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Preoperative therapy for localized prostate cancer: A comprehensive overview

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Abstract

At the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, two studies of preoperative systemic therapy for localized prostate cancer garnered significant attention. In the first, investigators evaluated various permutations of conventional hormonal therapies prior to prostatectomy, with detailed biomarker studies focused on tissue androgens. In the second, investigators assessed the novel CYP17 lyase inhibitor abiraterone prior to prostatectomy. Both studies provide a wealth of biological information, but the question remains – will preoperative systemic therapy ultimately be incorporated into clinical algorithms for prostate cancer? Herein, the existing literature for both preoperative hormonal and chemotherapeutic approaches is reviewed. We performed a MEDLINE search of published prospective and retrospective clinical studies assessing preoperative systemic therapy for prostate cancer from 1982 onwards, revealing a total of 75 publications meeting these criteria. Of these, 55 possessed a number of patients (i.e., greater than 10) deemed worthy of the current analysis. Beyond outlining these datasets, we discuss the relevance of clinical and pathologic endpoints in assessing preoperative therapy.

Keywords

Abiraterone; docetaxel; hormone therapy; prostatectomy; surgery; prostate cancer

Introduction

In 2012, an estimated 241,740 cases of prostate cancer will be diagnosed.(1) Several decades ago, a substantial proportion of these patients may have initially presented with metastatic disease. Since the advent of prostate specific antigen (PSA) screening, however, the vast majority of patients present with localized disease (although this trend is subject to change given recent recommendations against PSA screening).(2-3) Several therapeutic

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options exist for the patient with localized disease, such as active surveillance, definitive radiation therapy, and prostatectomy. Currently available clinical guidelines utilize risk stratification schema to define appropriate treatment options. As one example, the National Comprehensive Cancer Network (NCCN) utilizes baseline PSA, Gleason grade and clinical stage to assign either low-, intermediate, or high-risk status.(4) While the tool may be useful in determining candidacy for active surveillance in certain low-risk patients, the decision between surgery and radiation remains challenging.

Although a head-to-head trial comparing surgery and radiation is unlikely to be performed, efforts have been made to independently improve clinical outcome with each of these modalities. One strategy has been to utilize systemic therapy as an adjunct to radiation. A series of randomized trials have confirmed that 3 years of ADT in association with radiation can optimize outcomes for patients with certain high-risk features.(5-6) Such compelling data for adjuvant ADT does not exist following prostatectomy. Adjuvant ADT for 2 years following prostatectomy has recently been suggested to yield excellent long-term outcomes for patients with high-risk disease, with 5-year biochemical recurrence free survival (bRFS) and overall survival (OS) in excess of 92% and 95%, respectively.(7) However, there is no randomized data to support this approach. The use of preoperative ADT is also a controversial topic. In theory, preoperative therapy has the potential to decrease tumor burden and facilitate more complete surgical resection. With newer and more potent hormonal agents (i.e., abiraterone and enzalutamide), there has been renewed interest in studying this approach.(8-9) At the 2012 meeting of the American Society of Clinical Oncology (ASCO), two presentations related to preoperative therapy in prostate cancer were highlighted. In the current review, preoperative therapy trials performed over the past two decades will be reviewed as a means of placing these recent datasets in appropriate context. We performed a MEDLINE search of published prospective and retrospective clinical studies assessing preoperative systemic therapy, revealing a total of 75 publications meeting these criteria. Of these, 55 possessed a number of patients (i.e., greater than 10) deemed worthy of the current analysis.

Preoperative Hormonal Therapy

As highlighted in Table 1, there have been a multitude of efforts to characterize the effect of preoperative hormonal therapy. Several of the larger experiences deserve particular mention, and are detailed in this section. In the largest randomized evaluation of preoperative hormone therapy to date, Schulman *et al* randomized 402 patients with clinically localized prostate cancer (either cT2 or cT3 disease) to either prostatectomy alone or 3 months of goserelin/flutamide followed by prostatectomy.(10) Four-year follow-up results indicate a greater rate of pathological down-staging (i.e., pT stage lesser than the previously defined cT stage) with neoadjuvant therapy (15% *vs* 7%, P<0.01). Furthermore, neoadjuvant therapy led to a lesser frequency of positive margins in patients with both cT2 and cT3 tumors.

Soloway et al reported a second randomized study in which 282 patients with cT2b prostate cancer (age <75 and baseline PSA < 50 ng/mL) were randomized to receive either leuprolide/flutamide followed by prostatectomy or prostatectomy alone.(11) The study was unique in the extended duration of clinical follow-up, with up to 5 years of PSA assessments subsequent to randomization. Though there was a significant decrease in positive margin rate and PSA level, there was little difference in the rate of bRFS with neoadjuvant therapy (64.8% in patients who received ADT followed by surgery *vs* 67.6% in patients who received surgery alone; P=0.66). Interestingly, it was noted that amongst those patients with negative margins at the time of prostatectomy, a greater proportion of patients who had received neoadjuvant androgen ablation experienced biochemical relapse (33% *vs* 17.4%).

In a third large, randomized effort, Prezioso *et al* evaluated 167 patients with clinically localized prostate cancer who met the following eligibility criteria: (1) cT1a-T2b disease, (2) life expectancy in excess of five years, and (3) World Health Organization (WHO) scale performance status 0-2.(12) Patients were randomized to receive leuprolide and cyproterone for 3 weeks prior to surgery, or surgery alone. While no patients exhibited a pathologic complete response (pCR), negative surgical margins were more frequent in the group that received neoadjuvant therapy (61% *vs* 40%). Furthermore, the rate of lymph node involvement (11% *vs* 3%) was higher in this group. With respect to laboratory parameters, PSA and testosterone levels were significantly reduced with neoadjuvant treatment as compared to surgery alone (P=0.0001).

Important insights can also be gleaned from several prospective yet non-randomized efforts. In one such example, Lee *et al* reported data related to 258 patients with cT2-T3 prostate cancer. In this study, 124 patients with cT2b-T3 disease received 3 months of leuprolide with flutamide, while 118 patients with cT2a disease received no hormone therapy – both groups received prostatectomy as definitive treatment. In this study, despite the differences in baseline clinical stage, patients who received neoadjuvant hormone therapy had a lower positive margin rate (15.3% *vs* 49.2%). Furthermore, a substantial proportion of patients (7 of 16, or 43.8%) with cT3 disease were down-staged with neoadjuvant treatment, and most of these patients were disease-free at a median follow-up approaching 4 years.

Similar observations were made by Fair *et al*, summarizing the experience with neoadjuvant hormone therapy at the Memorial Sloan-Kettering Cancer Center.(13) This report included 69 patients with clinically localized prostate cancer treated on a phase II study with 3 months of flutamide and goserelin. The patients were matched to other individuals receiving surgery alone (n=72). The report by Fair *et al* also summarized results from an ongoing phase III study in which 114 patients were to be randomized to surgery alone or a similar preoperative therapy regimen followed by surgery. Overall, it was observed that bRFS was higher in those patients who received neoadjuvant hormone therapy (89% *vs* 86%); however, this difference was not statistically significant. More patients who received neoadjuvant hormone therapy did have organ-confined disease (73% *vs* 56%), and fewer had margin positive disease (17% *vs* 36%). In the face of the subtle difference in bRFS, the implications of these pathologic findings are unclear.

The implications of pT0 disease were more specifically assessed in a series of 174 patients with cT1-3 prostate cancer who received either leuprolide or goserelin in combination with flutamide or bicalutamide for 3 months prior to prostatectomy. Attention was given to those 38 patients in the series who achieved pT0 disease. Using a match-pair analysis (accounting for clinical stage and Gleason score), there was no significant difference in bRFS between the groups. These findings challenge the assertion that the pT0 rates identified in more recent studies could serve as surrogates for long-term outcomes.

Two additional presentations from the 2012 ASCO Annual Meeting address preoperative hormonal therapy for localized disease. First, Mostaghel *et al* reported a prospective effort including 35 patients with intermediate- to high-risk prostate cancer, classified as the presence of a Gleason grade on biopsy ranging from 7-10 and a baseline PSA < 20 ng/mL. (14) The intent of the study was to maximize the degree of intratumoral androgen suppression – previous work from the investigators had demonstrated incomplete suppression using a luteinizing hormone-releasing hormone (LHRH) antagonist alone. (15-16) Patients were treated with 1 of 3 regimens: (1) goserelin and dutasteride (Arm A), (2) goserelin, dutasteride, and bicalutamide (Arm B), or (3) goserelin, dutasteride, bicalutamide and ketoconazole (Arm C). After 12 weeks of therapy with standard doses of these agents, patients received radical prostatectomy. With the assumption that standard

castration (goserelin with bicalutamide) reduces intratumoral dihydrotestosterone (DHT) levels to 1.0 ng/g, the primary endpoint of the study was to demonstrate a decrease in DHT levels by more than 0.7 ng/g. Secondary objectives included analysis of serum androgen levels, assessment of tumor volume, and assays for androgen receptor (AR) and AR-regulated gene expression.

Ultimately, 12 patients were accrued to Arm A, 10 to Arm B, and 13 to Arm C. The median age of the three treatment arms were 62, 66, and 60, and the median PSA values were 11.9, 5.8 and 7.9, respectively. A historical cohort of patients (n=12) receiving goserelin and bicalutamide had a median tissue DHT level of 0.92. By comparison, the DHT level in arms A, B and C were 0.02, 0.04, and 0.02, respectively, thus achieving the primary endpoint of the study. The percentage changes in DHT levels from baseline were similar in the three treatment arms; however, the degree of testosterone reduction was greatest with the four-drug combination of goserelin, dutasteride, bicalutamide and ketoconazole (i.e., Arm C). These results provide *in vivo* demonstration of an anticipated phenomenon – specifically, the 5-! -reductase inhibitor dutasteride (a component of each experimental arm) reduces levels of DHT. With respect to the clinical outcomes in the study, two complete pathologic complete responses (pCRs) were observed (one in Arm B and one in Arm C). In the more liberally defined category of “near pCR” (i.e., ≤ 0.2 cc of residual tumor tissue), there were a total of 7 patients (2 in Arm A, 2 in Arm B, and 3 in Arm C). The implications of these clinical outcomes are more challenging to interpret. As outlined in subsequent sections of this manuscript, there has been no clear link demonstrated between CRs and downstream clinical endpoints, such as bRFS or overall survival (OS).

While Mostaghel *et al* examined hormonal strategies that have long been in place for advanced disease, Taplin *et al* examining neoadjuvant therapy with the novel cytochrome P450 17-hydroxylase-(17,20)-lyase (CYP17 lyase) inhibitor abiraterone.(17) The study design differed from the previous study in several respects. First, patients included in this study had high-risk disease defined by ≥cT3 disease, PSA ≥ 20 ng/mL at baseline, Gleason grade ≥ 7 (4+3), or PSA velocity > 2 ng/mL/yr. Notably, patients with node positive disease were also eligible. Eligible patients were randomized during an initial 12-week phase to receive either LHRH analogue alone (Arm A) or in combination with abiraterone and prednisone (Arm B). After this 12-week period, patients had a biopsy and prostatic androgen levels were assayed in primary tissue - notably, this served as the primary aim of the study. After this 12 week period, all patients enrolled in the study received a further 12 weeks of LHRH analogue, abiraterone, and prednisone followed by prostatectomy. At the time of prostatectomy, the degree of pathologic response was assessed, and AR signaling mediators were also assessed.

A total of 58 patients were enrolled.(17) Over the 24 week span, PSA dropped to near undetectable levels in both arms (0.06 and 0.04 in Arms A and B, respectively). At the time of prostatectomy, 1 of 27 evaluable patients in Arm A had a pCR as compared to 3 of 29 patients in Arm B (P=0.61). A different definition of “near pCR” was employed in this study - specifically, those patients with ≤ 5 mm of tumor remaining fell into this category. In Arms A and B, the rate of near pCR was 11% (3/27) and 24% (7/29), respectively. As with the previously noted study by Mostaghel *et al*, a key problem in interpreting this data is the lack of any existing correlation between pCR rates and bRFS or other endpoints. Furthermore, the varying definitions of “near pCR” across studies challenge the utility of this term.

With respect to the primary endpoint of the study, there was a marked reduction of DHT and dehydroepiandrosterone (DHEA) levels in Arm A and Arm B at 12 weeks (P<0.0001 for both).(17) Other assays of tissue hormones suggest an elevation in pregnenolone and progesterone with abiraterone at 12 weeks (P<0.0001 for both); notably, this phenomenon is

expected with use of a CYP17 lyase inhibitor. Unfortunately, given the limited sample included in this study, it is doubtful that any meaningful correlation with be made between these biomarkers and long-term clinical outcome.

Preoperative Chemotherapy

Until recently, the cornerstone of therapy for mCRPC was docetaxel. Though other chemotherapeutic agents (i.e., mitoxantrone) had previously demonstrated a palliative benefit in mCRPC, two pivotal randomized studies examining docetaxel yielded a survival benefit.(18-20) Several studies of neoadjuvant docetaxel preceded the FDA approval of the drug in 2004 for metastatic, castration-resistant disease.(9) In 2003, Hussain *et al* reported a study including 21 patients with high-risk disease defined as follows: (1) ≥ cT2b, (2) PSA ≥ 15 ng/dL, or (3) Gleason score 8-10. A total of 3-6 cycles of 3-weekly docetaxel/ estramustine were administered prior to local definitive therapy. Of note, the local definitive therapy approach was not consistent – 10 patients ultimately received prostatectomy, while 11 patients received radiation therapy. The definition of response utilized in this report was a unique one – CR was defined as disappearance of palpable abnormalities in the prostate and radiographic evidence of disease, along with a > 90% decline in PSA from baseline. In contrast, partial response (PR) was defined as an improvement in physical and radiographic abnormalities, with a decline in PSA ranging from 50-90% from baseline. With these definitions, 100% of patients on the study demonstrated a response − 52% of patients had a CR, while 48% of patients had a PR. Toxicities were generally modest, with the most frequently reported adverse events (Aes) being neutropenia and anemia.

The combination of docetaxel/estramustine was examined in two other reports. Prayer-Galleti *et al* examined a distinct high-risk cohort, defined by (1) ≥ cT3, (2) PSA ≥ 15 ng/mL, and/or (3) Gleason score ≥ 8.(21) A total of 22 patients were enrolled and treated first with LHRH analogue until PSA stabilization, and then with docetaxel/estramustine. The response criteria used in this study were identical to those in the previous study of Hussain *et al*. Using these guidelines, 15% of patients achieved CR and 80% of patients had a PR. Additionally, of the patients who responded to this neoadjuvant therapy, the 5-year disease-free survival rate was 85%. Narita *et al* studied a similar high-risk population, with the only difference being that patients in this trial had Gleason scores ≥ 9.(22) Patients underwent 12 weeks of complete androgen blockage with leuprolide/bicalutamide followed by 6 weeks of docetaxel/estramustine prior to radical prostatectomy and CR was achieved if the tumor was undetectable. Of the 18 patients who received treatment, 2 patients (11.1%) achieved a pCR. The majority of patients (77.8%) were without disease- or PSA-recurrence at 18 months.

Docetaxel has also been combined with other cytotoxic agents as explored in two reports. Garzotto *et al* reported the effects of neoadjuvant treatment with docetaxel and mitoxantrone for four 28-day cycles in a group of 57 individuals with (1) cT2 or surgically resectable cT3 disease, (2) PSA ≥ 15 ng/mL, and/or (3) Gleason score ≥ 4+3.(23) As might be expected with this aggressive cytotoxic regimen, neutropenia was the most common grade 4 event along with hyperglycemia. While no patients achieved a pCR, 27 of the 54 patients (49.9%) who completed therapy demonstrated 5-year bRFS. Friedman et al explored the efficacy of docetaxel combined with capecitabine with a patient population classified by (1) ≥ cT2 disease, (2) PSA ≥ 15 ng/mL, and/or (3) Gleason score ≥ 8.(24) Fifteen patients were enrolled and completed 3 to 6 courses of therapy. Though all but one patient experienced a drop in serum PSA, only 6 of 15 patients had a 50% or greater decrease in PSA. No pCRs were observed.

Although docetaxel combinations have been more extensively studied in the preoperative setting, there are several examples of studies exploring monotherapy. Febbo *et al* examined

a weekly docetaxel treatment for 6 months prior to radical prostatectomy and its effect on 19 high-risk prostate cancer patients.(25) Specifically, the patient population criteria included (1) ≥ cT3 disease, (2) PSA ≥ 20 ng/mL, and/or (3) Gleason score ≥ 8. No pCRs were observed, and 21% of patients achieved a PR (classified as a 50% decrease in tumor volume). Additionally, short-term docetaxel monotherapy prior to radical prostatectomy was studied by Driecer *et al* with a patient population characterized by (1) ≥ T2bN0M0 disease, (2) PSA ≥ 15 ng/mL, and/or (3) Gleason score ≥ 8.(26) Twenty-nine patients participated and received 6 weekly doses of docetaxel and 28 underwent radical prostatectomy. At roughly 2 years, 71% of patients were disease-free without evidence of biochemical recurrence.

Conclusions/Future Directions

The studies cited herein provide varied approaches to neoadjuvant therapy for localized prostate cancer. Although these efforts include hundreds of patients spanning across multiple trials, preoperative hormonal therapy and chemotherapy presently do not represent a standard of care. Multiple endpoints incorporated in these studies also challenge interpretation of the data. For instance, the definitions of CR reported in these studies vary from a clinical response (i.e., disappearance of palpable nodularities and radiographic lesions) to pathologic response. The metrics used to characterize disease-free survival also vary markedly amongst the studies with have cited, with 2-, 3- and/or 5-year milestones reported. Notably, the clinical significance of these endpoints (i.e., correlation with overall or cancer-specific survival) has not been firmly established. In the setting of metastatic, castratin-resistant prostate cancer, OS has been adopted as a key metric for drug approval. Improvements in OS were observed in the pivotal trials of docetaxel, sipuleucel-T, cabazitaxel, abiraterone, enzalutamide and radium-223.(18-19, 27-31) It is doubtful that neoadjuvant studies in localized prostate cancer will be able to achieve this endpoint for several reasons. First, survival in localized prostate cancer may span over decades, and the magnitude of drug effect must therefore be large to discern even a small difference in survival. Second, even within subsets of localized prostate cancer (i.e., high-risk disease or intermediate-risk disease), patient outcomes are extremely heterogeneous, thereby diluting any treatment effect.

Beyond the clinical endpoints examined, the eligibility for the studies cited in this review vary markedly. For instance, in the aforementioned study by Schulman *et al* randomizing 402 patients to either surgery alone or combined androgen blockade for three months followed by surgery, patients with both cT2 and cT3 disease were enrolled, as were patients with a baseline PSA of up to 100 ng/mL.(10) In contrast, in the experience by Soloway *et al* (which employed a similar randomization), only cT2b patients with a baseline PSA of less than 50 ng/mL were enrolled.(11) With such varied eligibility, any cross-trial comparison of results is virtually impossible. This is not the first time such a dilemma has been encountered. In 1999, the Prostate Cancer Working Group (PCWG) convened to address appropriate eligibility criteria for clinical trials involving patients with progressive prostate cancer despite castrate levels of testosterone.(32) To accommodate subsequent metrics proposed in the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, the PCWG2 criteria were generated, which included an amalgam of PSA assessments and radiographic evaluations.(33-34) The PCWG2 criteria have been adopted by the majority of phase III studies for castrate resistant disease.

The studies highlighted at the 2012 ASCO Annual Meeting underscore another key point. Specifically, the studies presented offer little opportunity to demonstrate any sort of meaningful clinical benefit from the pharmacologic interventions – they were simply underpowered to do so. Rather, the immediate goals were more focused on biological

endpoints.(14, 17) The preoperative setting is unique as pre-treatment and post-treatment tissue can be explored in a manner that does not add risk. The same opportunity does not exist in the context of neoadjuvant therapy preceding definitive radiation. Here, post-treatment biopsies are indicated for research purposes only, and frequently offer a very limited yield of viable tissue. The opportunity to study tumor biology may be essential to the fate of preoperative systemic therapies in localized prostate cancer. While clinical endpoints (i.e., bRFS, pT0 rates, etc.) have not clearly demonstrated a predictive role in defining OS, it is possible that biological endpoints (i.e., changes in intratumoral androgens, etc.) may represent a highly personalized predictive tool. We have recently reported data suggesting that the capture of circulating tumor cells (CTCs) may be feasible in localized prostate cancer.(35) It is our hope that larger studies exploring this phenomenon in the setting of localized disease will yield the same prognostic and predictive value seen in the setting of metastatic, castration-resistant disease.(36)

Preoperative therapy studies also offer a chance to confirm antitumor mechanisms for novel agents. For example, phase I study of the clusterin antisense oligonucleotide clusterin was reported in 2005. In this study, 25 patients with localized prostate cancer received one month of therapy.(37) Pharmacodynamic studies showed dose-related increases in OGX-011 concentrations in prostate tissue, and dose dependent decreases in clusterin expression both by polymerase chain reaction (PCR) and immunohistochemistry (IHC). Notably, this report preceded publication of studies in mCRPC, where combinations of docetaxel and OGX-011 were explored.(38-39) Several other examples of either ongoing or completed studies are listed in Table 3 – agents such as ipilimumab and bevacizumab, which have been explored in the setting of more advanced disease, are being closely examined in the preoperative setting.(40-41)

As a general paradigm, prostate cancer therapeutics approved for late-stage disease have taken a trajectory in which they are explored in earlier disease settings. Abiraterone, for instance, was assessed in the post-docetaxel setting in the COU-AA-301 study, and more recent data from the COU-AA-302 study now suggests efficacy in the setting of chemotherapy-naïve patients.(8, 42) A Southwest Oncology Group (SWOG) trial is now assessing abiraterone in those patients who have had an initial suboptimal PSA response to ADT, and the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study will explore abiraterone in patients with newly diagnosed metastatic disease.(43-44) If these efforts prove successful, they may move abiraterone even further forward in the course of disease treatment. The lessons learned from the preoperative studies cited herein will be particularly important – specifically, the academic community should strive to: (1) develop standardized metrics for response assessment and (2) evaluate the implications of surrogate endpoints (i.e., pCR and disease-free survival). Until this occurs, it may be difficult to translate efforts taken in the preoperative setting to improvements in patient care.

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Competing Interest

Sumanta K. Pal, MD: “I declare that I participated in the concept and design, collection and assembly of data, manuscript writing and final approval of the manuscript. I have no potential conflicts of interest to disclose.”

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Table 1

Studies assessing neoadjuvant hormonal approaches in high-risk localized prostate cancer. (pCR rate = pathologic complete response rate; PFS = progression-free survival; OS = overall survival; NR=Not reported; RP = radical prostatectomy).

Author	Year	N	Patient Population	Study Design	pCR Rate
Schulman *et al*(10)	2000	402	cT2-T3, PSA < 100 ng/mL	Goserelin/Flutamide × 3 months → RP *vs* RP alone	5/191(3%)
Witjes *et al*(45)	1997	354	cT2- T3	Goserelin/Flutamide× 3 months → RP *vs* RP alone	4/164 (2%)
Soloway *et al*(11)	2002	282	cT2b, PSA < 50ng/mL	Leuprolide/Flutamide × 3 months → RP *vs* RP alone	0/121 (0%)
Fair *et al*(46)	1999	274	cT1-T2	Goserelin/Flutamide → RP	4/139(3%)
Lee *et al*(47)	1997	258	cT2-T3	Leuprolide/Flutamide × 3 months → RP	1/16 (6%)
Klotz *et al*(48)	2003	213	cT1b-T2c	Cyproterone acetate × 3 months → RP *vs* RP alone	0/112 (0%)
Prezioso *et al*(12)	2004	167	cT1a-T2b	Leuprolide × 3 months) + Cyproterone acetate × 3wks → *vs* RP alone	0/81 (0%)
Gleave et al(49)	2000	156	cT1c-T3a, Gleason≥7 or PSA ≥10 ng/mL	Cyproterone acetate/Diethylstilbesterol or Leuprolide/Flutamide × 8 months → RP	20/156 (13%)
Cookson et al(50)	1997	141	cT1b-T3, PSA < 50 ng/mL	Goserelin/Flutamide × 3 months	3/69 (4%)
Taplin et al(17)	2012	56	cT3, Gleason ≥ 3+4, or PSA ≥ 20 ng/mL	LHRH agonist → RP *vs* LHRH agonist/abiraterone/prednisone → RP	4/56 (7%)
Dalkin et al(51)	1996	56	cT1c-T2a, PSA > 4ng/mL	Goserelin Acetate × 3 months → RP *vs* RP alone	0/28 (0%)
Aus et al(52)	1994	56	cT1b-T3a	Tripterolin/Cyproterone acetate × 3 months → RP	0/28 (0%)
Berglund *et al*(53)	2012	55	cT3-T4	Goserelin/Flutamidex 4 months → RP	1/50 (2%)

Table 2

Studies assessing neoadjuvant chemohormonal approaches in high-risk localized prostate cancer. (pCR rate = pathologic complete response rate; PFS = progression-free survival; OS = overall survival; NR=Not reported)

Author	Year	N	Patient Population	Study Design	Responce Definition	pCR Rate
Narita *et al* (22)	2012	18	(1) cT3, (2) Pre-op PSA ≥ 15 ng/mL, and/or (3) Gleason 9/10	Phase 2: Leuprolide/Bicalutamide × 3 months, then Docetaxel/ Estramustine × 1.5 months	CR: Complete eradication of tumor, no detectable viable cell in whole specimen.	2/18 (11.1%)
Garzotto *et al* (23)	2010	57	(1) cT2 or resectable cT3a, (2) PSA ≥ 15 ng/mL, and/or Gleason grade ≥ 4+3	Phase I/II: Docetaxel/Mitoxantrone × 4 months	CR: Complete eradication of tumor.	0/54 (0%)
Chi *et al*(54)	2008	72	(1) cT2 or cT3, (2) PSA ≥ 10 ng/mL, and/or (3)Gleason grade ≥ 7	Phase II: Docetaxel/buserelin acetate × 6 months	CR: Complete eradication of tumor.	2/64 (3%)
Friedman *et al*(24)	2008	15	(1) cT2 or greater (2) PSA ≥ 15 ng/mL, and/or (3) Gleason grade ≥ 8	Phase II: Docetaxel/Capecitabine × 3-6 months	CR: Complete eradication of tumor.	0/15 (0%)
Prayer-Galetti *et al*(21)	2007	22	(1) cT3 or greater (2) PSA ≥ 15 ng/mL, and/or (3) Gleason grade ≥ 8	Phase II: Triptorelin until PSA nadir, then Docetaxel/Estramustine × 4 months	CR: No palpable lesion, no radiographic e/ o disease, > 90% decline in PSA from baseline	3/21 (14%)
Febbo *et al*(25)	2005	19	(1) cT3 (2) PSA > 20 ng/mL, and/or (3) Gleason grade 8-10 or ≥ 4+3	Phase II: Docetaxel × 6 months	CR: Complete eradication of tumor	0/19 (0%)
Berger *et al*(55)	2004	5	(1) cT2 and/or (2) Gleason grade 8	Phase II: Docetaxel × 6 months	CR: Complete eradication of tumor	0/5 (0%)
Driecer *et al*(26)	2004	29	1) cT2bN0M0 (2) PSA ≥ 15 ng/mL, and/or (3) Gleason grade ≥ 8	Phase II: Docetaxel × 1.5 months	CR: Complete eradication of tumor	0/29 (0%)
Hussain *et al*(56)	2003	21	1) cT2b or greater (2) PSA ≥ 15 ng/mL, and/or (3) Gleason grade 8-10	Phase I/II: Docetaxel/Extramustine × 3-6 months	CR: No palpable lesion, no radiographic e/ o disease, > 90% decline in PSA from baseline	11/21 (52%)

Table 3

Trials assessing targeted agents and other novel therapeutics for prostate cancer in the neoadjuvant setting.

Idetifier	N	Estimated Completion	Study Design	Objectives
NCT01088529(57)	66	Mar 2013	Randomized phase II: Abiraterone + LHRH analogue *vs* LHRH analogue	!! 1°: Rate of < pT2 stage !! 2°: Changes in androgen levels !! 2°: Differences in positive margin rate !! 2°:Safety profile
NCT00321646(58)	42	Dec 2011	Phase II: Docetaxel + bevacizumab	!! 1°: Efficacy !! 2°: Safety
NCT00715104(59)	40	Dec 2011	Phase II: Sipuleucel-T	!! 1°: Immune response within prostate tissue !! 2°: Other immunologic and immunohistochemical assays
NCT00809458(60)	15	Aug 2012	Phase II: Vitamin E	!! 1°: Reduction in serum biomarkers, including PSA !! 2°: Safety/tolerability
NCT00828308(61)	30	Dec 2011	Phase II: Ixabepilone	!! 1°: PSA response at 12 weeks
NCT01547299(62)	50	Aug 2013	Randomized Phase II: MDV3100 *vs* MDV3100 + leuprolide/dutasteride	!! 1°: pCR rate !! 2°: PSA response !! 2°: Positive margin rate !! 2°: Testosterone and DHT !! Safety and tolerability
NCT01194271(63)	20	Sep 2014	Phase II: Ipilimumab + leuprolide etc.)	!! 1°: Immunologic markers (NY-ESO1, CD4+ICOS+ T-cells, effector T-cells, etc
NCT01385059(4)	46	Jul 2013	Randomized phase II: *vs* observation	!! 1°: Pre-metastatic niche density Axitinib !! 2°: Time to biochemical recurrence !! 2°: STAT3 levels