and this is related to androgen insensitivity, decreased transcription of AR target genes, and CRPC development.<sup>63,64</sup>

The study also highlighted the difficulties encountered in this space, with slow accrual, high screening failure rate, and early trial termination. The more optimistic outlook on the results of this trial is probably the fact that the immediate arm appears to gain increasing benefit for absolute mortality difference after the 5 first years; approximately 15% by the end of 7 years, and 25% after 8 years, yet these are estimated results, as the median study FU was only 5 years, and very few events occurred in later years.<sup>61</sup>

A similar phase trial, ELAAT (Clinicaltrials.gov identifier: NCT00439751), was designed by the Canadian Urological Oncology Group to assess the optimal timing of ADT in men with PSA rise

post-RT, but failed to reach its accrual goal. In an attempt to improve significance by increasing the cohort size, a pooled analysis of the TOAD and ELAAT data was performed ( $n=261+78=339$ ). The reasons to start ADT in the two trials were development of symptoms, metastases on conventional imaging, or PSA-DT of  $\leq 6$  months. The combined analysis showed no difference in all-cause mortality (HR 0.75,  $p=0.37$ ) or PC-specific mortality, whereas time to local progression, distant progression, and prostate cancer complications differed significantly in favor of immediate ADT. Several explanations may account for the loss of significance for OS in the combined analysis: ELAAT accrued older patients with a higher all-cause mortality risk and a lower relative risk of PC-specific mortality (relative to the overall mortality risk) and had a smaller difference in PSA between the immediate and deferred arms (3.98 and 18.1 ng/ml respectively for the ELAAT group, *versus* 3.52 and 30.2 ng/dl for the TOAD group); on the other hand, more patients in TOAD had a relapse-free interval of less than 2 years from RT (30% *versus* 10% for ELAAT), indicating that TOAD had more high-risk patients for which immediate treatment would be potentially more beneficial.<sup>65</sup>

#### *Intermittent versus continuous ADT*

A large Canadian Cancer Trial Group phase III trial assessed intermittent *versus* continuous ADT in 1,386 patients with rising PSA ( $>3$  ng/ml) at more than 1 year after RT.<sup>66</sup> Interestingly, RT could be either primary or salvage, hence introducing heterogeneity in terms of prognosis and therefore survival. The trial had a non-inferiority design and met its primary outcome; at a median FU of 6.9 years, the median OS was 8.8 years in the intermittent group *versus* 9.1 years in the continuous ADT group (HR for death: 1.02, 95% CI 0.86–1.21,  $p=0.009$ ), with an estimated 7-year cumulative rates of PC-specific death at 18% *versus* 15% respectively (HR: 1.18, 95% CI 0.90–1.55,  $p=0.24$ ). Other than meeting the non-inferiority threshold, intermittent treatment had a more favorable toxicity profile and resultant quality of life in respect to urinary problems ( $p=0.006$ ), hot flashes, ( $p<0.001$ ) and libido ( $p<0.001$ ), with a trend towards improvement of fatigue ( $p=0.07$ ). The authors highlight that the role of predictive factors such as age, GS, and PSA kinetics in the selection of patients for intermittent therapy remains to be defined. They recognize that the known long-term morbidity of

ADT, such as in the development of metabolic syndrome and cardiovascular disease. Interestingly, the reported rate of deaths unrelated to PC attributed to a cause other than complication of treatment initiated after castration resistance or other primary cancer was higher in the continuous ADT group (35.9% *versus* 28%). Overall, any potential benefit on PC-specific mortality of continuous ADT might be balanced by the benefit of avoiding death from other causes, such as cardiovascular disease, using intermittent ADT.

Given the heterogeneity in the long-term response to intermittent therapy, early identification of aggressive diseases would be useful. Higano's team have shown that the duration of the first off-treatment interval is prognostic for time to CRPC and death in these patients.<sup>67</sup> The same group demonstrated that patients with longer time of PSA rise ( $\geq 60$  days) after the first non-castrate level testosterone ( $> 50$  ng/dl) during the first off-treatment have good outcomes in terms of risk of developing CRPC, and it could be used for stratification and patient selection in terms of treatment strategies and optimal time for re-starting ADT.<sup>68</sup>

#### *Addition of ADT to salvage local treatment and oligometastatic disease*

The French phase III GETUG 16 trial<sup>69</sup> assessed the addition of short-term, 6-month ADT to salvage RT (66 Gy in 33 fractions) in patients with rising PSA (between 0.2 and 2 ng/dl), previously undetectable post-RP. At a median FU of 63 months, the addition of ADT resulted in improved 5-year biochemical and clinical PFS (80% *versus* 62%, HR: 0.50,  $p < 0.0001$ ) across all patient subgroups, to the price of moderately increased hot flushes and sweats (8% *versus* 1% of  $\geq G2$  events), without any serious cardiovascular or other toxicity. The highest benefit was observed for the patients with a baseline PSA of  $> 0.5$   $\mu\text{g/l}$  and a PSA-DT of  $\leq 6$  months. The MFS was not estimated in this trial, as only the first progression event was recorded, and this would usually be local progression with or without PSA progression. Given the low baseline PSA levels and the low-risk features of the study cohort (e.g., 90% of the cohort had a Gleason score of up to 7), a longer FU would be necessary to reliably demonstrate any effect on MFS. In this sense, it is impossible to assess the real benefit of the ADT addition to RT on ultimate OS outcomes.

Radiotherapy in the GETUG-16 trial consisted of the prostate bed (including the seminal vesicle area), with a recommendation for pelvic irradiation only in patients who did not have node dissection during radical prostatectomy, and only if the risk of nodal involvement was greater than 15% according to the Partin tables. The phase III NRG Oncology/RTOG 0534 SPPORT trial<sup>70</sup> randomised more precisely, according to the field of salvage RT and the addition of ADT, in a 3-arm fashion: prostate bed RT (64.8–70.2 Gy) *versus* prostate bed RT (64.8–70.2 Gy) with short-term ADT (4–6 months) *versus* prostate bed RT (64.8–70.2 Gy) and pelvic RT (45 Gy) with short-term ADT (4–6 months). In the 1792 randomised patients, freedom from progression was 71%, 83%, and 89%, respectively, at a median FU of 6.4 years, with statistical significance demonstrated between each treatment arm, i.e., with each treatment addition. Freedom from distance metastasis also showed a trend for benefit at 5 years (91.7% *versus* 94.4% *versus* 95.2%), with a significant reduction for the triple modality arm ( $p = 0.0140$ ) compared to baseline, but without any significant differences in OS.

Designed prior to the establishment of GnRH analogues as first choice hormonal therapy with RT, the RTOG 9601 trial randomised patients with PSA between 0.2 and 4.0 ng/ml post-RP [(both persistently elevated PSA and rises after an initial complete biochemical response) to salvage RT and 2 years bicalutamide treatment (150 mg daily) *versus* salvage RT and placebo]. The study has the longest reported median FU (13 years) and showed a significant benefit for 12-years OS (76.3% *versus* 71.3%,  $p = 0.04$ ), metastatic PC (14.5% *versus* 23%,  $p = 0.005$ ), and PC-specific mortality (5.5% *versus* 13.4%,  $p < 0.0001$ ) at 12 yrs. Patients with a lower Gleason score ( $\leq 7$ ), a PSA level of less than 0.7 ng/ml, or negative surgical margins may have less benefit from the addition of antiandrogen therapy.<sup>71</sup> The RTOG 9601 team performed a subsequent subgroup analysis showing a lack of benefit for PSA levels  $< 0.6$  ng/ml (HR: 1.16; 95% CI, 0.79–1.70) and increased late grades 3 to 5 cardiac and neurologic toxic effects (odds ratio, 3.57; 95% CI, 1.09–15.97;  $p = 0.05$ ). In contrast, in patients with PSA  $> 1.5$  ng/ml, there was a 25% 12-year absolute benefit (HR: 0.45, 95% CI: 0.25–0.81).<sup>72</sup>

The ongoing British RADICALS-HT trial addresses not only the question of addition of GnRH analogues or bicalutamide to

post-operative RT (immediate or salvage), but also of the optimal duration of treatment, using a 3-arm randomization (RT alone *versus* RT plus 6 months of hormonal treatment *versus* RT plus 24 months of hormonal treatment) (Clinicaltrials.gov identifier: NCT00541047).

With the implementation of next generation imaging techniques in the clinical workflow,<sup>73</sup> a considerable proportion of relapsing prostate cancer patients are diagnosed with an oligometastatic disease, an intermediate state between a localized relapse, and a widespread metastatic status. In the last years, MDT modalities like stereotactic body radiotherapy (SBRT) or salvage lymph node dissection have emerged as valid treatment options to treat these patients, to postpone systemic therapies, and in some cases to improve outcome.<sup>74,75</sup> Although two major prospective studies published so far proposed MDT as alternative to systemic ADT,<sup>34,31</sup> emerging evidence suggest a potential synergistic effect of this combined strategy to improve outcome of these patients.<sup>76,77</sup> Ongoing trials are prospectively testing the use of SBRT with or without 6 months of concomitant ADT (Clinicaltrials.gov identifier: NCT04302454), the impact of intermittent ADT with or without elective nodal pelvic irradiation (Clinicaltrials.gov identifier: NCT03630666), or elective nodal irradiation *versus* SBRT, both combined with 6 months of ADT,<sup>78</sup> in patients with an exclusive oligometastatic nodal relapse. Androgen receptor targeted agents are also tested with SBRT in other ongoing clinical trials.<sup>79</sup>

### Chemotherapy

Unsurprisingly, docetaxel trials have focused on high-risk BCR patients, given their higher risk for distant metastasis. Following a number of encouraging phase II trials,<sup>80–82</sup> two phase III trials have been reported on the use of docetaxel for BCR.

In the phase III TAX 3503 trial,<sup>83</sup> which was terminated early, 413 patients high-risk BCR patients (PSA-DT  $\leq$  9 months and PSA  $\geq$  1 ng/ml) were randomised to receive 18 months of ADT (leuprolide and bicalutamide), with or without, docetaxel (75 mg/m<sup>2</sup> IV 3-weekly, 10 cycles). The final analysis included data from the trial and a subsequent registry created after completion of study accrual to secure the primary endpoint. At a median FU of 33.6 months, the study showed a trend towards improving median

PFS (26.2 months *versus* 24.7 months, HR: 0.80, 95% CI 0.61–1.04,  $p=0.09$ ) and in OS for the intention-to-treat population (medians not reached, HR 0.51, 95% CI 0.23–1.10,  $p=0.08$ ), with good testosterone recovery in both arms.

Another phase III trial assessed the addition of docetaxel (70 mg/m<sup>2</sup> IV 3-weekly, 6 cycles) to ADT in 254 patients with rising PSA and high-risk criteria after primary local therapy.<sup>84</sup> For inclusion in the trial, patients had to present with one or more of the following: node-positive adenocarcinoma, positive surgical margins, GS  $\geq$  8, PSA velocity  $>0.75$  ng/ml per year, PSA-DT  $\leq$  6 months, and time to PSA recurrence  $\leq$  12 months. At a median FU of 10.5 years, there was no significant difference in PSA-PFS (20.3 months *versus* 19.3 months, HR: 0.85, 95% CI: 0.62–1.16,  $p=0.31$ ), or radiologic PFS (8.9 years *versus* 9 years, HR: 1.03; 95% CI 0.74–1.43,  $p=0.88$ ), while the OS data was not mature (12-year survival rate 60% *versus* 55%, HR: 0.86, 95% CI 0.56–1.31,  $p=0.49$ ). The use of docetaxel had no significant effect on quality of life during the first 12 months of treatment.

A third phase III trial is currently ongoing (Clinicaltrials.gov identifier: NGR-GU002) assessing docetaxel in patients with persistently elevated PSA  $\geq$  0.2 ng/ml (Clinicaltrials.gov identifier: NCT03070886). A number of phase II docetaxel-based combination trials have been reported, some of which demonstrated significant toxicity (Table 2).<sup>85–87</sup>

It ought to be highlighted that the STAMPEDE trial allowed for previously treated relapsing non-metastatic patients with PSA progression only, although the reported numbers for previously treated M0 (which would include the pure BCR patients) were small both for the control (3%), docetaxel (2%), docetaxel/zoledronic acid (4%), and abiraterone acetate (3%) arms.<sup>88,89</sup> The results for these PSA-relapse only patients have not been separately reported, so no relevant conclusions can be made.

### Next-generation hormonal agents

Given the impressive impact next-generation hormonal agents (NHA) have had in the mCSPC and mCRPC settings, it is not surprising that there would be attempts to see whether the benefit could extend to their use in the much earlier stage of BCR.

No phase III trial evidence is reported yet. The ongoing 3-arm randomised EMBARK trial (enzalutamide plus leuprolide *versus* placebo plus leuprolide *versus* enzalutamide monotherapy) in BCR patients with high-risk features (PSA-DT  $\leq$  9 months, PSA  $\geq$  2.0 ng/ml post-RP, and  $\geq$  5.0 ng/ml and  $\geq$  nadir + 2.0 ng/ml post-RT) has completed accrual, with results pending.<sup>90</sup>

The ongoing EORTC 1532 is a randomised phase II trial evaluating the efficacy of darolutamide *versus* ADT in men with asymptomatic hormone-naïve PC (non-metastatic or up to 4 non-visceral lesions) and a PSA  $\geq$  2 ng/dl (Clinicaltrial.gov identifier: NCT02972060). The hypothesis of this study is that AR antagonists may have a similar efficacy in reducing PSA compared to ADT, with a better tolerability due to the maintenance of normal systemic testosterone levels. The primary endpoint is PSA response at 24 weeks.

The phase II STREAM trial assessed the combination of prostate bed RT (66 Gy), 6 months of ADT and enzalutamide in patients with a GP  $\geq$  7, and a PSA recurrence within 4 years of RP, with PSA levels of 0.2–4.0 ng/ml. In a cohort of 38 men, the combination had a good safety profile, without any grade 4/5 or unexpected toxicities. The primary endpoint of 2-year PFS was 65% (95% CI: 47, 78) *versus* 51% (95% CI: 33, 67) for historic controls. PSA remained at undetectable levels in 69% at 2 years, and the 3-year PFS was 53% (95% CI 37, 68).<sup>91</sup>

The ongoing randomised phase II SALV-ENZA trial is designed to assess the combination of salvage prostate bed RT (66.6–70.2 Gy) with 6 months of enzalutamide *versus* placebo in high-risk BCR patients (GS  $\geq$  8 and either pT3 or positive margins).<sup>92</sup> Although it is important that this is a randomised trial, the standard arm omits ADT, which is a de-escalation compared to current standards, evoking the assumption that enzalutamide would sufficiently replace ADT. In addition, the trial includes only patients with PSA up to 0.7 ng/ml, which, based on previous evidence, likely excludes patients with higher PSA levels that are more likely to benefit from a combinatorial approach to RT, notably with ADT.

The ongoing randomised RTOG3506 (STEEL) trial also assesses the addition of 2 years of enzalutamide to salvage RT and 2 years of ADT and

stratifies for high-risk factors (GS 8–10, locoregional node involvement at RP, seminal vesicle invasion, persistently elevated PSA after RP, and PSA > 0.7 ng/ml).<sup>93</sup>

The phase I CARLHA-GEP12<sup>94</sup> trial assessed the combination of RT with 6 months of abiraterone acetate with ADT in patients in BCR post-RP. Abiraterone was started 1 month prior to RT, while ADT was started either together with RT or 1 month prior. The addition of AA did not increase pelvic toxicity, however showed increased G3 liver toxicity at the standard dose of 1000 mg daily. The phase II trial is ongoing at the recommended dose of 750 mg daily.

The South American phase II LACOG-0415 is a trial that assessed two NHA agents, abiraterone acetate and apalutamide, in a 3-arm randomised fashion (apalutamide alone *versus* apalutamide and abiraterone *versus* abiraterone and ADT) in patients in BCR (PSA  $\geq$  4 ng/dl and PSA-DT < 10 months) post-RP or RT ( $n=22$  patients), as well as in a node-positive patient cohort (not candidate to local therapy) and an mCSPC cohort. The hypothesis driving the study was that ADT-free alternatives with the use of NHA could provide high efficacy with a favorable safety profile in patients with advanced CSPC. In the total cohort of 128 patients, the double NHA combination as well as the abiraterone/ADT combination achieved high efficacy in terms of the primary endpoint of PSA decline of  $\leq$  0.2 ng/ml at week 25 [70.5% (95% CI: 54.8–83.2%) and 73.8% (95% CI: 58.0–86.1%) respectively], while apalutamide monotherapy did not [57.1% (95% CI: 41.0–72.3%)]. Radiologic disease control and PSA decline of  $\geq$  80% and  $\geq$  50% at week 25 were similar amongst treatment arms. Interestingly, there were no differences in quality of life between the 3 arms. No results per sub-cohort were presented; it is therefore not possible to know how the results translate for the BCR sub-cohort, which accounted for only 17.2% of the total cohort.<sup>95</sup>

The ongoing randomised phase II FORMULA-509 trial assesses the addition of the same combination (abiraterone and apalutamide) to salvage RT and ADT for high-risk BCR patients such as PSA  $\geq$  0.7 ng/ml, pathologic N+ disease, or numerous adverse risk factors (e.g., pT3b–T4, primary pattern 5 disease) (Clinicaltrials.gov identifier: NCT03141671).



The phase II BALANCE (Clinicaltrials.gov identifier: NRG GU-006) trial assesses in a placebo-controlled fashion the addition of 6 months apalutamide to salvage RT in high-risk BCR patients, including patients that never negativized their PSA post-RP. As the trial does not allow for ADT, patients with PSA > 1 ng/ml are excluded, aiming to use PSA as a biomarker for the use of NHA (Clinicaltrial.gov identifier: NCT03371719).

The ongoing phase II SPARTAR trial, designed by the team that performed the STREAM trial, assesses the addition of both an NHA and chemotherapy to a hormone-radiation in the high-risk BCR setting (relapse within 4 years of RP, GS  $\geq$  8 or GS 7 with high-risk features such as pT3, N+ or positive margins). Trial treatment consists of ADT and apalutamide 120 mg daily, concurrently with RT followed by 6 cycles of 3-weekly docetaxel 75 mg/m<sup>2</sup>. The ADT/apalutamide treatment is scheduled to continue for 36 weeks or until unacceptable toxicity or disease progression, and the study. The trial primary endpoint is 3-year PFS, with a hypothesis of improving it to 75% from a historic 50%.<sup>96</sup>

## Immunotherapy

### Vaccines

Following on evidence from a smaller phase II trial,<sup>97</sup> the randomised PROTECT phase III trial assessed the use of sipuleucel T in 176 patients with rising PSA post-RP. Although sipuleucel achieved a 48% increase in PSA-DT ( $p=0.038$ ), the median time to biochemical failure, the study primary endpoint, did not differ between the two arms (18 months *versus* 15.4 months, HR: 0.936, 95% CI 0.637–1.376,  $p=0.737$ ).<sup>98</sup> Although the study indicated biological activity for sipuleucel T in this setting, including documenting robust and sustained induced immune responses, a much larger cohort number and more robust endpoint with longer FU would be needed to accurately assess the potential of this cellular immunotherapy modality for BCR.

Several early phase trials involving TAA-based vaccines, including the poxviral Prostavac vaccines and PSMA vaccines, have reported moderate anti-tumour specific responses and prolongation in PSA-DT (Table 2).<sup>99–105</sup> Furthermore, the adenovirus/PSA vaccine APP21 is currently assessed as a monotherapy *versus* combination

with ADT in a randomised phase II trial (Clinicaltrials.gov identifier: NCT00583752).

### Checkpoint inhibition

Some steps have also been made in the direction of using checkpoint inhibition in BCR. The anti-CTLA4 tremelimumab was assessed in combination with short-term (6 months) bicalutamide treatment in a phase I trial, reporting G3 diarrhoea and rash as dose-limiting toxicities. In 3 out of 11 patients (27%) delayed prolongation of PSA-DT was observed several months after completing treatment.<sup>106</sup> Nivolumab monotherapy for up to 2 years is currently assessed in high-risk BCR patients with PSA-DT < 10 months (Clinicaltrials.gov identifier: NCT03637543).

An ongoing trial assesses the use of nivolumab monotherapy in patients with MMR-deficient/MSI-high and PC with rising PSA (Clinicaltrials.gov identifier: NCT04019964). The trial also includes patients with high tumour mutational burden (>20 mut/Mb) and CDK12-alterations.

### Immunotherapy combination trials

A currently ongoing phase II trial (Clinicaltrials.gov identifier: NCT03315871) involves the use of the Prostavac recombinant vaccine in biochemically recurrent PC, in combination with bintrafusp alpha, a bifunctional anti-PD-L1/anti-TGFbetaR2 fusion protein in biochemically recurrent PC patients, as well as CV301, a poxviral based TAA vaccine targeting MUC1 and CEA. A combination of the pTVG-HP vaccine with pembrolizumab is also currently ongoing (Clinicaltrials.gov identifier: NCT03600350).

Recently, a phase I/II trial of a combination synthetic DNA therapy of plasmids encoding for PSA and PSMA (INO-5150) and interleukin-12 (INO-9012) in 62 patients with rising PSA reported a good safety profile, with immunogenicity observed in 76% and 85% of patients remaining progression-free at 72 weeks.<sup>107</sup>

## Targeted therapy and other agents

### PARP inhibitors

The PARP inhibitor olaparib is currently evaluated in a phase II trial designed to test the hypothesis that PARPi monotherapy may be active in

men with high-risk BCR. The enrichment stage of the trial includes confirmation of presence of a mutation in a gene of the DNA repair pathway. In the reported interim results of the trial, olaparib without ADT showed a satisfactory tolerance profile and interesting activity. It should be noted that 35% of men had a BRCA/ATM alteration, 15% of patients showed a PSA50 response, including two complete PSA responses (all of whom had a BRCA2 mutation), another 20% had minor PSA responses, and median PSA progression-free survival was greater in men with *versus* without BRCA2/ATM muts (9 *versus* 4 mo;  $p=0.02$ ).<sup>108</sup>

The phase II ROAR trial (Clinicaltrials.gov identifier: NCT03533946) evaluates rucaparib in the same setting, requiring a BRCAness signature tested on liquid or soft tissue biopsy, with a primary endpoint of PSA50 response.

A combination of olaparib with the anti-PDL1 agent durvalumab is also evaluated in a phase II trial on BCR patients with alterations in the DNA repair pathway genes (Clinicaltrials.gov identifier: NCT03810105).

#### Antiangiogenics

A number of anti-angiogenic drugs, including bevacizumab, sunitinib, and lenalidomide have been investigated in phase II trials with moderate results, alone or in the context of multimodality treatment (Table 2).<sup>86,87,109–111</sup> The only phase III trial involved thalidomide, an anti-angiogenic drug with immunomodulatory properties, has been tested in a placebo-controlled phase III trial in association with ADT with a crossover phase, showing an effect on time to further PSA progression (17.1 months *versus* 6.6 months,  $p=0.0002$ ).<sup>112</sup>

#### PI3K/Akt and metabolic pathways

Two phase II trials involving AKT inhibitors have failed to show any meaningful activity as monotherapy or in combination with anti-androgen therapy (Table 2).<sup>113,114</sup>

Cox inhibitors, notably celecoxib which also inhibits activation of Akt by phosphorylation in PC cells, have also been evaluated in phase II studies showing significant effect on PSA-DT but conflicting results in terms of toxicity (Table 2).<sup>115,116</sup>

The combination of atorvastatin and celecoxib was also investigated (Table 2).<sup>117</sup> A meta-analysis on the use of statins in prostate cancer found it was associated with a 21% reduction in the risk of BCR among those treated with RT (HR: 0.79,  $p=0.01$ , 10 studies), whereas it was not associated with BCR among those treated with RP (HR: 0.94, 95% CI 0.81–1.09,  $p=0.43$ , 15 studies). In the overall cohort, statin use was associated with a 22% reduction in the risk of metastasis, and a 24% reduction in risk of both all-cause and prostate cancer-specific mortality.<sup>118</sup>

Vitamin supplementation has also been investigated in several early trials (monotherapy or combinations) with moderate results (Table 2).<sup>119–123</sup> Finally, in a meta-analysis of 5 retrospective studies, metformin use was marginally associated with reduction in the risk of BCR (HR: 0.82, 05% CI: 0.67–1.01,  $p=0.06$ ).<sup>124</sup>

#### Other targeted therapies

A number of phase II trials evaluated difference targeted therapies on pathways involved in prostate cancer development, with results ranging from complete lack of efficacy in term of PSA response to modest improvements to PSA-DT (Table 2).<sup>125,126</sup>

#### Discussion

Given the disease evolution of PC, especially with the introduction of new treatments in the mCSPC, nmCRPC and mCRPC settings, a sufficiently long-life expectancy is necessary for BCR to influence mortality. As a result, trials with follow-up longer than 10 years are needed to accurately assess the impact of systemic treatment in BCR. Furthermore, any survival gain should be balanced against the side-effects of treatment and the effects on overall quality of life in these men that feature a long disease-specific expectancy at the time of BCR diagnosis. It is therefore important, when considering initial systemic therapy for BCR, to optimize the timing of therapy and patient selection.

The so far available phase III evidence indicates that early salvage RT provides benefit which is greater at lower PSA levels. In contrast, the absolute benefit from the addition of hormone therapy in such low PSA levels would be less. Higher PSA levels are likely to be associated with increased

probability of detecting metastatic disease, notably distant, with molecular imaging. It transpires those patients with higher PSA levels may preferentially derive treatment benefit from hormone therapy for occult distant metastatic disease. It has become progressively clear, therefore, that not all biochemically relapsed men need systemic treatment.

In this direction, the current ESMO guidelines advise that early ADT alone is not recommended for men with BCR unless they have a rapid PSA-DT, symptomatic local disease, or proven metastases and that, in the absence of metastatic disease, such men should be offered intermittent rather than continuous treatment.<sup>127</sup> The cut-off for rapid PSA-DT is not precisely determined nor universally applied. EAU guidelines use a 12-month cut-off to indicate high-risk BCR patients,<sup>19</sup> trials have used a range of 5–15 months, and it has been clearly demonstrated that a PSA-DT of <3 months indicates a poor prognosis and increased risk for metastatic disease.

The absolute PSA value at the time of BCR has gained more evidence for its value as prognostic and predictive factor. The *post-hoc* analysis of the RTOG 9601 trial probably provides the strongest available evidence in this direction, indicating a lack of benefit from hormonal therapy for PSA levels <0.6 ng/ml, with increased associated toxicity and, conversely, a 12-year absolute benefit of 25% in patients with PSA > 1.5 ng/ml, compared to the 5% absolute benefit in the overall study cohort.<sup>71,72</sup> It seems, therefore, that we are starting to sieve through this large space of BCR, making a distinction between those patients for which salvage RT alone would be sufficient as standard treatment, and those who require hormonal therapy, short- or long-term.

When considering docetaxel, the two reported phase III trials reported on PFS, with one failing to show benefit, and the other showing borderline benefit, whilst OS data were not mature in the former and not reported in the latter.<sup>83,84</sup> Both studies aimed to include high-risk BCR patients, but their criteria for this were not identical, and they also differed in the docetaxel regimen and number of cycles. This is reminiscent of the landscape of docetaxel trials for locally advanced, non-metastatic disease, with contradicting results amongst trials that differed in the definition of high-risk disease, docetaxel regimen, accrual power and timing of treatment, and failure to

show OS survival benefit despite improvements in failure-free survival.<sup>128</sup>

Table 1 summarizes the current evidence from phase III and leading phase II trials, as well as the current consensus recommendations based on ESMO and EAU guidelines. Table 2 summarizes the historical trial data for agents that are no longer under active investigation. Currently, international consensus recommends the addition of ADT if high-risk features, such as PSA over a given cut-off (varying between 0.5 and 0.7 ng/ml),<sup>129,130</sup> short PSA-DT, symptoms, or macroscopic disease. Regarding duration of this ‘adjuvant’ ADT, while awaiting the results of the RADICALS-HT trial, the best available evidence comes from GETUG-16, in the form of a short-term (6 months) LHRH analogue treatment. The future phase III studies investigating NHAs will undoubtedly shape the field and are eagerly awaited. An interesting angle on the design of available phase II NHA trials is that they looked into the monotherapy option, aiming to assess where ADT use can be spared with (although initial phase II data are rather disappointing), as well as into combination options.

## Conclusion

Because of the heterogeneous and dynamically evolving BCR stage, and in order for future studies to be more informative and more efficient in directing clinical practice, patients ought to be ideally stratified per high-risk features such as PSA levels and PSA-DT, as well as according to primary treatment modality (RP *versus* RT). As more sophisticated molecular techniques enter the arena, it is possible to envisage a future for biochemically relapsed PC where liquid biopsies would provide a dynamic molecular mapping that would guide patient selection, optimal treatment modality, and optimal treatment timing.

## Conflict of interest statement

KK: Participation to advisory boards for: Amgen, Astellas, Astrazeneca, AAA, Bayer, Clovis, Curevac, ESSA, Genentech, Janssen, MSD, Orion, Sanofi. Honoraria are provided to Gustave Roussy, my institution. TZ: Honoraria (to institution)/travel grants — Janssen, Amgen, Ferring, Debiopharm, Bayer, Astellas. Research Grants — Varian Medical Systems GB: Advisory boards and symposia: Amgen, Janssen Oncology, Sanofi, Astellas-Pharma, Roche, Bayer, Genesta. Travel

**Table 1.** Summary of current phase III evidence and principal phase II trial data on systemic treatment for BCR.

BCR setting	International guidelines	Indications	Systemic therapy type	Current evidence (phase III trials)	Principal phase II trials
After RP	Early salvage RT to prostate bed +/- WPRT (ideally at PSA < 0.5 ng/ml) Consider ADT for 6-24 mo for high-risk patients Discuss close surveillance and possible deferred salvage RT for patients with low-risk biochemical recurrence (PSA DT > 1 yr and pGS < 8/ISUP grade < 4)	PSA progression [0.2-2.0 ng/ml (GETUG-AFU 16)] [≥0.1 and ≤1.0 ng/ml (RT0G 0534)]	Hormonal manipulation	GETUG-AFU 16: RT +/- 6 months ADT (LH-RH agonists); benefit in 5-year biochemical and clinical PFS (80% versus 62%, HR: 0.50, p < 0.0001). More benefit in PSA-DT < 6 months and PSA > 0.5 ng/ml. <sup>69</sup> RT0G 9601: RT +/- 2 years of bicalutamide; benefit in 12-year OS (76.3% versus 71.3%, p = 0.04), metastatic PC (14.5% versus 23%, p = 0.005) and PC-specific mortality (5.5% versus 13.4%, p < 0.0001). <sup>71</sup> Lack of benefit for PSA levels < 0.6 ng/ml (HR: 1.16). <sup>72</sup> RADICALS: RT versus RT + 6 months of ADT versus RT + 24 months of ADT; ongoing ( <i>Clinicaltrials.gov</i> identifier: NCT00541047). NRG Oncology/RT0G 0534 SPPORT: prostate bed RT versus prostate bed RT + 6 months ADT versus prostate bed RT with WPRT + 6 mo ADT. Better freedom from failure and MFS with WPRT (HR 0.52, p < 0.014) <sup>70</sup>	STREAM (phase II): RT + ADT/enzalutamide for 6 months; 2-year PFS 65% versus 51% for historic controls, 3-year PFS 53%, undetectable PSA at 2-years: 69% <sup>91</sup> LACOG-0415 (phase II): apalutamide versus apalutamide + abiraterone acetate versus abiraterone acetate + ADT; PSA decline of < 0.2 ng/ml at week 25 for the apalutamide + abiraterone and abiraterone/ADT arms (70.5% and 73.8% respectively), no significant decline for the apalutamide alone arm (57.1%) <sup>95</sup>
After RT	Local salvage or observation with delayed ADT (ADT for symptomatic local disease, proven metastases, PSA DT < 3 mo)	PSA progression (GS ≥ 7 between 2-10 yrs after RP)	Vaccines	PROTECT: sipuleucel-T versus control; no difference in median to biochemical failure (18 months versus 15.4 months, HR: 0.936, p = 0.737) [ <i>Beer CCR 2011</i> ] <sup>98</sup>	
After RT/RP	Development of symptoms or metastases on conventional imaging or PSA doubling time decreasing to ≤ 6 months Rapid PSA DT ≤ 6/9 months Time to PSA recurrence ≤ 12 mo, GS ≥ 8, node +	PSA at relapse of > 3.0 ng/ml > 1 year after radical RT	Hormonal manipulation	NCIC Clinical Trials Group: intermittent versus continuous ADT; intermittent non-inferior to continuous (OS 8.8 versus 9.1 years, HR for death: 1.02; 7-year PC-specific death 18% versus 15%, HR: 1.18, p = 0.24) <sup>66</sup> TOAD: immediate versus delayed ADT (> 2 years); immediate ADT borderline improved 5-year OS (HR: 0.54, p = 0.047) but not in the PSA-relapse subgroup (86.4% versus 91.2%, HR: 0.59, p = 0.19) <sup>61</sup> ELAAT: intermittent versus deferred ADT; failed to reach accrual goal [ <i>Clinicaltrials.gov</i> identifier: NCT00439751] TOAD + ELAAT pooled analysis: no difference in all-cause or PC-specific mortality (HR 0.75; p = 0.37) <sup>65</sup> TAX 3503: 18 months ADT + bicalutamide +/- docetaxel x 10 cycles; terminated early, trend towards improving median PFS (26.2 versus 24.7 months, HR: 0.80, p = 0.09) and OS (NR versus NR, HR: 0.51, p = 0.08) <sup>83</sup> RisingPSA: hormonal therapy +/- docetaxel x 6 cycles; no significant difference in PSA-PFS (20.3 versus 19.3 months, HR: 0.85, p = 0.31), radiologic PFS (8.9 versus 9 years, HR: 1.03; p = 0.88), OS data was not mature (12-year OS 60% versus 55%, HR: 0.86, p = 0.49) <sup>84</sup>	

ADT, androgen deprivation therapy; BCR, biochemical recurrence; HR, hazard ratio; mo, months; MFS, metastasis-free survival; OS, overall survival; PC, prostate cancer; PFS, progression-free survival; pGS, pathological Gleason score; PLND, pelvic lymph node dissection; PSA-DT, prostate-specific antigen doubling time; RP, radical prostatectomy; RT, radiotherapy; WPRT, whole pelvis radiotherapy.



**Table 2.** Summary of historical early phase trial data on systemic treatment for BCR.

Type of treatment	Trial	Design	Indications	Interventions	Results	Reference
<i>Chemotherapy</i>						
Docetaxel + rapid androgen cycling		Phase II	Progressive metastatic disease or rising PSA	Docetaxel q4wks × 6 (cohort 1) or docetaxel q3wks × 9 (cohort 2) + testosterone depletion + leuprotride	Cohort 1: no complete PSA responses; cohort 2: 13% complete PSA responses at 18 mo. Significant haematological toxicity	Yu et al. <sup>87</sup>
Docetaxel + sunitinib	NCT00734851	Phase II	BCR	Docetaxel q3wks × 4 + sunitinib 37.5 mg 2wks on 3	Trial terminated for unacceptable toxicity, PFS24: 51% [95% CI: 33, 67%], mPFS: 26.2 mo (95% CI: 12.5-NR)	Armstrong et al. <sup>87</sup>
<i>Vaccines</i>						
Sipuleucel-T	STAND (NCT01431391)	Phase II	BCR, PSA-DT ≤ 12 mo	Alternate sequences of ADT (12 mo) with sipuleucel-T (3 infusions 2-weekly)	Similar time to PSA recurrence (21.8 versus 22.6 mo, <i>p</i> = 0.357); Sipuleucel-T → ADT induces greater anti-tumour T-cell responses ( <i>p</i> < 0.0001)	Antonarakis et al. <sup>99</sup>
Prostvac (pox-viral vaccine)	ECOG 9802	Phase II	BCR, PSA-DT < 12 mo	Prostvac-V/Prostac-F injections until biochemical or clinical progression or a maximum of 12 mo, with ADT addition upon progression	Prostvac: 6-mo PFS 63%, PSA-DT increase from 5.3 mo to 7.7 mo; ADT addition: 74% complete PSA responses at 7 mo	DiPaola et al. <sup>100</sup>
Prostvac	NCT02649439	Phase II	BCR (>0.8 ng/ml post-RP or > 2 ng/ml post RPI), PSA-DT 5–15 mo	Prostvac × 6 mo versus surveillance × 6 mo → Prostvac × 6 mo	Delayed but sustained PSA declines in 38% of pts (range 10–99%)	Madan et al. <sup>101</sup>
DOM-PSMA <sub>27</sub>		Phase I/II	BCR, PSA-DT > 3 mo	DOM-PSMA <sub>27</sub> versus DNA only (control) vaccine × 5	Increase of PSA-DT (11.97 mo to 16.82 mo, <i>p</i> = 0.0417)	Chudley et al. <sup>102</sup>
pTVG-HP (MVI-816, encoding PAP)	NCT01341652	Phase II	BCR, PSA-DT < 12 mo	pTVG-HP/GM-CSF versus GM-CSF alone	2-yr MFS no difference (41.8% versus 42.3%); longer MFS in vaccine-treated patients with PSA-DT < 3 mo (12.0 v 6.1 mo; HR, 4.4; <i>p</i> = 0.03)	McNeel et al. <sup>103</sup>
TARP (T-cell receptor alternate reading frame protein)	NCT02362451	FIH Phase I	HLA-A*0201-restricted BCR patients	TARP WT27-35 and EE29-37-9V peptides with GM-CSF (Arm A) or as autologous DCs pulsed with peptides and KLH (Arm B)	Decreased Slope Log(PSA) at 24 wks (72%) and 48 wks (74%) [ <i>p</i> = 0.0012 and <i>p</i> = 0.0004]; 50% decrease in tumour growth rate ( <i>p</i> = 0.003)	Wood et al. <sup>104</sup>
PSMA/TARP peptide vaccine	NCT00694551	Phase I	HLA-A2 (+) BCR pts	PSMA and TARP Peptide Vaccine With Poly IC-LC Adjuvant at 3 dose levels (100 mcg, 300 mcg, 1 mg)	Mean fold increase 2.7 for PSMA CD4 [ <i>p</i> = 0.0001] and 2.45 for TARP CD4 [ <i>p</i> = 0.0006]; no CD8 response. No observed DL T. 10/29 pts had excellent PSA stabilisation (mean: 458 dl). Association between strength of CD4 response and PSA-DT	Whitehurst et al. <sup>105</sup>
<i>Anti-angiogenics</i>						

(continued)

Table 2. (continued)

Type of treatment	Trial	Design	Indications	Interventions	Results	Reference
Bevacizumab	NCT00776594	Phase II	BCR	6-mo ADT +/- bevacizumab	2-year RFS (13 [11–15] mo versus 10 [10–12] mo) and PSA < 0.2 ng/ml at 6 mo (73.8% versus 36%) both higher in combination arm	Clinicaltrials.gov
Bevacizumab + docetaxel	NCT00658697	Phase II	BCR, PSA-DT ≤ 10 mo	Docetaxel 75 mg/m <sup>2</sup> q3 wks × 4, bevacizumab 15 mg/kg q 3 wks × 8, ADT × 18 mo	At 1 yr: 20% no PSA-PD, 46% no ADT restart, 83% metastasis-free; G3/4 toxicity: 51%	McKay et al. <sup>86</sup>
Bevacizumab	NCT00776594	Phase II	BCR, PSA-DT ≤ 18 mo	ADT +/- bevacizumab 15 mg/kg q 3 wks × 8, ADT × 18 mo	Improved RFS for bevacizumab (13.3 mo versus 10.2 mo; HR, 0.47; 95% CI, 0.29 to 0.77; <i>p</i> = 0.002). Hypertension with ADT + bevacizumab (36%)	McKay et al. <sup>109</sup>
Lenalidomide	NCT00348595	Phase I/II	BCR	Lenalidomide 5 mg versus 25 mg/d 3 wks on 4 × 6 mo	PSA slope greater with 25 mg versus 5 mg [-0.172 (-0.24 to -0.11) versus -0.033 (-0.11 to 0.04), <i>p</i> = 0.005; G3/4 toxicity: 12%	Keizman et al. <sup>110</sup>
ATN-224 [oral Cu(2+)/Zn(2+) -superoxide dismutase 1 (SOD1) inhibitor]	NCT00405574	Phase II	BCR, PSA-DT < 12 mo	ATN-224 300 mg versus 30 mg/d	PSA-PFS 30 (95% CI 21–40+) versus 26 (95% CI 24–39+) wks. PSA slope decrease ( <i>p</i> = 0.0006) and PSA-DT increase ( <i>p</i> = 0.032) at low-doses	Lin et al. <sup>123</sup>
Imatinib mesylate	NCT01316458	Phase II	BCR	Imatinib mesylate 400 mg × 2/d	Discontinued early due to lack of efficacy (median PSA-DT 5.8 versus 7.2 mo, <i>p</i> = 0.64) and toxicity (55% DCR)	Lin et al. <sup>111</sup>
<i>PI3K/Akt and metabolic pathways</i>						
Perifosine (Akt inhibitor)	NCT00058214	Phase II	BCR	Loading dose of perifosine 900 mg orally on d1, then 100 mg daily.	No PSA response (≥ 50% decrease), median PFS: 6.64 mo (4.53–12.81 mo), only 20% of pts showed a PSA decline	Chee et al. <sup>113</sup>
Celecoxib	NCT00073970	Phase II	BCR	Celecoxib 400 mg × 2/d	Slowing of PSA-DT in 90% of pts at 3 mo ( <i>p</i> = 0.001) sustained at 18 mo ( <i>p</i> = 0.001)	Pruthi et al. <sup>115</sup>
Celecoxib	NCT00136487	Phase II	BCR, PSA-DT 6–24 mo	Celecoxib 400 mg × 2/d versus placebo	Slowed PSA velocity in 40%, versus 20% ( <i>p</i> = 0.8). Terminated early due to cardiovascular concerns	Smith et al. <sup>116</sup>
Celecoxib + atorvastatin	NCT01220973	Phase II	BCR	Atorvastatin 20 mg/d + celecoxib 200 mg × 2/d for 6 mo	53.8% rate of PSA decline of ≥ 25% at 6 mo, no serious toxicity	Goodin et al. <sup>117</sup>
Calcitriol	NCT00004043	Phase II	BCR	Cancitriol 0.5 mcg/kg × 1/wk	Failed to achieve PSA responses (50% reduction), achieved prolongation of PSA-DT from 7.8 mo to 10.3 mo ( <i>p</i> = 0.03)	Beer et al. <sup>119</sup>

(continued)

Table 2. (continued)

Type of treatment	Trial	Design	Indications	Interventions	Results	Reference
Calcitriol + naproxen	NCT00383487	Phase II	BCR	Calcitriol 45 mcg × 1/ wk + naproxen 375 mg × 2/d	14/18 (77.7%) evaluable pts showed prolongation of PSA-DT, no serious toxicity	Srinivas and Feldman <sup>120</sup>
Calcifediol	NCT00018538	Phase II	BCR	Calcifediol	80% of pts had increases in PSA-DT	Abdel-Wahab <i>et al.</i> <sup>121</sup>
Fenretinide	NCT00080899	Phase II	BCR	Fenretinide 900 mg/m <sup>2</sup> twice daily for 1 week, every 3 weeks, for 1 year	0% PSA response, 30% PSA-SD	Cheung <i>et al.</i> <sup>122</sup>
<i>Other targeted therapies</i>						
Rosiglitazone (PPAR $\gamma$ agonist) + bicalutamide	NCT00182052	Phase II	BCR, PSA-DT < 24 mo	Rosiglitazone 4 mg × 2/d versus placebo	No increase in PSA-DT ( $p = 1.00$ ) or time-to-PSA-progression ( $p = 0.76$ )	Smith <i>et al.</i> <sup>126</sup>
Valproic acid (histone deacetylase inhibitor)	NCT00670046	Phase II	BCR, PSA-DT < 10 mo	Valproic acid × 2/d for up to 1 yr versus observation	Increase in PSA-DT (83% versus 50%). Complete PSA response (i.e. PSA-DR > 12 mo) 66.7% versus 16.7%	ClinicalTrials.gov
Lapatinib (EGFR TKI)	NCT00265070	Phase II	BCR post-RP	Lapatinib 250 mg × 1/d	No significant PSA responses, PSA stabilisation in 80%, significant increase in PSA-DT (from 3.7 mo to 5.44 mo, $p = 0.006$ ). Median PFS was numerically longer in the EGFR overexpressing pts (17.40 mo versus 6 mo, $p = 0.50$ ), and pts with a KRAS 38 mutation had a shorter PFS compared to the non-mutant KRAS pts	Liu <i>et al.</i> <sup>125</sup>
R04929097 ( $\gamma$ -secretase/Notch inhibitor)	NCT01200810	Phase II	BCR	Bicalutamide +/– R04929097	Stopped prematurely (development of the study drug discontinued)	ClinicalTrials.gov

ADT, androgen-derivation therapy; BCR, biochemical recurrence; d, days; DCR, discontinuation rate; FH, first-in-human; G, grade; GM-CSF, granulocyte-macrophage colony stimulating factor; KLH, keyhole limpet hemocyanin; mcg, micrograms; mg, milligrams; PD, progressive disease; PFS, progression-free survival; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$ ; PSA, prostate-specific antigen; PSA-DT, PSA doubling time; PSMA, prostate-specific membrane antigen; RFS, relapse-free survival; RP, radical prostatectomy; RT, radiotherapy; TARP, -cell receptor alternate reading frame protein; TKI, tyrosine kinase inhibitor; wk(s), week(s); yr, year.

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### References

- Bray F, Ferlay J, Soerjomatarm I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
- Ferlay J, Ervik M, Lam F, *et al.* Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer, <https://gco.iarc.fr/today> (2020, accessed 17 December 2020).
- Patrikidou A, Lorient Y, Eymard JC, *et al.* Who dies from prostate cancer? *Prost Cancer Prost Dis* 2014; 17: 348–352.
- Siegel RL, Miller KD and Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; 70: 7–30.
- Mottet N, Bellmunt J, Briers E, *et al.* EAU – ESTRO – ESUR – SIOG guidelines on prostate cancer. Arnhem, The Netherlands: EAU Guidelines Office, 2020.
- Roach M III, Hanks G, Thames H Jr, *et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; 65: 965–974.
- Brajtford JS, Leapman MS and Cooperberg MR. The CAPRA score at 10 years: contemporary perspectives and analysis of supporting studies. *Eur Urol* 2017; 71: 705–709.
- Cooperberg MR, Hilton JF and Carroll PR. The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. *Cancer* 2011; 117: 5039–5046.
- Walz J, Chun FK, Klein EA, *et al.* Nomogram predicting the probability of early recurrence after radical prostatectomy for prostate cancer. *J Urol* 2009; 181: 601–608.
- Pompe RS, Bandini M, Preisser F, *et al.* Contemporary approach to predict early biochemical recurrence after radical prostatectomy: update of the Walz nomogram. *Prostate Cancer Prostatic Dis* 2018; 21: 386–393.
- Pound CR, Partin AW, Eisenberger MA, *et al.* Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591–1597.
- Roehl KA, Han M, Ramos CG, *et al.* Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol* 2004; 172: 910–914.
- Freedland SJ, Humphreys EB, Mangold LA, *et al.* Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005; 294: 433–439.
- Kupelian PA, Mahadevan A, Reddy CA, *et al.* Use of different definitions of biochemical failure after external beam radiotherapy changes conclusions about relative treatment efficacy for localized prostate cancer. *Urology* 2006; 68: 593–598.
- Artibani W, Porcaro AB, De Marco V, *et al.* Management of biochemical recurrence after primary curative treatment for prostate cancer: a review. *Urol Int* 2018; 100: 251–262.
- Boorjian SA, Thompson RH, Tollefson MK, *et al.* Long-term risk of clinical progression after biochemical recurrence following radical prostatectomy: the impact of time from surgery to recurrence. *Eur Urol* 2011; 59: 893–899.
- Antonarakis ES, Feng Z, Trock BJ, *et al.* The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* 2012; 109: 32–39.
- Hancock SL, Cox RS and Bagshaw MA. Prostate specific antigen after radiotherapy for prostate cancer: a reevaluation of long-term biochemical control and the kinetics of recurrence in patients treated at Stanford University. *J Urol* 1995; 154: 1412–1417.
- Van den Broeck T, van den, Bergh RCN, Briers E, *et al.* Biochemical recurrence in prostate cancer: the European Association of urology prostate cancer guidelines panel recommendations. *Eur Urol Focus* 2019; 5: 967–987.
- Van den Broeck T, van den, Bergh RCN, Arfi N, *et al.* Prognostic value of biochemical recurrence



- following treatment with curative intent for prostate cancer: a systematic review. *Eur Urol* 2019; 75: 967–987.
21. Hu Z, Li Z, Ma Z and Curtis C. Multi-cancer analysis of clonality and the timing of systemic spread in paired primary tumors and metastases. *Nat Genet* 2020; 52: 701–708.
  22. Gundem G, Van Loo P, Kremeyer B, *et al.* The evolutionary history of lethal metastatic prostate cancer. *Nature* 2015; 520: 353–357.
  23. Hong MK, Macintyre G, Wedge DC, *et al.* Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. *Nat Commun* 2015; 6: 6605.
  24. Aryee MJ, Liu W, Engelmann J, *et al.* DNA methylation alterations exhibit intraindividual stability and interindividual heterogeneity in prostate cancer metastases. *Sci Transl Med* 2013; 5: 169ra10.
  25. Grasso CS, Wu YM, Robinson DR, *et al.* The mutational landscape of lethal castration-resistant prostate cancer. *Nature* 2012; 487: 239–243.
  26. Morigi JJ, Stricker PD, van Leeuwen PJ, *et al.* Prospective comparison of <sup>18</sup>F-fluoromethylcholine versus <sup>68</sup>Ga-PSMA PET/CT in prostate cancer patients who have rising PSA After curative treatment and are being considered for targeted therapy. *J Nucl Med* 2015; 56: 1185–1190.
  27. Afshar-Oromieh A, Avtzi E, Giesel FL, *et al.* The diagnostic value of PET/CT imaging with the <sup>68</sup>Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging* 2015; 42: 197–209.
  28. Eiber M, Maurer T, Souvatzoglou M, *et al.* Evaluation of hybrid <sup>68</sup>Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med* 2015; 56: 668–674.
  29. Javdar H, Ballas LK, Choyke PJ, *et al.* Appropriate use criteria for imaging evaluation of biochemical recurrence of prostate cancer after definitive primary treatment. *J Nucl Med* 2020; 61: 552–562.
  30. Ost P, Reynders D, Decaestecker K, *et al.* Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicentre phase II trial. *J Clin Oncol* 2018; 36: 446–453.
  31. Ost P, Reynders D, Decaestecker K, *et al.* Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence (STOMP): five-year results of a randomized phase II trial. *J Clin Oncol* 2020; 38(Suppl): 10.
  32. Siva S, Bressel M, Murphy DG, *et al.* Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *Eur Urol* 2018; 74: 455–462.
  33. Bowden P, See AW, Frydenberg M, *et al.* Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: interim outcomes of a prospective clinical trial. *Int J Cancer* 2020; 146: 161–168.
  34. Phillips R, Shi WY, Deek M, *et al.* Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. *JAMA Oncol* 2020; 6: 650–659.
  35. Castro E, Goh C, Olmos D, *et al.* Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol* 2013; 31: 1748–1757.
  36. Castro E, Goh C, Leongamornlert D, *et al.* Effect of BRCA mutations on metastatic relapse and Cause-specific survival after radical treatment for localised prostate cancer. *Eur Urol* 2015; 68: 186–193.
  37. Cui M, Gao X-S, Gu X, *et al.* BRCA2 mutations should be screened early and routinely as markers. *Oncotarget* 2017; 8: 40222–40232.
  38. Kim SH, Park WS, Yun SI, *et al.* Overexpression of BRCA1 or BRCA2 in prostatectomy specimens is predictive of biochemical recurrence after radical prostatectomy. *Histopathol* 2016; 68: 673–679.
  39. Klein EA, Cooperberg MR, Magi-Galluzzi C, *et al.* A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol* 2014; 66: 550–560.
  40. Cuzick J, Swanson GP, Fisher G, *et al.* Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol* 2011; 12: 245–255.
  41. Erho N, Crisan A, Vergara IA, *et al.* Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One* 2013; 8: e66855.
  42. Karnes RJ, Choerung V, Ross AE, *et al.* Validation of a genomic risk classifier to predict prostate cancer-specific mortality in men with adverse pathologic features. *Eur Urol* 2018; 73: 168–175.
  43. Van der Broeck T, Moris L, Gevaert T, *et al.* Validation of the Decipher test for predicting

- distant metastatic recurrence in men with high-risk nonmetastatic prostate cancer 10 years after surgery. *Eur Urol Oncol* 2019; 2: 589–596.
44. Cooperberg MR, Davicioni E, Crisan A, *et al.* Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. *Eur Urol* 2015; 67: 326–333.
  45. Gore JL, du Plessis M, Santiago-Jimenez M, *et al.* Decipher test impacts decision making among patients considering adjuvant and salvage treatment after radical prostatectomy: interim results from the multicenter prospective PRO-IMPACT study. *Cancer* 2017; 123: 2850–2859.
  46. Gore JL, du Plessis M, Zhang J, *et al.* Clinical utility of a genomic classifier in men undergoing radical prostatectomy: the PRO-IMPACT trial. *Pract Radiat Oncol* 2020; 10: e82–e90.
  47. Jiang Y, Mei W, Gu Y, *et al.* Construction of a set of novel and robust gene expression signatures predicting prostate cancer recurrence. *Mol Oncol* 2018; 12: 1559–1578.
  48. Assinder SJ and Bhoopalan V. A promising future for prostate cancer diagnostics. *Diagnostics (Basel)* 2017; 7: 6.
  49. Huang TB, Dong CP, Zhou GC, *et al.* A potential panel of four-long noncoding RNA signature in prostate cancer predicts biochemical recurrence-free survival and disease-free survival. *Int Urol Nephrol* 2017; 49: 825–835.
  50. Shao N, Tang H, Qu Y, *et al.* Development and validation of lncRNAs-based nomogram for prediction of biochemical recurrence in prostate cancer by bioinformatics analysis. *J Cancer* 2019; 10: 2927–2934.
  51. Shao N, Zhu Y, Wan FN, *et al.* Identification of seven long noncoding RNAs signature for prediction of biochemical recurrence in prostate cancer. *Asian J Androl* 2019; 21: 618–622.
  52. Xu J, Lan Y, Yu F, *et al.* Transcriptome analysis reveals a long non-coding RNA signature to improve biochemical recurrence prediction in prostate cancer. *Oncotarget* 2018; 9: 24936–24949.
  53. Gebensleben H, Holmes EE, Goltz D, *et al.* PD-L1 promoter methylation is a prognostic biomarker for biochemical recurrence-free survival in prostate cancer patients following radical prostatectomy. *Oncotarget* 2016; 7: 79943–79955.
  54. Li H, Wang Z, Zhang Y, *et al.* The immune checkpoint regulator PDL1 is an independent prognostic biomarker for biochemical recurrence in prostate cancer patients following adjuvant hormonal therapy. *J Cancer* 2019; 10: 3102–3111.
  55. Campos-Fernandez E, Barcelos LS, Gomes de, Souza A, *et al.* Research landscape of liquid biopsies in prostate cancer. *Am J Cancer Res* 2019; 9: 1309–1328.
  56. Rahbar K, Kidd MS, Drozdov IA, *et al.* A blood-based multi-mRNA liquid biopsy with >90% accuracy for diagnosis and assessment of prostate cancers. *J Clin Oncol* 2020; 38(15 Suppl): 5574–5574.
  57. Shen J, Hraby GW, McKiernan JM, *et al.* Dysregulation of circulating microRNAs and prediction of aggressive prostate cancer. *Prostate* 2012; 72: 1469–1477.
  58. Pak S, Suh YS, Lee DE, *et al.* Association between postoperative detection of circulating tumor cells and recurrence in patients with prostate cancer. *J Urol* 2020; 203: 1128–1134.
  59. Garcia-Albeniz X, Chan JM, Paciorek A, *et al.* Immediate versus deferred initiation on of androgen deprivation on therapy in prostate cancer patients with PSA-only relapse. An observational follow-up study. *Eur J Cancer* 2015; 51: 817–824.
  60. Fu AZ, Tsai H-T, Haque R, *et al.* Mortality and androgen-deprivation therapy as salvage treatment for biochemical recurrence after primary therapy for clinically localized prostate cancer. *J Urol* 2017; 197: 1448–1454.
  61. Duchesne GM, Woo HH, Bassett JK, *et al.* Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. *Lancet Oncol* 2016; 17: 727–737.
  62. Francini E, Gray KP, Xie W, *et al.* Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). *Prostate* 2018; 78: 889–895.
  63. Taylor BS, Schultz N, Hieronymus H, *et al.* Integrative genomic profiling of human prostate cancer. *Cancer Cell* 2016; 18: 11–22.
  64. Edlind MP and Hsieh AC. PI3K-AKT-mTOR signaling in prostate cancer progression and androgen deprivation therapy resistance. *Asian J Androl* 2014; 16: 378–386.
  65. Loblaw A, Bassett J, D’Este C, *et al.* Timing of androgen deprivation therapy for prostate cancer patients after radiation: planned combined analysis of two randomized phase 3 trials. *J Clin Oncol* 2018; 36: 5018.

66. Crook JM, Callaghan CJ, Duncan G, *et al.* Intermittent androgen suppression for rising PSA level after radiotherapy. *New Eng J Med* 2012; 367: 895–903.
67. Yu EY, Gulati R, Telesca D, *et al.* Duration of first off-treatment interval is prognostic for time to castration resistance and death in men with biochemical relapse of prostate cancer treated on a prospective trial of intermittent androgen deprivation. *J Clin Oncol* 2010; 28: 2668–2673.
68. Kuo KF, Hunter-Merrill R, Gulati R, *et al.* Relationships between times to testosterone and prostatespecific antigen rises during the first “off treatment” interval of intermittent androgen deprivation are prognostic for castration resistance in men with non-metastatic prostate cancer. *Clin Genitourin Cancer* 2015; 13: 10–16.
69. Carrie C, Hasbini A, de Laroche G, *et al.* Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* 2016; 17: 747–756.
70. Pollack A, Karrison TG, Balogh AG, *et al.* Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: the NRG oncology/RTOG 0534 SPPORT trial. *Int J Rad Oncol Biol Phys* 2018; 102: 1605.
71. Shipley WU, Seiferheld W, Lukka HR, *et al.* Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Eng J Med* 2017; 376: 417–428.
72. Dess RT, Sun Y, Jackson WC, *et al.* Association of presalvage radiotherapy PSA levels after prostatectomy with outcomes of long-term antiandrogen therapy in men with prostate cancer. *JAMA Oncol* 2020; 6: 735–743.
73. Müller J, Ferraro DA, Muehlemaier UJ, *et al.* Clinical impact of <sup>68</sup>Ga-PSMA-11 PET on patient management and outcome, including all patients referred for an increase in PSA level during the first year after its clinical introduction. *Eur J Nucl Med Mol Imag* 2019; 46: 889–900.
74. Deek MP and Tran PT. Oligometastatic & oligoprogression disease and local therapies in prostate cancer. *Cancer J* 2020; 26: 137–143.
75. Bravi CA, Fossati N, Gandaglia G, *et al.* Long-term outcomes of salvage lymph node dissection for nodal recurrence of prostate cancer after radical prostatectomy: not as good as previously thought. *Eur Urol* 2020; 78: 661–669.
76. Ost P, Jereczek-Fossa BA, Van As N, *et al.* Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naïve recurrence: a multi-institutional analysis. *Eur Urol* 2016; 69: 9–12.
77. Vaugier L, Palpacuer C, Rio E, *et al.* Early toxicity of a phase 2 trial of combined salvage radiation therapy and hormone therapy in oligometastatic pelvic node relapses of prostate cancer (OLIGOPELVIS GETUG P07). *Int J Radiat Oncol Biol Phys* 2019; 103: 1061–1067.
78. De Bruycker A, Spiessens A, Dirix P, *et al.* PEACE V - Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): a study protocol for a randomized controlled phase II trial. *BMC Cancer* 2020; 20: 406.
79. Lancia A, Zilli T, Achard V, *et al.* Oligometastatic prostate cancer: the game is afoot. *Cancer Treat Rev* 2019; 73: 84–90.
80. Goodin S, Medina P, Capanna T, *et al.* Effect of docetaxel in patients with hormone-dependent prostate-specific antigen progression after local therapy for prostate cancer. *J Clin Oncol* 2005; 23: 3352–3357.
81. Hussain A, Dawson N, Amin P, *et al.* Docetaxel followed by hormone therapy in men experiencing increasing prostate-specific antigen after primary local treatments for prostate cancer. *J Clin Oncol* 2005; 23: 2789–2796.
82. Taplin ME, Xie W, Bublely GJ, *et al.* Docetaxel, estramustine, and 15-month androgen deprivation for men with prostate-specific antigen progression after definitive local therapy for prostate cancer. *J Clin Oncol* 2006; 24: 5408–5413.
83. Morris MJ, Mota JM, Lacuna K, *et al.* Phase 3 randomised controlled trial of androgen deprivation therapy with or without docetaxel in high-risk biochemically recurrent prostate cancer after surgery (TX3503). *Eur Urol Oncol* 2021; 4: 543–552.
84. Oudard S, Latorzeff I, Caty A, *et al.* Effect of adding docetaxel to androgen-deprivation therapy in patients with high-risk prostate cancer with rising prostate-specific antigen levels after primary local therapy. A randomized clinical trial. *JAMA Oncol* 2019; 5: 623–632.
85. Rathkopf D, Carducci MA, Morris MJ, *et al.* A phase II trial of docetaxel with rapid androgen cycling as a treatment for patients with prostate cancer. *J Clin Oncol* 2008; 26: 2959–2965.
86. McKay RR, Gray KP, Hayes JH, *et al.* Docetaxel, bevacizumab, and androgen deprivation therapy for biochemical disease recurrence after definitive local therapy for prostate cancer. *Cancer* 2015; 121: 2603–2611

87. Armstrong AJ, Halabi S, Healy P, *et al.* A phase 2 multimodality trial of docetaxel/prednisone with sunitinib followed by salvage radiation therapy in men with PSA recurrent prostate cancer after radical prostatectomy. *Prost Cancer Prost Dis* 2016; 19: 100–106.
88. James ND, Sydes MR, Clarke NW, *et al.* Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016; 387: 1163–1177.
89. James ND, de Bono JS, Spears MR, *et al.* Abiraterone for prostate cancer not previously treated with hormone therapy. *N Eng J Med* 2017; 377: 338–351.
90. Miller K, Mulders P, Freedland SJ, *et al.* EMBARK: a phase 3, randomized, efficacy and safety study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in men with high-risk nonmetastatic prostate cancer progressing after definitive therapy. *Ann Oncol* 2016; 27: 243–265.
91. Armstrong AJ, Bitting RL, Healy P, *et al.* Phase II trial enzalutamide and androgen deprivation therapy (ADT) with salvage radiation in men with high-risk PSA recurrent prostate cancer (PC): the STREAM trial. *J Clin Oncol* 2019; 37: 29.
92. Kapoor R, Deek MP, McIntyre R, *et al.* A phase II randomized placebo-controlled double-blind study of salvage radiation therapy plus placebo versus SRT plus enzalutamide with high-risk PSA-recurrent prostate cancer after radical prostatectomy (SALV-ENZA). *BMC Cancer* 2019; 19: 572–583.
93. Posadas EM, Gay HA, Pugh SL, *et al.* RTOG3506 (STEEL): a study of salvage radiotherapy with or without enzalutamide in recurrent prostate cancer following surgery. *J Clin Oncol* 2020; 38: TPS5601.
94. Supiot S, Campion L, Pommier P, *et al.* Combined abiraterone acetate plus prednisone, salvage prostate bed radiotherapy and LH-RH agonists (CARLHA-GEP12) in biochemically-relapsing prostate cancer patients following prostatectomy: a phase I study of the GETUG/GEP. *Oncotarget* 2018; 9: 22147–22157.
95. Maluf FC, Fay AP, Carrera Souza V, *et al.* Phase II randomized study of abiraterone acetate plus prednisone (AAP) added to ADT versus apalutamide alone (APA) versus AAP+APA in patients with advanced prostate cancer with noncastrate testosterone levels: (LACOG 0415). *J Clin Oncol* 2020; 38: 5505.
96. Zhang T, Koontz BF, Tagawa ST, *et al.* A phase II salvage trial of AR inhibition with ADT and apalutamide with radiation therapy followed by docetaxel in men with PSA recurrent prostate cancer (PC) after radical prostatectomy (STARTAR). *J Clin Onc* 2019; 37: TPS5097.
97. Beinart G, Rini BI, Weinberg V, *et al.* Antigen-presenting cells 8015 (Provenge) in patients with androgen-dependent, biochemically relapsed prostate cancer. *Clin Prostate Cancer* 2005; 4: 55–60.
98. Beer TM, Bernstein GT, Corman JM, *et al.* Randomized trial of autologous cellular immunotherapy with Sipuleucel-T in androgen-dependent prostate cancer. *Clin Cancer Res* 2011; 17: 4558–4567.
99. Antonarakis ES, Kibel AS, Yu EY, *et al.* Sequencing of sipuleucel-T and androgen deprivation therapy in men with hormone-sensitive biochemically recurrent prostate cancer: a phase II randomized trial. *Clin Cancer Res* 2017; 23: 2451–2459.
100. DiPaola RS, CVhen YH, Bublely GJ, *et al.* A national multicenter phase 2 study of prostate-specific antigen (PPSA) pox virus vaccine with sequential androgen ablation therapy in patients with PSA progression; ECOG 9802. *Eur Urol* 2015; 68: 365–371.
101. Madan RA, Karzai F, Bilusic M, *et al.* Immunotherapy for biochemically. Recurrent prostate cancer. *J Clin Oncol* 2018; 36: 215.
102. Chudley L, McCann K, Mander A, *et al.* DNA fusion-gene vaccination in patients with prostate cancer induces high-frequency CD8+ T-cell responses and increases PSA doubling time. *Cancer Immunol Immunother* 2012; 61: 2161–2170.
103. McNeel DG, Eickhoff JC, Johnson LE, *et al.* Phase II trial of a DNA vaccine encoding prostatic acid phosphatase (pTVG-HP [MVI-816]) in patients with progressive, nonmetastatic, castration-sensitive prostate cancer. *J Clin Oncol* 2019; 37: 3507–3517.
104. Wood LV, Fojo A, Roberson BD, *et al.* TARP vaccination is associated with slowing in PSA velocity and decreasing tumor growth rates in patients with stage D0 prostate cancer. *Oncimmunol* 2016; 5: e1197459.
105. Whitehurst M, Zhao X, Schell M, *et al.* Abstract B38: Pilot study of combination PSMA peptide and TARP peptide vaccine with poly-IC:LC adjuvant in HLA-A2 positive patients with elevated PSA after initial definitive treatment of prostate cancer. *Cancer Immunol Res* 2015; 3: B38.



106. McNeel DG, Smith HA, Eickhoff JC, *et al.* Phase I trial of tremelimumab in combination with short-term androgen deprivation in patients with PSA-recurrent prostate cancer. *Cancer Immunol Immunother* 2012; 61: 1137–1147.
107. Shore ND, Morrow MP, McMullan T, *et al.* CD8 T cells impact rising PSA in biochemically relapsed cancer patients using immunotherapy targeting tumor-associated antigens. *Molecular Ther* 2020; 28: 1238–1250.
108. Antonarakis ES, Wang H, Teplý BA, *et al.* Interim results from a phase 2 study of olaparib (without ADT) in men with biochemically-recurrent prostate cancer after prostatectomy, with integrated biomarker analysis. *J Clin Oncol* 2019; 37(Suppl. 15): 5045.
109. McKay RR, Zurita AJ, Werner L, *et al.* A randomized phase II trial of short-course androgen deprivation therapy with or without bevacizumab for patients with recurrent prostate cancer after definitive local therapy. *J Clin Oncol* 2016; 34: 1913–1920.
110. Keizman D, Zahurak M, Sinibaldi V, *et al.* Lenalidomide in nonmetastatic biochemically relapsed prostate cancer: results of a phase I/II double-blinded, randomized study. *Clin Cancer Res* 2010; 16: 5269–5276.
111. Lin AM, Rini BI, Weinberg V, *et al.* A phase II trial of imatinib mesylate in patients with biochemical relapse of prostate cancer after definitive local therapy. *Br J Urol Int* 2006; 98: 763–769.
112. Figg WD, Hussain MH, Gulley JL, *et al.* A double-blind randomized crossover study of oral thalidomide versus placebo in patients with stage D0 androgen-dependent prostate cancer following limited hormonal ablation. *J Urol* 2009; 181: 1104–1113.
113. Chee KG, Longmate J, Quinn DI, *et al.* The AKT inhibitor perifosine in biochemically recurrent prostate cancer: a phase II California/Pittsburgh cancer consortium trial. *Clin Genitourin Cancer* 2007; 5: 433–437.
114. Ferrari A, Chen Y, Hudes G, *et al.* Androgen receptor (AR) modulation by bicalutamide (Bic) and MK-2206 (MK) in prostate cancer (PC) patients (pts) with rising PSA at high risk of progression after local treatment (tx). *Ann Oncol* 2016; 27: 243–265.
115. Pruthi RS, Derksen JE, Moore D, *et al.* Phase II trial of celecoxib in prostate-specific antigen recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. *Clin Cancer Res* 2006; 12: 2172–2177.
116. Smith MR, Manola J, Kaufman DS, *et al.* Celecoxib versus placebo for men with prostate cancer and a rising serum prostate-specific antigen after radical prostatectomy and/or radiation therapy. *J Clin Oncol* 2006; 24: 2723–2728.
117. Goodin S, Stein MN, Shih W, *et al.* A phase II study of atorvastatin and celecoxib in patients with rising PSA following local therapy for prostate cancer (PC). *J Clin Oncol* 2012; 30(Suppl. 5): 89.
118. Raval AD, Thakker D, Negi H, *et al.* Association between statins and clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2016; 19: 151–162.
119. Beer TM, Lemmon D, Lowe BA, *et al.* High-dose weekly oral calcitriol in patients with a rising PSA after prostatectomy or radiation for prostate carcinoma. *Cancer* 2003; 97: 1217–1224.
120. Srinivas S and Feldman D. A phase II trial of calcitriol and naproxen in recurrent prostate cancer. *Anticancer Res* 2009; 29: 3605–3610.
121. Abdel-Wahab M, Schwartz G, Howard G, *et al.* Calcifediol in recurrent prostate cancer-A phase II trial. *Proc Am Soc Clin Oncol* 2003; 22: 1708.
122. Cheung E, Pinski J, Dorff T, *et al.* Oral fenretinide in biochemically recurrent prostate cancer: a California cancer consortium phase II trial. *Clin Genitourin Cancer* 2009; 7: 43–50.
123. Lin J, Zahurak M, Beer TM, *et al.* A non-comparative randomized phase II study of two doses of ATN-224, a copper/zinc superoxide dismutase inhibitor, in patients with biochemically recurrent hormone-naïve prostate cancer. *Urol Oncol* 2013; 31: 581–588.
124. Raval AD, Thakker D, Vyas A, *et al.* Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. *Prost Cancer Prost Dis* 2015; 18: 110–121.
125. Liu G, Chen Y-H, Kolesar J, *et al.* Eastern cooperative oncology group phase II trial of lapatinib in men with biochemically relapsed, androgen dependent prostate cancer. *Urol Oncol* 2013; 31: 211–218.
126. Smith MR, Manola J, Kaufman DS, *et al.* Rosiglitazone versus placebo for men with prostate carcinoma and a rising serum prostate-specific antigen level after radical prostatectomy and/or radiation therapy. *Cancer* 2004; 101: 569–574.
127. Parker C, Castro E, Fizazi K, *et al.* Prostate cancer: ESMO clinical practice guidelines for

- diagnosis, treatment and follow-up. *Ann Oncol* 2020; 31: 1119–1134.
128. Vale CL, Burdett S, Rydzewska LH, *et al.* Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. *Lancet Oncol* 2016; 17: 243–256.
129. Gandaglia G, Fossati N, Karnes RJ, *et al.* Use of concomitant androgen deprivation therapy in patients treated with early salvage radiotherapy for biochemical recurrence after radical prostatectomy: long-term results from a large, multi-institutional series. *Eur Urol* 2018; 73: 512–518.
130. Spratt DE, Dess RT, Zumsteg ZS, *et al.* A systematic review and framework for the use of hormone therapy with salvage radiation therapy for recurrent prostate cancer. *Eur Urol* 2018; 73: 156–165.

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