Systematic Review of Systemic Therapies and Therapeutic Combinations with Local Treatments for High-risk Localized Prostate Cancer

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Abstract

Context: Systemic therapies, combined with local treatment for high-risk prostate cancer, are recommended by the international guidelines for specific subgroups of patients; however, for many of the clinical scenarios, it remains a research field.

Objective: To perform a systematic review, and describe current evidence and perspectives about the multimodal treatment of high-risk prostate cancer.

Evidence acquisition: We performed a systematic review of PubMED, Embase, Cochrane Library, European Society of Medical Oncology/American Society of Clinical Oncology Annual proceedings, and clinicalTrial.gov between January 2010 and February 2018 following the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.

Evidence synthesis: Seventy-seven prospective trials were identified. According to multiple randomized trials, combining androgen deprivation therapy (ADT) with external-beam radiotherapy (EBRT) outperforms EBRT alone for both relapse-free and overall survival. Neoadjuvant ADT did not show significant improvement compared with prostatectomy alone. The role of adjuvant ADT after prostatectomy in patients with high-risk disease is still debated, with lack of data from phase 3 trials in pN0 patients.
Novel androgen pathway inhibitors have been tested only in early-phase trials in addition to primary treatment. GETUG 12, RTOG 0521, and nonmetastatic subgroup of the STAMPEDE trial showed improved relapse-free survival for docetaxel in patients treated with EBRT plus ADT, although mature metastasis-free survival data are still pending. Both the SPCG-12 and the VACSP#553 trial showed no improvement in relapse free survival for adjuvant docetaxel after prostatectomy.

Conclusions: In contrast to the clearly demonstrated survival benefits of long-term adjuvant ADT when used with EBRT, its role after prostatectomy remains unclear especially in pN0 patients. Adding docetaxel to EBRT-ADT improves relapse-free survival, with immature results on overall survival. Novel androgen receptor pathway inhibitors are currently being tested in the neoadjuvant and adjuvant setting.

Patient summary: Treatment of high-risk prostate cancer is based on a multimodality approach that includes systemic treatments. The best treatment or therapy combination remains to be defined.

1. Introduction

Prostate cancer is the second leading cause of malignant tumors in men worldwide after lung cancer, and it still represents the fifth cause of cancer-specific mortality (CSM) [1]. The definition of high-risk prostate cancer is still heterogeneous, but it is most commonly defined as men having one or more of these features [2,3]: initial prostate specific antigen (iPSA) >20 ng/ml, biopsy Gleason score (bGS) >7, and clinical stage ≥T2c. High-risk prostate cancer is clearly the most concerning form of localized disease with 35.5% cumulative mortality at 15 yr [4]. The addition of androgen deprivation therapy (ADT) to external-beam radiotherapy (EBRT) improved overall survival (OS) compared with radiotherapy alone (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.45–0.80; p = 0.0004) [5]. Surgery, in selected patients from nonrandomized studies, was associated with 10-yr CSM rates ranging from 3% to 11% depending on the definition used [6]. The rationale behind the combination of treatments is to eradicate as much as possible the primary tumor as well as the micrometastatic clones. The cytotoxic mechanisms of chemotherapy, for example, have a potential effect not only on differentiated cancer cells, but also on prostate cancer stem cells, which do not express androgen receptor [7]. ADT, conversely, is effective against androgen-sensitive cells, and it is able to radiosensitize prostate cancer cells to radiation therapy [8]. It was also suggested that the combination of ADT and chemotherapy has a synergic and more powerful effect compared with their sequential use [9]. A recent meta-analysis, including data from different studies (GETUG-AFU 15 [10], CHAARTED [11], and STAMPEDE [12]), confirmed the positive effect of adding docetaxel with an HR of 0.77 (95% CI 0.68–0.87) for OS and 0.64 (95% CI 0.58–0.70) for failure-free survival in metastatic castration-naïve patients. In nonmetastatic patients, the use of chemotherapy significantly improved failure-free survival (HR 0.70; 95% CI 0.61–0.81) and data were immature for OS analysis [13]. Next-generation ADT (abiraterone and enzalutamide) improves OS in castration-resistant prostate cancer (CRPC) [14], and trials are now testing these agents at early stages. This systematic review aims to assess the literature broadly in the era of second-generation androgen receptor pathway inhibitors, exploring and analyzing novel and future systemic therapies, or therapeutic combinations, in association with the most common primary treatments for high-risk prostate cancer.

2. Evidence acquisition

We performed a systematic review based on five different search sources between January 2010 and February 2018: PubMED (Supplementary material), Embase, Cochrane Library, ClinicalTrial.gov, European Society of Medical Oncology Congress proceedings in the Annals of Oncology, and American Society of Clinical Oncology (ASCO) annual meeting proceedings in ASCO Meeting Library. Medical Subject Headings and Emtree vocabularies were applied, respectively, for PubMED/Cochrane Library and Embase. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines [15]. Inclusion criteria followed the PICOS items: participants, interventions, comparisons, outcomes, and study design. Participants (P) must have adenocarcinoma of the prostate and have at least one of the following high-risk features:

1. Clinical (c) T stage ≥2c and/or initial PSA ≥15 ng/ml and/or biopsy GS ≥8 (high grade) or any cT stage and cN1
2. Pathological (p) T stage >2 and/or pGS ≥8 (high grade) and/or positive surgical margins and/or pN1
3. Detectable PSA after radical prostatectomy (RP) or PSA nadir >2 ng/ml after EBRT

4. High risk of postoperative pathological features (point 3) or high risk for progression or cancer-related death

The intervention (I) was defined as a combination of primary treatment (RP or EBRT) and systemic neoadjuvant, concomitant, or adjuvant therapies. Regarding comparative studies (C), we accepted those with the following characteristics: primary treatment versus primary treatment combined with adjuvant, neoadjuvant, or concomitant therapy; comparison of two multimodal treatments; and comparison of different adjuvant or neoadjuvant schedules. The scope of our review was broad in order to overview the recent literature in the field. Primary outcomes (O) were OS/overall mortality, cancer-specific survival/CSM, disease recurrence, and progression. Secondary outcomes remained undefined to respect the broad scope of the review and permit the assessment of future perspectives. We selected prospective studies (S) including pilot studies—phases 1, 2, 3, and 4. Ongoing trials were also included to describe future perspectives. Terminated studies were included because these might also contain relevant information (eg, termination for high toxicity rates).

We used exclusion criteria following the PICOS scheme: P — prostate cancer different from adenocarcinoma; cT < 2c with the exception of cT2 if not better specified; in vitro, ex vivo, or animal experiments; I — brachytherapy and proton therapy; C — primary treatment with adjuvant or neoadjuvant therapy versus systemic treatment alone, comparison of different primary treatments, quality of life; O — specific exclusion criteria were not applied; S — meta-analyses, pooled data, post hoc analyses, observational prospective studies, retrospective studies or lack of information on the study typology, and withdrawn studies. Screening of titles and abstracts was done by a single author, and the final selection of studies was based on a collegial consensus. The risk of bias assessment followed the Cochrane recommendations (Higgins JPT, Green S [editors]; Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) and the Cochrane Collaboration 2011; available from http://handbook.cochrane.org).

3. Evidence synthesis

From 11 406 items, we finally obtained 77 studies for the qualitative review (PRISMA flow diagram in Fig. 1). We summarized the review results in a narrative way. The main results of the review are reported in Table 1-3; complete details of the ongoing trials are shown in Table 4 and 5. The risk of bias was assessed only for randomized controlled trials (RCTs) and not for comparative nonrandomized trials considering the presence of a single nonrandomized comparative study (Supplementary Table 1).

3.1. ADT and radiotherapy

The combination of first-generation ADT with EBRT has been studied extensively during the last decades in phase 3 RCTs, including some studies already published before the period considered by this review (Supplementary Table 2). In the neoadjuvant setting, two main studies assessed the survival effect of luteinizing hormone-releasing hormone (LHRH) agonists + EBRT versus EBRT alone: RTOG 8610 [16] found that 4 mo of neoadjuvant goserelin 3.6 mg improved CSM compared with EBRT alone, and these results were confirmed by the TROG 96.01 trial with 10 yr CSM rates of 22.0% for EBRT without neoadjuvant ADT, and 18.9% and

11.4% for 3 and 6 mo neoadjuvant ADT, respectively (Supplementary Table 2) [17]. The EORTC 22863 phase 3 trial [5] also demonstrated the benefit of concomitant-adjuvant long-term (3 yr) ADT compared with EBRT alone, reaching 10-yr disease-free survival (DFS) rates of 47.7% versus 22.7% and OS rates of 58.1% versus 39.8% (Supplementary Table 2). In the NCT00116220 trial [18], 6 mo of LHRH agonist + flutamide 250 mg three times a day in association with EBRT showed 8-yr OS rates of 74% for this treatment versus 61% (p= 0.01) with EBRT alone. The effect of long-term ADT was assessed in the RTOG 8531 trial [19], which evaluated CSM when goserelin 3.6 mg was added from the last week of radiotherapy until disease progression compared with salvage ADT resulting, respectively, in OS and CSM that favored the adjuvant arm (Supplementary Table 2). RTOG 9202 [20,21] and EORTC 22961 [22] assessed DFS and overall mortality, respectively, when long-term adjuvant ADT was added to EBRT. In the RTOG 9202 trial, 2 yr of adjuvant goserelin 3.6 mg after primary EBRT showed improved 15-yr DFS and CSS with a risk reduction of 30%, but no difference for other-cause mortality (Supplementary Table 2) [20,23]. EORTC 22961 showed improved 5-yr CSM rates in the 3-yr adjuvant ADTarm compared with 6-mo ADT (3.2% vs 4.7%) and 5-yr overall mortality rates, respectively, of 15.2% and 19% (p = 0.65 for noninferiority; Supplementary Table 2) [22]. Intermittent adjuvant LHRH analog did not demonstrate any difference compared with 5-yr continuous treatment in terms of biochemical recurrence-free survival (BRFS) and also for noninferiority [24] (Table 1). The PCSIV trial (NCT00223171) [25] assessed OS for patients treated with primary EBRT, randomizing them to the 36- or 18-mo adjuvant ADT; final results showed overlapping 10-yr OS of 62.4% versus 62.0% (Table 1). The NCT00116220 trial [18,26] compared 6-mo EBRT + ADT versus EBRT alone, showing, after 16.6 yr of median follow-up, OS rates of 31% (95% CI 20.52 – 41.09) for EBRT alone versus 44% (95% CI 32.41 – 54.56) for EBRT with ADT in the subgroup of patients with absence or minimal cardiovascular comorbidity. This result was inverted for patients with moderate to severe comorbidities. SPCG6 studied patients with localized and locally advanced prostate cancer randomizing them to bicalutamide 150 mg versus placebo after different types of primary treatment (EBRT, RP, watchful waiting). Bicalutamide or placebo lasted until progression. After a follow-up of almost 15 yr, the treatment arm improved OS (HR 0.77; 95% CI 0.63 – 0.94, p = 0.01) compared with the control arm for locally advanced patients [27].

3.2. ADT and RP

Neoadjuvant and adjuvant ADT have been tested with prostatectomy in men with high-risk prostate cancer. Available results showed no difference in biochemical recurrence, but the studies were not statistically powered to determine any survival benefit in OS compared with patients treated by surgery alone and the follow-ups were not long enough [28]. Recently, degarelix, an LHRH antagonist, was tested before surgery compared with degarelix + bicalutamide versus LHRHa + bicalutamide in patients with intermediate/high-risk features. No difference (p = 0.449) in pT0 rates was apparent between the arms in this randomized phase 2 study [29]. Previous data [30] showed that the administration of adjuvant ADT (goserelin 3.6 mg or bilateral orchiectomy) after RP for patients with lymph-node involvement increases progression-free survival (HR 3.42; 95% CI 1.96 – 5.98; p < 0.0001), but the study did not achieve the expected sample size for this endpoint (primary endpoint). Interestingly, ADT was shown to increase OS and prostate cancer – specific survival, which were secondary endpoints [30]. The recent CU 1005 trial was an open-label, randomized, noninferiority phase 2 trial that included 209 high-risk prostate cancer patients after surgery. It compared 9-mo

adjuvant LHRHa + bicalutamide 50 mg/d with bicalutamide 150 mg/d to assess BRFS. The combination arm resulted in improved BRFS compared with bicalutamide alone [31] after a median follow-up of about 2 yr (Table 2). There are still no long-term or conclusive results about the use of adjuvant ADT in patients with high-risk prostate cancer without lymph-node invasion, and confirmative trials are needed to support this indication. From this perspective, PRIORITI (NCT01753297) and AFU/GETUG 20/0310 (NCT01442246) trials are ongoing to evaluate adjuvant ADT after prostatectomy (Table 5). RADICALS-HD (NCT00541047) included > 2800 patients in the phase 3 trial that has been assessing cancer-specific survival; patients who needed adjuvant radiotherapy after surgery were randomized to EBRT or EBRT + 6-mo ADT or EBRT + 24 mo ADT, and results are expected in the near future.

3.3. Taxanes

Early-phase trials have analyzed the pharmacokinetic profile and safety of taxanes + ADT (NCT01420250) combinations [32 – 34], demonstrating treatment feasibility in men with localized disease (Table 4). Three trials have shown a benefit adding docetaxel to ADT plus EBRT in high-risk localized prostate cancer, as evidenced by increasing biochemical-free survival — variably defined in RTOG0521, GETUG12, and in STAMPEDE M0 cohorts. Longer-term follow-up is required and planned to define the clinical relevance of these findings in terms of metastasis-free survival (MFS) [35] and OS. The GETUG-12 phase 3 trial [36,37] randomized 413 patients with high-risk disease to 3 yr of goserelin 10.8 mg alone or combined with four cycles of docetaxel 70 mg/m^2 + estramustine 10 mg/kg/d given every 3 wk. Both EBRT and RP were possible local treatments, and they were given in 87% and 5% of men, respectively (7% of men with lymph-node invasion had no local therapy). The 8-yr relapse-free survival was 62% in the chemohormonal group and 50% in the ADT group ($p = 0.017$), demonstrating superiority for the combined therapy over ADT alone (Table 3). Long-term analysis of MFS and OS is planned.

STAMPEDE [12] is a multiarm, multistep trial that assessed failure-free survival and OS in patients with metastatic and nonmetastatic prostate cancer. The nonmetastatic subgroup was characterized by at least two of the following unfavorable features: cT3 – 4, bGS 8 – 10, and PSA ≥40 ng/ml. Patients were originally randomized to different arms: (1) standard of care (SOC) defined as ADT for at least 2 yr, (2) SOC + docetaxel, (3) SOC + zoledronic acid, and (4) SOC + docetaxel and zoledronic acid. In the docetaxel comparison, 1145 patients had nonmetastatic disease of whom 62% had a planned EBRT (EBRT was made mandatory for men with localized disease since 2011). Docetaxel improved failure-free survival over SOC in the nonmetastatic subgroup (HR 0.60, 95% CI 0.45 – 0.80; $p = 0.283 \times 10^{-3}$). OS data are immature and will be assessed in the coming years (Table 1). RTOG 0521 [38] randomized patients to receive docetaxel + ADT or ADT alone after EBRT: preliminary data were presented in congress and supported a 4% higher OS rate favoring the chemotherapy arm (one sided $p = 0.03$; Table 1). The DFCI 05-043 phase 3 trial (NCT00116142) is assessing OS in patients treated with EBRT + ADT comparing concomitant docetaxel with primary treatment alone. A recent meta-analysis [13] assessed the role of docetaxel + SOC versus SOC to improve failure-free survival; data from four published and unpublished RCTs (GETUG-12, STAMPEDE, TAX3501, and RTOG 0521) showed an absolute improvement in failure-free survival for the treatment arm in these high-risk prostate cancer cohorts (HR 0.70, 95% CI 0.61 – 0.81, $p < 0.0001$). In all these randomized trials, OS results are immature due to the limited number of deaths. Two unpublished phase 3 trials have tested docetaxel after prostatectomy. SPCG12 [39]

randomized 459 patients after prostatectomy to six cycles of docetaxel or surveillance. The median follow-up was 56.8 mo. No improvement in biochemical DFS (Table 2), defined as a rising PSA of > 0.5 ng/ml, was demonstrated. The lack of combination of docetaxel to ADT in this trial and the inclusion of patients not classically considered as very high risk for relapse (eg, those with pT2, Gleason 7 cancers) may explain these negative findings. The rather small VA CSP#553 trial [40] showed no significant improvement in progression-free survival, after a median follow-up of 62.4 mo, when 18 wk of docetaxel was added to SOC compared with SOC alone, possibly because the trial was lacking statistical power (Table 2). Two other studies are currently evaluating the role of taxanes in men with high-risk disease. PEACE-2 is a European randomized phase 3 factorial design trial testing cabazitaxel and pelvic EBRT + ADT in men with very high-risk prostate cancer. The planned sample size is 1048 patients, and the trial is accruing patients in France, Spain, and Belgium (Table 4) [41]. The PUNCH 90203 trial (NCT00430183) randomized 750 men with high-risk disease to six cycles of neoadjuvant docetaxel + LHRH agonist + prostatectomy versus prostatectomy alone, with biochemical progression-free survival as the primary endpoint. The final data collection date for primary outcome measure is foreseen for October 2018 (Table 5).

3.4. Other chemotherapy agents

All trials testing chemotherapy compounds other than docetaxel have reported negative findings. The SWOG 9921 trial randomized 983 patients after RP to mitoxantrone + ADT (2 yr goserelin + bicalutamide) versus ADT alone, but the study was terminated early due to an excess of acute myelogenous leukemia (three cases). Long-term follow-up (median 11 yr) results indicate no OS benefit (p = 0.74) for mitoxantrone + ADT (OS 87%) compared with ADT alone (86%) [42]. RTOG 9902 [43] randomized patients who underwent EBRT and ADT to receive multiagent chemotherapy (estramustine 280 mg + etoposide 50 mg/m^2 + paclitaxel 135 mg/m^2); the trial was also terminated for excess of thromboembolic toxicity. No OS improvement was observed (Table 1).

3.5. Bisphosphonates

PR04 (ISRTN61384873) [44] was a phase 3 trial involving 508 patients who were treated with 520 mg/d of sodium clodronate versus placebo, with local treatment consisting of EBRT in approximately 70%. The study included 254 patients per arm with cT2 – 4N0 – N1 prostate cancer. After a median follow-up of 12 yr, there was no difference in OS between the study groups (HR 1.12, 95% CI 0.89 – 1.42, p = 0.94). More recently, in the STAMPEDE trial, SOC was tested with or without zoledronic acid [12]; in the nonmetastatic subgroup, no benefit was shown with zoledronic acid use (HR 1.08, 95% CI 0.66 – 1.76; Table 1). The ZEUS trial [45] aimed to prevent the onset of bone metastases in castration-naïve patients with high-risk features for metastatic progression (GS 8 – 10 and/or PSA ≥ 20 ng/ml and/or pN1), with or without primary treatment. After a median follow-up of 4.8 yr, in the subgroup of patients who underwent primary curative treatment, no improvement was demonstrated (43% vs 38% metastatic events; p = 0.66). The TROG 03.04/RADAR study randomized patients (cT2a and bGS 7 – 10, PSA ≥ 10 ng/ml or cT2b-4, N0, M0) to 6-mo neoadjuvant ADT with or without 12 mo adjuvant ADT, and both with or without 18-mo adjuvant zoledronic acid. One-year adjuvant ADT was beneficial for CSM (HR 0.70 [0.50, 0.97]; p = 0.035) and distant progression (HR 0.71 [0.56, 0.90]; p = 0.004). However, there was no significant influence of zoledronic acid on any outcome after a median follow-up of 10.4 yr [46]. These data are supported by a

meta-analysis [13] showing no survival benefit when bisphosphonates are added to SOC (HR 1.03, 95% CI 0.89 – 1.18, p = 0.724) compared with SOC alone, even when zoledronic acid was considered independently (HR 0.98; 95% CI 0.82 – 1.16, p = 0.782).

3.6. Next-generation androgen receptor pathway inhibitors

Novel androgen receptor pathway inhibitors are approved for the treatment of men with metastatic CRPC. In castration-naïve patients, these compounds can affect androgen-regulated tumor cells more effectively than previous molecules, which had insufficient androgen-receptor inhibition properties. From this perspective, LATITUDE and STAMPEDE trials showed that abiraterone 1000 mg/d + prednisone/prednisolone 5 mg/d + ADT increased OS compared with placebo + ADT in metastatic castration-naïve patients [47,48]. It is still unclear if abiraterone has a significant impact on OS in combination with local treatment for high-risk, non-metastatic disease; however, results from a prespecified analysis of STAMPEDE in the subgroup of patients with planned radiotherapy showed a positive effect on failure-free survival for the abiraterone arm [48]. Recently, a phase 2 study showed that 12 wk of abiraterone + LHRHa decreased the intraprostatic androgen level more efficaciously than LHRHa alone, and that long exposure (12 vs 24 wk) to abiraterone + LHRHa increased the proportion of pathological complete response (pCR) from 4% to 10% [49] . Enzalutamide was also studied in the neoadjuvant setting (24-wk treatment) showing no pCR in the enzalutamide-alone arm but 4.3% pCR in association with dutasteride + LHRHa [50]. These results suggest that longer and more intense ADT can drive a stronger molecular and pathological response. Based on these assumptions, various phase 3 trials are studying the role of new-generation androgen receptor pathway inhibitors next to primary treatment. The ENZARAD trial (NCT02446444) is recruiting patients to assess the role of enzalutamide when combined with ADT and EBRT (Table 4). Recently the ATLAS (NCT02531516) study has started recruiting patients to randomly receive apalutamide (ARN-509), a second-generation androgen receptor pathway inhibitor, together with LHRH agonist + EBRT (NCT02531516) with MFS as the primary endpoint (Table 4).

3.7. Discussion and limitations

High-quality RCTs showed that EBRT + ADT prolongs survival in the neoadjuvant-concomitant [16,17], neoadjuvant-concomitant-adjuvant [18,20,21,23,26], and concomitant-adjuvant [5,19,22,27] settings. In general, the current evidence supports the following: (1) any ADT duration is better than no ADT [5,16 – 18], (2) long-term ADT (eg, 3 yr) is slightly better in OS than a short duration (6 mo) [22], but (3) it remains unknown whether a duration of <3yr [25] In some patients or > 3 yr in very high-risk patients is more appropriate. Hypothetically, the association of second-generation androgen receptor pathway inhibitors with EBRT can result in an added benefit for patients, especially those at a high risk of micrometastatic disease. From this perspective, abiraterone (STAMPEDE [48]), enzalutamide (ENZARAD), and apalutamide (ATLAS) are currently under investigation to treat high-risk prostate cancer, but definitive survival results are still pending. In some models, chemotherapy administered simultaneously with ADT may increase efficacy compared with the two treatments administered in sequence [9]. Considering that ADT is a known radiosensitizer [8], it is hypothesized that the combination of chemotherapy and ADT in men treated locally with radiation may improve their outcome. Three randomized trials (GETUG 12, RTOG 0521, and STAMPEDE) and a meta-analysis [13] have currently available data in the field showing better relapse-free survival for docetaxel in combination with EBRT + ADT compared with EBRT + ADT

alone. However, most guidelines do not support routine use of chemotherapy in high-risk prostate cancer because relapse-free survival, including PSA recurrence as an event, has not been considered sufficient to justify the use of such combination. Clinical relapse-free survival, MFS, and OS results are expected in the near future. Chemotherapy, in combination with prostatectomy, has not been associated with improved outcomes. VACSP#553 trial [40] and SPCG12 did not demonstrate any benefit for docetaxel after RP [39], and no recurrence-free survival benefit was shown for docetaxel + degarelix at 1 yr when compared with degarelix alone in the neoadjuvant setting [51]. Neoadjuvant ADT + RP is not recommended by international guidelines as a result of the lack of OS improvement in the settings where it was studied, mostly intermediate- or moderately high-risk disease [28]. However, reinforced androgen receptor pathway inhibition may improve outcomes in the neoadjuvant or adjuvant settings for patients with truly high-risk disease considering the positive survival results from LATITUDE [47] and STAMPEDE [48] in men with castration-naïve metastatic disease. Early-phase studies are ongoing to assess the potentialities of neoadjuvant abiraterone, apalutamide, and enzalutamide. The CU 1005 trial [31] showed improved biochemical relapse-free survival for high-risk patients treated with LHRHa + bicalutamide 50 mg compared with bicalutamide 150mg alone, but hard endpoints are needed to demonstrate a consistent survival benefit. The role of adjuvant ADT after surgery in patients with no lymph-node invasion still remains an open question. One RCT included 352 patients with pT3 – 4 disease, without lymph-node invasion, to assess relapse-free survival as the primary endpoint [52] for patients treated with adjuvant flutamide 250 mg three times a day, compared with no adjuvant therapy. This study showed a significant improvement for the treatment arm (HR 0.51, 95% CI 0.32 – 0.81; median follow-up 72 mo). However, there are still no long-term survival data, and new results are expected from the AFU-GETUG 20 and PRIORITI trials. The variability of high-risk prostate cancer definitions in the literature, and the combination of intermediate- and high-risk patients in several studies limited the inclusion of several trials in our review. The variability in outcome definitions (Supplementary Table 3) is also a limitation.

4. Conclusions

Treatment of high-risk prostate cancer is a field in evolution, with promising results for multimodal therapies next to EBRT or RP as primary therapies. The association of ADT with EBRT clearly improves results compared with EBRT alone. However, there is still a lack of evidence regarding a survival benefit when ADT is associated with RP and further studies are needed to assess this point, especially with novel compounds. Phase 3 trials assessing docetaxel-based chemotherapy in men with high-risk prostate cancer are maturing, and data on clinical relapse-free survival, MFS, and OS are expected soon. Next-generation androgen receptor pathway inhibitors are currently being tested in combination with primary treatment with promising preliminary results.

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Table 1 – Summary of the results of clinical trials using systemic treatments together with EBRT as local treatment

Reference	Phase	TT	Risk factors	EBRT	Arms	SS	Endpoints
ADT							
Bolla et al. [5] EORTC 22863	3	CO + AD	cT1–2 + WHO G3 or cT3–4	EBRT Pelvis 45 Gy/25 f or 50 Gy/25 f Prostate 70 Gy/35 f	Arm 1: 3-yr goserelin 3.6 mg	207	10-yr DFS [1] 47.7% 10-yr OS [2] 58.1% 10-yr PCM 10.3%
					Arm 2: None	208	10-yr DFS [1] 22.7% ($p < 0.0001$) 10-yr OS [2] 39.8% ($p = 0.0004$) 10-yr PCM 30.4% ($p < 0.0001$)
Lawton et al. [20] RTOG 9202	3	NA + CO + AD	cT2c–4 + cN0 + iPSA <150	EBRT Pelvis 44 Gy/24 f or 46 Gy/23 f Prostate 65 Gy/36 f or 70 Gy/35 f	Arm 1: NA goserelin 3.6 mg + flutamide 750 mg/d + AD 2-yr goserelin 3.6 mg	758	15-yr DFS [1] 16% 15-yr OS [2] 21% 15-yr CSS [2] 84% 15-yr DM [2] 17%
					Arm 2: NA goserelin 3.6 mg + flutamide 750 mg/d + AD None	762	15-yr DFS [1] 10% ($p < 0.0001$) 15-yr OS [2] 17% ($p = 0.09$) 15-yr CSS [2] 78% ($p = 0.002$) 15-yr DM [2] 26% ($p < 0.0001$)
Ito et al. [24]	3	AD	cT3–4, cN0, cM0	CRT Prostate 72 Gy/36 f + 20 mo ADT	Arm 1: Continuous LHRHa until 5 yr	136	5-yr biochemical RFS [1] 84.8%
					Arm 2: Intermittent LHRHa	144	5-yr biochemical RFS [1] 82.8% ($p = 0.56$)
Nabid et al. [25] NCT00223171 PCSIV	3	CO-AD	≥1 risk factor: cT3–4, iPSA > 20, bGS > 7, and cN0, cM0	EBRT Pelvis 44 Gy/22 f Prostate 70 Gy/35 f	Arm 1: 3-yr goserelin 10.8 mg Arm 2: 1.5-yr goserelin 10.8 mg	310 320	10-yr OS [1] 62.4% 10-yr OS [1] 62.0% ($p = 0.8412$)
James et al. [48] STAMPEDE	3	NA-CO-AD	cT3–4, bGS 8–10, iPSA ≥40, and cN0–1, cM0	3D-CRT/IMRT Prostate 74 Gy/37 f ± Pelvis 46–50 Gy/37 f (55 Gy/37 f IMRT) (obligatory only for cN0)	Arm 1: ADT Arm 2: ADT + abiraterone 1000 mg/d + prednisolone 5 mg/d	396 396	Reference OS [1] HR 0.64 (0.38–1.08) FFS [1] HR 0.18 (0.12–0.28)
Chemohormonal							
Chen et al. [32]	1	CO	cT3 or 4 or bGS ≥8 or iPSA ≥20	IMRT Prostate 78 Gy/39 f	LHRHa + docetaxel 10–20 mg/m^2	18	MTD [1] 20 mg/m^2/wk 2-yr BRFS [2] 94%
Marshall et al. [33]	1	CO	cT ≥2c and/or bGS ≥8 and/or PSA ≥20 and cM0	IMRT Prostate 77.4 Gy/43 f	LHRHa + bicalutamide 50 mg/d + docetaxel 10–30 mg/m^2 + dexamethasone 10 mg	19	MTD [1] 25 mg/m^2/wk
Sandler et al. [38] RTOG 0521	3	AD	cT ≥2 + bGS8 or bGS 7–8 + iPSA 20–150 or bGS 9–10 + iPSA ≤150	3D-CRT/IMRT Prostate 72.0 Gy/40 f–75.6 Gy/42 f + Pelvis 46.8 Gy	Arm 1: 6 cycles, 3 weekly docetaxel 75 mg/m^2 + prednisone 10 mg/d + 20-mo LHRHa	282	4-yr OS [1] 93% 5-yr DFS [2] 73%
					Arm 2: 20-mo LHRHa	281	4-yr OS [1] 89% ($p = 0.03$) 5-yr DFS [2] 66% ($p = 0.05$)
James et al. [12] STAMPEDE	3	NA	cT3–4, bGS 8–10, iPSA ≥40, and cN0–1, cM0	3D-CRT/IMRT Prostate 74 Gy/37 f ± Pelvis 46–50 Gy/37 f (55 Gy/37 f IMRT) (obligatory only for cN0 since 2011)	Arm 1: ADT (control arm)	460	Reference
					Arm 2: ADT + 6 cycles, 3 weekly docetaxel 75 mg/m^2	230	OS [1] HR 1.11 (0.67–1.85) FFS [1] HR 0.77 (0.55–1.99)
					Arm 3: ADT + 2-yr zoledronic acid 4 mg 3–4 weekly	227	OS [1] HR 0.74 (0.42–1.29) FFS [1] HR 0.84 (0.60–1.17)
					Arm 4: ADT + 6 cycles, 3 weekly docetaxel 75 mg/m^2 + zoledronic acid 4 mg 3–4 weekly	228	OS [1] HR 0.79 (0.45–1.40) FFS [1] HR 0.69 (0.48–0.99)

Table 1 (*Continued*)

Reference	Phase	TT	Risk factors	EBRT	Arms	SS	Endpoints
Rosenthal et al. [43] RTOG 9902	3	AD	any cT + iPSA 20–100 ng/ml + bGS ≥ or cT ≥2 + bGS 8–10 + iPSA ≤100 ng/ml and N0, M0	EBRT Pelvis 46.8 Gy/26 f Prostate 70.2 Gy/39 f	Arm 1: 2-yr ADT + estramustine 280 mg TID + etoposide 50 mg/m^2 BID + paclitaxel 135 mg/m^2	200	10-yr OS [1] 63% 10-yr DFS [2] 26% 10-yr DM [2] 14%
					Arm 2: 2-yr ADT	197	10-yr OS [1] 65% ($p = 0.81$) 10-yr DFS [2] 22% ($p = 0.61$) 10-yr DM [2] 16% ($p = 0.41$)
Others							
Corn et al. [53]	1	NA + CO + AD	cT2c–4 and/or bGS 8–10 and/or iPSA >20 and cM0	IMRT Prostate 75.6 Gy/42 f	Sunitinib 12.5–25–37.5 mg + 2-yr leuprolide 22.5 mg or goserelin 10.8 mg	17	RP 2D [2] 25 mg/d DLT [2] 37.5 mg/d
Azria et al. [54]	1	CO	cT ≥3 or bGS ≥8 or iPSA ≥20 and cM0	EBRT Prostate 74 Gy/37 f	Everolimus 5–7.5–10 mg/d + leuprolide + bicalutamide	15	MTD [1] 7.5 mg/d
Carles et al. [55]	2	NA + CO + AD	cT3a M0 + bGS >7 or iPSA >20 or cT4M0 or cN1	3D-CRT Pelvis 45 Gy/25 f or 46 Gy/23 f Prostate 70.2 Gy/39 f or 70 Gy/35 f	Estramustine 600 mg/m^2/d + 3 cycles vinorelbine 25 mg/m^2 + 3-yr LHRHa	50	5-yr PFS [1] 72%
Bolla et al. [34]	2	CO + AD	cT1–2 + bGS 8–10 or iPSA >20 or cT3–4, N0, M0 or cN1/pN1, M0	3D-CRT/IMRT Pelvis 46 Gy/23 f Prostate 70 Gy/35 f	3-yr LHRHa + 6 cycles, 3 weekly docetaxel 20 mg/m^2/wk	50	Grade 3–4 toxicity <5% [1] 5-yr DFS [2] 66.72% 5-yr OS [2] 92.15%
Mason et al. [56] STAMPEDE	3	NA-CO-AD	At least 2 risk factors: cT3–4, bGS 8–10, iPSA ≥40, cN0–1, cM0	3D-CRT/IMRT Prostate 74 Gy/37 f ⊥ Pelvis 46–50 Gy/37 f (55 Gy/37 f IMRT) (obligatory only for cN0 since 2011)	Arm 1: ADT Arm 2: ADT + celecoxib 800 mg/d Arm 3: ADT + celecoxib 800 mg/d + 2-yr zoledronic acid 4 mg/15 min	245 124 121	Reference OS [1] HR 1.06 (0.59–1.91) OS [1] HR 0.94 (0.52–1.70)

a = agonist; A = active; AD = adjuvant; ADT = androgen deprivation therapy; bGS = biopsy Gleason score; BID = bis in die; BRFS = biochemical recurrence-free survival; c = clinical; CO = concomitant; CSS = cancer-specific survival; DFS = disease-free survival; DLT = dose limiting toxicity; DM = distant metastasis; EBRT = external beam radiotherapy; f = fractions; FFS = failure-free survival; GS = Gleason score; HR = hazard ratio; IMRT = intensity-modulated radiation therapy; LHRH = luteinizing hormone-releasing hormone; MT = multimodality treatment; MTD = maximal tolerated dose; NA = neoadjuvant; OS = overall survival; PCM = prostate cancer mortality; PFS = progression-free survival; PSA = prostate-specific antigen (ng/ml); RFS = recurrence-free survival; RP = radical prostatectomy; SS = sample size; TID = ter in die; TT = treatment timing; 3D-CRT = three-dimensional conformal radiation therapy.

[1] Primary endpoint.

[2] Secondary endpoint.

* HR with combination therapy in the EBRT subgroup.

** Accrual suspended for excess of thromboembolism.

Table 2 – Summary of the results of clinical trials using systemic treatments together with radical prostatectomy as local treatment

Reference	Phase	TT	Risk factors	Arms	SS	Endpoints
ADT						
Berglund et al. [57] SWOG 9109	2	NA	cT3–4, N0, M0	4-mo goserelin 3.6 mg + flutamide 250 mg BID	62	Organ-confined disease [1] 56% 10-yr PFS [2] 40% 10-yr OS [2] 68%
Chang et al. [31] CU 1005	2	AD	pT ≥3 or R1 or pN1 or pGS ≥8 or pT <3 + iPSA ≥20	Arm 1: LHRHa + bicalutamide 50 mg/d	107	2-yr BR rate [1] 19.6%
				Arm 2: Bicalutamide 150 mg/d	102	2-yr BR rate [1] 37.3% ($p = 0.004$)
Chemotherapy						
Maddox et al. [58]	2	NA	cT3, GS 8–10, iPSA ≥20, GS 7 with cT3	12-wk ixabepilone 20 mg/m^2/wk	16	Feasibility [1] 56% (6) experienced adverse event with dose modification 29% of patients with >50% reduction of tumor volume [1] pT0 0%
Ross et al. [59]	2	NA	cT3 + bGS7 or bGS ≥8 or cT3a-b or iPSA ≥20 or PSA velocity ≥2 ng/ml/yr	6 cycles, 3 weekly docetaxel 70 mg/m^2 + 5 cycles bevacizumab 15 mg/kg		
Ahlgren et al. [39] SPCG-12	3	AD	pT2 + PSM + pGS ≥4 + 3orpT3a + pGS ≥4 + 3orpT3b + pGS ≥4 + 3andN0, M0	Arm 1: 6 cycles, 3 weekly docetaxel 75 mg/m^2	230	Rising PSA >0.5 ng/ml [1] 47.9%
				Arm 2: Observation	229	Rising PSA >0.5 ng/ml [1] 38.9% ($p = 0.078$)
Lin et al. [40] VA CSG#553 NCT00132301	3	AD	pT3b-4 and/or pT3a + pGS ≥7 and/or pT2 + PSM + pGS ≥8 and/or PSA >20 ng/ml	Arm 1: 6 cycles, 3 weekly docetaxel 75 mg/m^2	140	PFS [1] 55.5 mo
				Arm 2: SOC	157	PFS [1] 45.6 mo ($p = 0.26$)
Chemohormonal						
Ploussard et al. [60]	Pilot	AD	pT3b-4 and/or pN1 and/or iPSA ≥20 and/or pGS ≥8	Arm 1: 3-yr triptorelin 11.25 mg + 8-wk paclitaxel 100 mg/m^2/wk	23	Safety and tolerability [1]13% (3), grade 3 treatment-related events
				Arm 2: 3-yr triptorelin 11.25 mg	24	–
Saldana et al. [61]	2	AD	pT3b-4 and/or pN1 and/or iPSA ≥20 and/or GS ≥8	Arm 1: 3-yr triptorelin 11.25 mg + 8-wk paclitaxel 100 mg/m^2/wk	22	8-yr cDFS [1] 95.4% 8-yr BRFS [2] 50% 8-yr OS [2] 90.9%
				Arm 2: 3-yr triptorelin 11.25 mg	26	8-yr cDFS [1] 88.5% ($p = 0.38$) 8-yr BRFS [2] 46% ($p = 0.79$) 8-yr OS [2] 84.6% ($p = 0.51$)
Hussain et al. [62]	1	AD	pT3 ± N1 or rising PSA ≥0.5	2-yr LHRHa + 7 cycles paclitaxel 40–60 mg/m^2/wk + 3D-CRT 64.8 Gy/36 f	51	Grade 3 toxicity Paclitaxel 40: 1/6 Paclitaxel 50: 7/17 Paclitaxel 60: 6/7 7-yr OS [2] 67%
Kumar et al. [63] NCT00669162	1/2	AD	pT2–3 + detectable/rising PSA ± PSM and pGS ≥8 and/or PSA DT ≤10 mo and/or pre-RT PSA ≥1.0 ng/ml and/or pT3bN0	7 cycles docetaxel 20 mg/m^2/wk + 6-mo goserelin 10.8 mg or leuprolide 22.5 mg + bicalutamide 50 mg + 3D-CRT/IMRT 66.0 Gy/33 f	32	Safety and tolerability [1] 9% (3), grade 3 toxicities
Hurwitz et al. [64] RTOG 0621	2	AD	pT ≥3 and PSA nadir ≤0.2 + pGS ≥8 or PSA nadir >0.2 + GS ≥7	6-mo LHRH agonist + antiandrogen + 6 cycles, 3 weekly docetaxel 75 mg/m^2 + pelvic EBRT 66.6 Gy	74	3-yr [1] >70%: 73%
Schweizer et al. [65] TAX 3501	3	AD	5-yr FFP ≤60%, M0	Arm 1: 6 cycles docetaxel 75 mg/m^2 + 18-mo leuprolide 22.5 mg (immediate)	55	Frequencies of progressive patients 10
				Arm 2: 18-mo leuprolide (immediate)	55	14
				Arm 3: Docetaxel + 18-mo leuprolide (differed)	56	9
				Arm 4: 18-mo leuprolide (differed)	62	8

Table 2 (*Continued*)

Reference	Phase	TT	Risk factors	Arms	SS	Endpoints
Zurita et al. [66]	2	NA	cT3 + GS ≥7 or cT4 and/or cN1,cM0 and bGS ≥8 + iPSA ≥25	1-yr LHRHa ± bicalutamide 50 mg/d + docetaxel 35 mg/m^2 (days 1, 8, 15, and 22 every 6 wk)	39	1-yr PSA recurrence 50% (10/20) pT0 8% (2/26)
Thalgott et al. [67]	2	NA	M0 And risk of 5-yr biochemical recurrence >40% (Kattan nomogram)	Buserelin 9.45 mg+ bicalutamide 50 mg/d + 3 cycles docetaxel 75 mg/m^2	30	13.3% complete PSA response [1] 48% T downstaging [1] 0% pT0
Narita et al. [68]	Pilot	NA	cT ≥3 and/or iPSA ≥15 and/or GS ≥9	1-yr leuprorelin 11.25 mg + bicalutamide 81 mg + 6 cycles docetaxel 30 mg/m^2 + estramustine 560 mg	18	pT0 [1] 11.1%
Kole et al. [69]	2	NA	cT2c-3 and/or iPSA ≥20 and/or GS ≥8	3-mo leuprolide 11.25 mg or goserelin 10.8 mg + 6-mo estramustine 280 mg	142	pT0 [1] 4.9%
Silberstein et al. [70]	2	NA	cT ≥3 and/or iPSA >20 and/or bGS ≥8	Goserelin 10.8 mg + paclitaxel 60–100 mg/m^2/wk + carboplatin 6 mg/ml-min/4 wk + 3 cycles estramustine 10 mg/kg/d	34	10-yr OS [1] 78% 10-yr CSS [1] 84% pT0 0%
Nosov et al. [51]	3	NA	cT ≥2c and/or bGS ≥8 and/or iPSA >20 ng/ml and/or N1	Arm 1: 6 cycles, 3 weekly docetaxel 75 mg/m^2 + monthly degarelix 240/80 mg	19	1-yr RFS [1] 16.7%
				Arm 2: Monthly degarelix 240/80 mg	8	1-yr RFS [1] 11.1% ($p = 0.6$)
Other						
Dean et al. [71]	2	NA	cT2c-3 and/or bGS ≥8 and/or iPSA ≥20 or a risk of relapse >50%	Goserelin + bicalutamide + 3-mo cixutumumab (IMC-A12) 10 mg/kg/2 wk	28	pT0 [1] (not available)
Vuky et al. [72]	2	NA	High risk prostate cancer	4 cycles, 3 weekly docetaxel 75 mg/m^2 + 4 cycles GVAX	6	Terminated for safety concerns 0% pT0 [1]
Ross et al. [73]	1	NA	cT≥3 and/or bGS ≥8 and/or PSA ≥20	Arm 1: 4-wk sonidegib 800 mg/d	7	86% Two-fold reduction of GLI1 mRNA
				Arm 2: None	7	0%

a = agonist; A = active; AD = adjuvant; ADT = androgen deprivation therapy; bGS = biopsy Gleason score; BID = bis in die; BRFS = biochemical recurrence-free survival; BR = biochemical recurrence; c = clinical; CSS = cancer-specific survival; DT = doubling time; 3D-CRT = three-dimensional conformal radiation therapy; DFS = disease-free survival; EBRT = external beam radiotherapy; f = fractions; FFP = freedom from progression; GS = Gleason score; IMRT = intensity-modulated radiation therapy; LHRH = luteinizing hormone-releasing hormone; MT = multimodality treatment; NA = neoadjuvant; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen (ng/ml); PSM = positive surgical margins; R = recruiting; S = suspended (the clinical study has stopped recruiting or enrolling participants early, but it may start again); RFS = recurrence-free survival; RT = radiation therapy; SS = sample size; TT = treatment timing.

[1] Primary endpoint.

[2] Secondary endpoint.

* Early terminated for slow accrual.

Table 3 – Summary of the results of clinical trials using systemic treatments together with either EBRT or radical prostatectomy as local treatments

Reference	Phase	TT	Risk factors	Arms	SS	Endpoints
Chemohormonal therapy						
Guttilla et al. [74]	2	AD	cT2c-3 or iPSA ≥20 or bGS ≥8 or N1	Arm 1: RP + ePLND + AD IMRT prostate 70 Gy/35 f + 7/8 wk docetaxel 30–40 mg/m^2/wk + 2-yr LHRHa	18	Safety and tolerability [1]: Arm 1: 9% gastrointestinal grade 3.
		CO		Arm 2: IMRT prostate/pelvis 80 Gy + 2-yr LHRHa	17	Arm 2: 6% gastrointestinal grade 3, 6% genitourinary grade 3.
Fizazi et al. [36] GETUG-12	3	NA	cT3–4 and/or bGS ≥8 and/or iPSA >20 and/or pN1 and M0	Arm 1: 4 cycles docetaxel 70 mg/m^2/3 wk + 5 d every 3 wk estramustine 10 mg/kg/d + 3-yr goserelin 10.8 mg + 3D-CRT 74–78 Gy/37–39 f prostate ± pelvis + PLND or RP	207	Safety and tolerability [1]48% grade 3–4 events
				Arm 2: 3-yr goserelin 10.8 mg + 3D-CRT 74 Gy/41 f–78 Gy/39 f prostate ± pelvis + PLND or RP	206	0% grade 3–4 events
Fizazi et al. [37] GETUG-12	3	NA	cT3–4 and/or bGS ≥8 and/or iPSA >20 and/or N1	Arm 1: 4 cycles docetaxel 70 mg/m^2/3 wk + 5 d every 3 wk estramustine 10 mg/kg/d + 3-yr goserelin 10.8 mg + 3D-CRT 74–78 Gy/37–39 f prostate ± pelvis + PLND or RP	207	8-yr RFS 62%
				Arm 2: 3-yr goserelin 10.8 mg + 3D-CRT 74 Gy/41 f–78 Gy/39 f prostate ± pelvis + PLND or RP	206	8-yr RFS 50% ($p = 0.017$)
Others						
Valicenti et al. [75]	1	NA	cT ≥2 + bGS ≥8 + iPSA ≤150 or iPSA >20–150 and bGS ≥7 or and/or pN1 and M0	1 cycle samarium 153 lexidronam (0.25–2.0 mCi/kg) + leuprolide or goserelin + flutamide 250 mg/d or bicalutamide 50 mg/d + prostate/pelvic EBRT 70.2 Gy/39 f	29	MTD 2.0 mCi/kg ^{153}Sm-EDTMP
NCT00294437 CECOG/prostate 1.2.001	3	AD	cT3–4 and iPSA >20 ng/ml and bGS8	Arm 1: Zoledronic acid 4 mg/100 ml		*
				Arm 2: None	376	Time to first bone metastasis [1]

a = agonist; A = active; AD = adjuvant; bGS = biopsy Gleason score; c = clinical; CO = concomitant; 3D-CRT = three-dimensional conformal radiation therapy; EBRT = external beam radiotherapy; (e)PLND = (extended) pelvic lymphadenectomy; f = fractions; GS = Gleason score; IMRT = intensity-modulated radiation therapy; LHRH = luteinizing hormone-releasing hormone; MT = multimodality treatment; MTD = maximal tolerated dose; NA = neoadjuvant; PSA = prostate-specific antigen (ng/ml); RFS = recurrence-free survival; RP = radical prostatectomy; SS = sample size; TT = treatment timing.

[1] Primary endpoint.

* Terminated for underfunding.

Table 4 – Summary of the ongoing trial setting using systemic treatments together with EBRT as local treatment

Reference	Phase	TT	Risk factors	EBRT	Arms	I endpoint	Status	SS	Estimated completion date
ADT									
NCT01439542 FASTR	2	CO-AD	cT3 or iPSA ≥20 or GS ≥8	SBRT 25 Gy/5f Pelvis 40 Gy/5f Prostate	1-yr LHRHa	Safety and tolerability	TE		Accrual goal not reached due to excess of toxicity
NCT02229734 FASTR-2	2	CO-AD	High-risk prostate cancer	SBRT 35 Gy\ Prostate	1.5-yr leuprolide 45 mg	Safety and tolerability	R	60	November 2019
NCT02772588	2	NA-CO-AD	cT ≥3 and/or iPSA ≥20 and/or GS ≥8	Ultrafractionated (SBRT)	6-mo apalutamide (ARN-509) + abiraterone 1000 mg/d + leuprolide	Biochemical failure	R	58	May 2019
NCT02064582	2	NA-CO-AD	High-risk prostate cancer	EBRT	Leuprolide 22.5 mg/45 mg + 6-mo enzalutamide 160 mg/d	Safety and tolerability	R	15	April 2019
NCT02508636	2	CO-AD	≥2 risk factors: cT3a3b iPSA ≥ 20 bGS 8–10 >33% cores cN1	EBRT	2-yr leuprolide 22.5 mg/45 mg + enzalutamide 160 mg/d	Safety and tolerability	R	53	June 2022
NCT02446444 ENZARAD	3	NA-CO-AD	cT2-4 and bGS 4 + 3 and iPSA >20 or GS 8–10 or N1	EBRT 78 Gy/39 f or 46 Gy/23 f + brachytherapy boost	Arm 1: 2-yr enzalutamide 160 mg/d + LHRHa Arm 2: 2-yr antiandrogen + LHRHa	OS	R	800	December 2021
NCT01546987 RTOG 1115	3	NA-CO-AD	cT≥2, bGS ≥8, iPSA <20 or bGS ≥9, iPSA ≤150 or bGS ≥8, iPSA ≥20–150 or bGS ≥7, iPSA ≥20–150	Dose escalated EBRT	Arm 1: 2-yr LHRHa + antiandrogen Arm 2: 2-yr LHRHa + antiadrogen + TAK700	OS	O	239	June 2020
NCT02531516 ATLAS	3	NA-CO-AD	cT ≥2c,GS ≥8 or GS ≥7, iPSA ≥20, cT2c	EBRT 74–80 Gy	Arm 1: 2.5-yr LHRHa + placebo bicalutamide + apalutamide 240 mg/d Arm 2: 2.5-yr LHRH agonist + bicalutamide 50 mg + placebo apalutamide	MFS	R	1500	October 2026
NCT02799706 EORTC 1414 PEGASUS	3	CO-AD	2 risk factors: cT3–4 cN1 bGS ≥8 PSA ≥20 ng/ml	IMRT 78–80 Gy	Arm 1; 1.5–3-yr degarelix Arm 2: 1.5–3-yr LHRHa	PFS	not R	885	June 2024
Chemohormonal therapy									
NCT03066154	1	CO	cN1 + cT ≥2c bGS ≥4 + 3	IMRT 77 Gy/35 f	Oral docetaxel (ModraDoc006/ritonavir) + ADT	MTD	R	24	January 2020
NCT01420250	1	CO	bGS ≥8 bGS7 and cT3–4 bGS7 but iPSA ≥20 and M0	IMRT 75.6 Gy/42 f	LHRHa + bicalutamide + cabazitaxel 4–10 m^2	MTD	O	20	September 2018

Table 4 (*Continued*)

Reference	Phase	TT	Risk factors	EBRT		Arms	I endpoint	Status	SS	Estimated completion date
NCT01952223 PEACE 2	3	CO	Any cT N0, cM0 bGS ≥6 At least 2 of: 1. bGS ≥8 2. cT3 or 4 3. iPSA >20 4. pN0–N1	IMRT or IGRT Pelvis 45–50 Gy Prostate 74–78 Gy	ADT	Arm 1: Pelvic EBRT Arm 2: Cabazitaxel 25 mg/m^2 + prostate EBRT Arm 3: Cabazitaxel 25 mg/m^2 + pelvic EBRT Arm 4; Prostate EBRT	PFS	R	1048	September 2026
NCT00651326 CAN-NCIC-PR12 DART	3	NA	cT3–4 and/or GS ≥8 and/or PSA >20 And N0	EBRT	ADT	Arm 1: 3 weekly 4cycles docetaxel Arm 2: None	DFS	TE	48	–
Foro Arnalot et al. [76] QRT SOGUG Eudract 2008-003554-14	2	CO	cT3–4 and/or bGS ≥8 and/or iPSA >20 and/or cN1	EBRT 73.8 Gy/41 f or 74 Gy/37 f		Arm 1: 3-yr LHRHa Arm 2: 3-yr LHRHa + 9-wk docetaxel 20 mg/m^2	5-yr BRFS [1]	O		–
Others										
NCT01048151	**1**	**CO**	**cT ≥3 or GS ≥8**	**EBRT**		**TNFerade**	**Safety and tolerability**	**U**	**20**	–
NCT02107430 SP004	2	AD	cT3–4 and/or GS 8–10 and/or PSA >20	EBRT		Arm 1: DCVAC/PCa Arm 2: None	5-yr PSA failure	A not R	62	September 2018
Singh et al. [77]	2	NA + CO	cT3 or GS ≥8 or PSA >20 or N1	EBRT		Arm 1: 2-yr ADT Arm 2: 2-yr ADT + tecemotide (L-BLP25 vaccine) + cyclophosphamide 300 mg/m^2 (single dose)	Changes in ELISPOT level of mucin-1–specific T cells	C	28	–
NCT01642732 UMCC 011.008	1	NA-CO	High-risk prostate cancer	EBRT		Everolimus 2.5–10 mg/d + leuprorelin 22.5/30 mg + bicalutamide 50 mg/d	Safety and tolerability	TE	Accrual goal not reached due to lack of accrual and funding expires	

a = agonist; A = active; AD = adjuvant; ADT = androgen deprivation therapy; bGS = biopsy Gleason score; BRFS = biochemical recurrence-free survival; c = clinical; CO = concomitant; DFS = disease-free survival; EBRT = external beam radiotherapy; f = fractions; GS = Gleason score; IGRT = image-guided radiation therapy; IMRT = intensity-modulated radiation therapy; LHRH = luteinizing hormone-releasing hormone; MFS = metastasis-free survival; MTD = maximal tolerated dose; NA = neoadjuvant; O = ongoing; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen (ng/ml); R = recruiting; S = suspended (the clinical study has stopped recruiting or enrolling participants early, but it may start again); SS = sample size; SBRT = stereotactic body radiation therapy; TE = terminated (the study has stopped recruiting or enrolling participants early and will not start again; participants are no longer being examined or treated); TT = treatment timing; U = unknown.

[1] Primary endpoint.

Table 5 – Summary of the ongoing trial setting using systemic treatments together with radical prostatectomy as local treatment

Reference	Phase	TT	Risk factors	EBRT	Arms	I endpoint	Status	SS	Estimated completion date
ADT									
NCT02789878	2	NA	cT3 and/or bGS ≥8 and/or iPSA ≥20 ng/ml	–	Arm 1: 3-mo goserelin 10.8 mg + abiraterone 1000 mg/d + prednisone 5 mg/d + 3-mo apalutamide (ARN-509) 240 mg/d Arm 2: 3-mo goserelin 10.8 mg + abiraterone 1000 mg/d + prednisone 5 mg/d	pT0	Not R	64	October 2019
NCT02949284	2	NA	bGS ≥8 or iPSA ≥20 ng/ml + no. of positive biopsy cores >1 and resectable prostate cancer cT1–3	–	Arm 1: 3-mo apalutamide (ARN-509) 240 mg/d + abiraterone 1000 mg/d + prednisone Arm 2: 3-mo apalutamide (ARN-509) 240 mg/d Arm 3; None	Postoperative potency rate	Not R	90	December 2018
NCT01255891	2	AD	pT3N0/Nx ± PSM and/or pGS ≥8 and/or iPSA >20	EBRT	LHRHa	5-yr BRFS and CRFS	U	46	–
NCT01753297 PRIORITI	4	AD	pT3a and post-RP PSA ≤0.2 and/or iPSA ≥20 and/or pGS ≥8, _ pN0, M0	–	Arm 1: 9-mo triptorelin 11.25 mg Arm 2; None	5-yr BRFS	O	226	June 2019
Rozet et al. [78] NCT01442246 AFU/GETUG 20/0310	3	AD	pGS >7 or pGS ≥7 + GS pattern 5 or pT3b and pN0, M0	–	Arm 1: 2-yr leuprolide 45 mg Arm 2: None	10-yr MFS	R	700	January 2023
Ornstein et al. [79] NCT01927627 CASE12812	2	AD	cT ≥3 and/or iPSA >20 and/or bGS >8 and/or pN1 with postop PSA <0.4 or risk of BR ≥35% at 5 yr	–	Enzalutamide 160 mg (40 mg 4co/d)	Time to progression	O	42	March 2019
Chemotherapy									
NCT01941550 CLUBNET	2	NA	5-yr relapse probability ≥60%	–	6 cycles cabazitaxel 1 mg/m^2	pT0	TE	11	–
NCT01650285 BrUOG 246	2	AD	pT3–4 and/or PSM and/or pT3b and/or pN1 and/or postop PSA >1–<2.0 + pT2–3	IMRT 64.8 Gy	3 doses cabazitaxel 5–20 mg/m^2	MTD	TE	5	–
NCT01079793	1/2	AD	pT3 or PSM pN0, M0 pGS = 7 with postop PSA >0 but ≤2 or GS ≥8 and postop PSA 0–2	IMRT adj	3 courses ixabepilone (dose escalation)	Phase 1 DLT MTD Phase 2 3-yr PFS	U	54	–
Chemohormonal therapy									
NCT02543255 ACDC	2	NA	cT2c-3, PSA >20, bGS 8–10	–	Arm 1: Abiraterone 1 g/d + prednisone 5 mg x 2/d + leuprolide 22.5 mg + cabazitaxel 25 mg/m^2 Arm 2: Abiraterone 1 g/d + prednisone 5 mg x 2/d + leuprolide 22.5 mg	pT0	R	76	August 2020
NCT02849990	2	NA	cT3a or cT3b–4 and/or bGS ≥8 and/or PSA >20 ng/ml	–	3-mo apalutamide (ARN-509) 240 mg/d + abiraterone 1000 mg/d + prednisone 5 mg x2/d + 3 doses of degarelix	pT0	Not R	22	July 2020
NCT00430183 PUNCH CALGB 90203	3	NA	Probability of 5-yr BFS >60%and/or bGS ≥8	–	Arm 1: 3 weekly, 6cycles docetaxel 75 mg/m^2 + 18–24 wk LHRHa Arm 2: None	3-yr BRFS	A not R	788	October 2018

Table 5 (*Continued*)

Reference	Phase	TT	Risk factors	EBRT	Arms	I endpoint	Status	SS	Estimated completion date
Guerif et al. [80] NCT01994239 GETUG-AFU22	2	AD	PSM 0-1, pN0-x, detectable PSA postop PSA ≥0.2 but ≤2 pN0-x, M0	EBRT Pelvis 46 Gy/23 f Prostate 66 Gy/33 f	Arm 1:6-mo degarelix Arm 2: None	5-yr event-free survival	R	120	June 2025
Other									
NCT01804712	1	NA	Preoperative probability to be free of disease at 5 yr <60% or GS ≥8	–	4 wk rituximab 375 mg/m^2/wk	Histology response	A not R	18	April 2019
NCT02111187	1	NA	cT3–4 and/or bGS 8–10 and/or iPSA >20	–	Arm 1: 4-wk LDE225 800 mg Arm 2: None	Gli1 expression	R	14	March 2017
NCT01385059	2	NA	cT ≥3a and/or iPSA >20 and/or cGS 8–9	–	Arm 1: 28-d axitinib Arm 2; None	No. of VEGFR1	O	60	January 2019
NCT01194271	2	NA	iPSA ≥20 or bGS ≥8	–	Leuprolide 22.5 mg + 2 doses of ipilimumab 10 mg/kg	Longitudinal peripheral blood values	C	19	–
NCT01759836	2	AD	pT3–4 or PSM or pGS ≥8	–	Arm 1: 1-yr atorvastatin 20 mg/d Arm 2: Placebo	BR	U	354	–

a = agonist; A = active; AD = adjuvant; ADT = androgen deprivation therapy; bGS = biopsy Gleason score; BID = bis in die; BRFS = biochemical recurrence-free survival; BR = biochemical recurrence; c = clinical; CO = concomitant; CRFS = clinical relapse-free survival; DLT = dose limiting toxicity; DRE = digital rectal examination; EBRT = external beam radiotherapy; f = fractions; GS = Gleason score; IMRT = intensity-modulated radiation therapy; LHRH = luteinizing hormone-releasing hormone; MFS = metastasis-free survival; MTD = maximal tolerated dose; NA = neoadjuvant; O = ongoing; PFS = progression-free survival; PSA = prostate-specific antigen (ng/ml); PSM = positive surgical margins; R = recruiting; RP = radical prostatectomy; TE = terminated (The study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated); TT = treatment timing; U = unknown; VEGFR = vascular endothelial growth factor receptor.

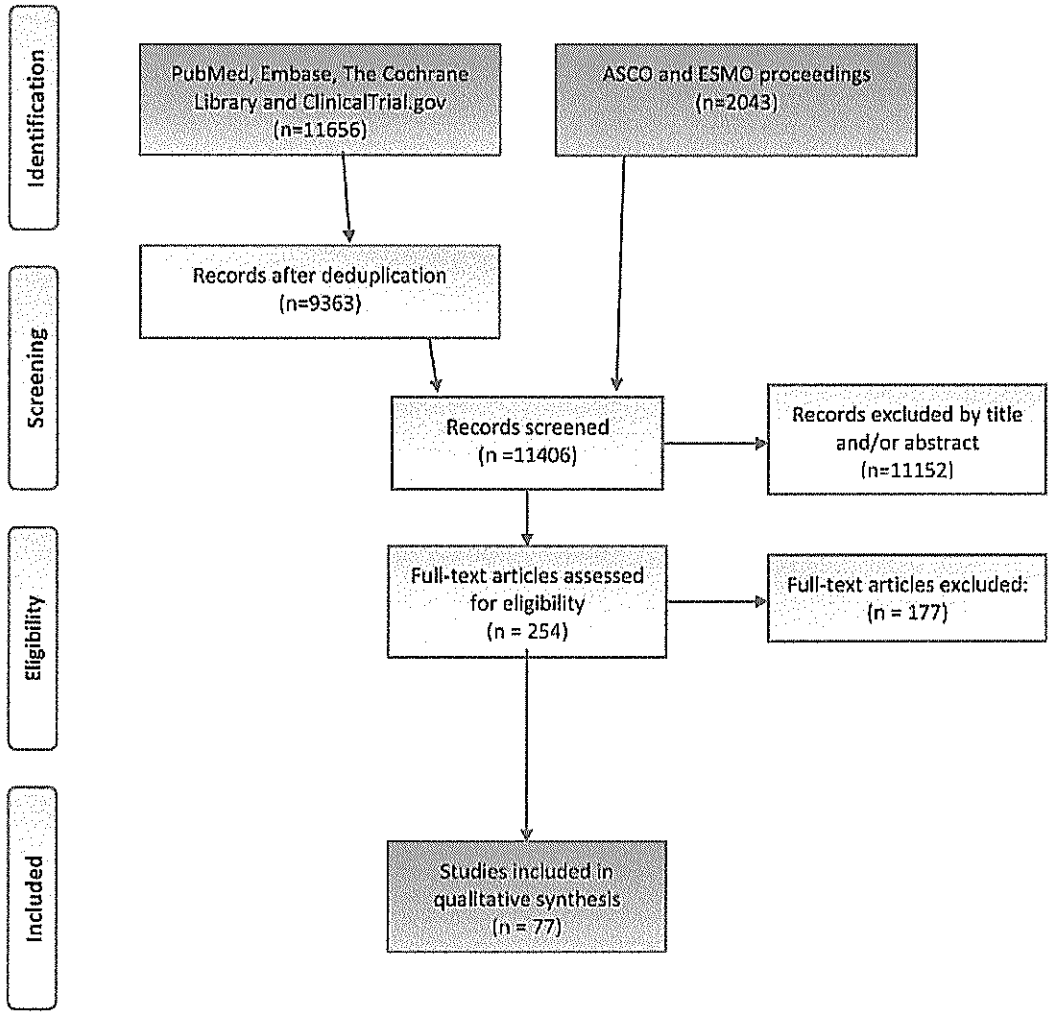

Fig. 1 – PRISMA flow diagram. ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.