**Investigational Product(s):**
Control arm of phase III Ipilimumab trial in post-docetaxel patients with advanced prostate cancer

**Investigator Name & Contact Information:**
- Please include first/last name and contact information.

Guru Sonpavde, MD  
Department of Medicine,  
Division of Hematology-Oncology, UAB Comprehensive Cancer Center,  
1824 6th Ave. S., WTI-520A  
Birmingham, AL 35294, USA  
E-mail: gsonpavde@uabmc.edu  
Phone: 1-205-975-3742, Fax: 1-205-975-9310

**Institution Name:**
- Please list the institution that will serve as the investigational site.

UAB Comprehensive Cancer Center (Birmingham, AL, USA) and McMaster University (Ontario, Canada)

**Study Title:**
- Please be as descriptive as you can.

Individual patient level analysis of control arms of randomized trials to assess impact of single agent daily prednisone on outcomes and toxicities in metastatic castration-resistant prostate cancer

**Study Rationale:**
- Provide a brief description of the research question and the rationale of how this study addresses the question. Provide a rationale and references, if applicable.

**Introduction**
Daily low dose oral prednisone has been commonly employed for the therapy of men with metastatic castration-resistant prostate cancer (mCRPC). Two randomized phase III trials in the 1990s compared low dose daily oral corticosteroids (either prednisone or hydrocortisone) with the combination of corticosteroid and mitoxantrone chemotherapy [1, 2]. Both trials demonstrated an improved palliative impact from the addition of mitoxantrone to corticosteroids, although corticosteroids alone did demonstrate a modest palliative benefit. Thereafter, the landmark phase III TAX327 trial comparing docetaxel-based chemotherapy with mitoxantrone-based chemotherapy administered oral prednisone (P) 10 mg daily to both arms [3]. Subsequent randomized trials attempting to combine biologic agents with docetaxel and evaluating cabazitaxel chemotherapy also administered daily oral P [4, 5]. P was combined routinely with abiraterone acetate and TAK700 (oroteronel) to mitigate mineralocorticoid excess [6-8]. However, the randomized phase III trials evaluating enzalutamide, radium223, sipuleucel-T and ipilimumab had control arms without P [9-13].

**Impact and necessity of daily prednisone is unknown**
Indeed, trials containing P alone in one of the arms have consistently demonstrated a modest palliative impact and PSA responses in ~15% of patients [1, 2, 6, 7, 14, 15]. P alone may suppress production of testosterone and symptomatic relief was associated with declines in adrenal androgens, androstenedione
and DHEAS, in one study [16]. Preclinically, suppression of angiogenesis by decreasing VEGF and IL-8 production mediated by binding to the glucocorticoid receptor has been demonstrated [17]. Conversely, even low dose daily corticosteroids can induce toxicities such as hyperglycemia, bone loss, myopathy, edema, hypertension and infections and potentially counteract the benefits of immunotherapy. It must also be emphasized that in this era with multiple active agents and better survival, once P is initiated, physicians tend to continue P indefinitely, a greater magnitude of cumulative toxicities from P may be observed. Moreover, prednisone may have tumor promoting effects mediated by binding to glucocorticoid receptors and antagonizing androgen pathway inhibition [18].

However, the impact of daily P on survival, as a single agent or in combination, remains unclear. Moreover, an extended period of prednisone may induce toxicities, exacerbate comorbidities and attenuate the benefits of sipuleucel-T immunotherapy [19]. The utility of P has assumed greater importance recently. Questions remain regarding the efficacy of sipuleucel-T immunotherapy following or preceding P containing therapy. A randomized phase II trial reported no negative impact on the immune response and manufacture of sipuleucel-T administered concurrently or sequentially with abiraterone acetate plus P, although impact on OS is unknown [20]. A retrospective analysis of the phase III AFFIRM trial suggested that baseline P use conferred inferior survival with both placebo and enzalutamide [21]. The results of this AFFIRM analysis suggest that patients receiving baseline P may have been selected for more symptomatic and aggressive disease prompting the institution of P. Indeed another retrospective analysis of the COU-AA-301 phase III trial comparing P combined with placebo or abiraterone acetate could not demonstrate a strong independent negative impact of baseline corticosteroid use, although the subsequent use of P in all patients on the trial may have obscured an impact of baseline corticosteroid use [22].

One trial-level meta-analysis of randomized trials in mCRPC suggests no significant impact on severe toxicities and OS with the use of daily oral P [23]. There was no statistically significant difference between subjects in the non-P and P groups for severe toxicities (IRR = 0.82, p = 0.712), toxicities as a reason for discontinuing trial therapy (RR = 1.24, p = 0.413) and OS (HR = 1.09, p = 0.531). A sub-analysis excluding 2 trials that contained docetaxel in only one arm demonstrated that the non-P groups exhibited significantly higher severe toxicities (IRR = 1.40, p = 0.007), higher toxicities as a reason to discontinue therapy (RR = 1.39, p = 0.017) and decreased survival as compared to subjects in the P groups (HR = 1.35, p = 0.002). However, this study had limitations of a trial level meta-analysis. Individual patient level data were unavailable to evaluate a potential differential benefit of P in those with poorer performance status or higher risk groups. The Scher and Small trials administered conventional docetaxel every 3 weeks plus P (DP) in one of the arms [24, 25]. However, the experimental arms contained weekly docetaxel combined with either DN101 or GVAX. Notably, in contrast to docetaxel every 3 weeks, docetaxel administered weekly has a different toxicity profile (especially less myelosuppression) and does not appear to extend OS compared to mitoxantrone [3]. Both the Scher and Small trials reported an inferiority of OS for the experimental arms, which may be a consequence of weekly docetaxel and/or a decrement due to DN101 or GVAX. Regarding the Fossa et al trial, the comparison of flutamide with P is not as optimal as a design comparing flutamide vs. flutamide plus prednisone to identify effects attributable solely to P [26]. The Petrylak trial combined D with estramustine phosphate, a drug almost abandoned in mCRPC due to toxicities [27]. The P containing arm in the Petrylak trial also administered mitoxantrone, which was proven to be inferior to D plus estramustine phosphate for OS, despite toxicity advantages. Finally, the Higano trial compared DP with single agent GVAX, although most patients in the GVAX arm did subsequently receive D, which may have led to the lack of statistical difference in and confounded the OS endpoint [28]. Moreover, the experimental arm contained a highly tolerable immunotherapeutic agent, while the standard P containing arm administered a chemotherapeutic agent, docetaxel, with significant toxicities.

Rationale to pool data from control arms of recent phase III trials to assess the impact of prednisone on survival and toxicities
While brief courses of corticosteroids confer palliative benefits, it is unclear if long-term daily oral prednisone confers more benefits than risks. A more comprehensive study to estimate the risk of toxicities and impact on overall survival (OS) with the use of daily oral prednisone is warranted. However, a prospective trial is unlikely to be conducted to probe this issue. Hence, we propose a pooled analysis of control arms of recent randomized trials, which either administered or did not administer prednisone. Additionally, recent trials conducted in the era of availability of docetaxel, i.e. pre-docetaxel vs. post-docetaxel patients, will enhance interpretability since the same prognostic factors may be associated with varying survivals if exposed to variable agents. These data will assist in designing trials and also improve clinical practice. For example if daily prednisone has no independent impact on OS, but does increase toxicities, a rationale can be made to avoid daily prednisone in daily practice and in control arms of randomized trials. Conversely, if an
independent favorable impact on survival is seen coupled with no excessive increase in toxicities, daily long-term oral prednisone may be justified.

Hypothesis
- Clearly state the specific hypothesis to be tested.

Oral daily prednisone has palliative benefits and does not have excessive toxicities but does not extend overall survival

Primary Objective(s) / Endpoint(s)
- Provide the main goal of the study and the study population. Provide a detailed definition that is directly linked to the primary objective. In some cases, the detailed description may be more appropriate in the statistical section. Novel or unconventional endpoints may require explanation in the rationale section. The primary endpoint will be linked to the justification of the sample size.

To conduct a retrospective analysis of control arms of randomized trials to evaluate the impact of daily oral single-agent prednisone:
1. efficacy outcomes (OS, PFS, PSA response, RECIST response)
2. toxicities: all grades and grade ≥3, and prednisone-specific toxicities

Secondary Objective(s) / Endpoint(s)

As above

Treatment:
- Please provide if applicable: specify dose, schedule, duration, any pre-medications, etc.

Study design

Study eligibility
There is no intervention since this is a retrospective study. Four randomized phase III trials (see table below) with a control arm including single agent placebo (or no anti-cancer therapy) or single-agent prednisone (+/- placebo) will be eligible for analysis. Patients on prednisone at baseline before trial initiation will be excluded from analysis and those receiving prednisone in combination with other agents will be excluded. Randomized trials conducted in the post-docetaxel era will be eligible, i.e. trials should explicitly state pre or post-docetaxel setting; this will ensure a more homogeneous control arm across trials.

Collected variables
Efficacy outcomes (OS, PFS, PSA response, pain response, RECIST response) and toxicity outcomes (toxicities of all grades and grade ≥3 toxicities) will be collected, with special emphasis on hyperglycemia, hypertension, hypokalemia, skeletal related events and edema. Baseline variables collected are: Eastern Cooperative Oncology Group performance status, disease site, lactate dehydrogenase, opioid analgesic use, albumin, hemoglobin, prostate-specific antigen, and alkaline phosphatase.

Study Population
- Please provide if applicable: specify age, gender, and other demographic information for trial population.


Sample Size and Sample Size Justification
- The sample size must reference the primary endpoint.
<table>
<thead>
<tr>
<th>Author</th>
<th>Control arm N (evaluable for efficacy)</th>
<th>Phase of trial (2 or 3)</th>
<th>Control arm N (evaluable for toxicities)</th>
<th>Pre or post-docetaxel</th>
</tr>
</thead>
</table>
| Trials with control arms containing Prednisone  
| Trials with control arms NOT containing Prednisone  
| Nelson, 2012 [33]      | N/A                                    | 3                        | 295                                      | Pre                   |

**Key Inclusion Criteria**
- List the inclusion criteria necessary to support the trial design and drug safety requirements.

Randomized phase II trials with a control arm including single agent placebo (or no anti-cancer therapy) or single-agent prednisone (+/- placebo) will be eligible for analysis. Patients on prednisone at baseline before trial initiation will be excluded from analysis and those receiving prednisone in combination with other agents will be excluded. Randomized trials conducted in the post-docetaxel era will be eligible, i.e. trials should explicitly state pre or post-docetaxel setting; this will ensure a more homogeneous control arm across trials.

**Key Exclusion Criteria**
- List the exclusion criteria necessary to support the trial design and drug safety requirements.

As above

**Study Assessments**
- Specify type and frequency of safety, efficacy, and outcome measures. Also indicate the method(s) used to assess measures.

See above in design section

**Correlative Studies**
- If applicable, please specify here.

None

**Data and Statistical Plan**
- Describe the planned statistical analysis including timing of the primary and secondary measurements and sample size calculation. The range of sophistication will depend on a number of factors, including the size and complexity of the study. At a minimum, the statistical assumptions surrounding the reporting of the primary endpoint should be included.
Patients from the control arm of randomized phase III trials in the pre or post-docetaxel settings will be pooled. Patients on prednisone at baseline before trial initiation will be excluded from analysis. Univariable and multivariable Cox regression analyses will evaluate the prognostic ability of candidate factors on efficacy outcomes (with primary endpoint of overall survival and secondary endpoints of PFS, PSA response, pain response, RECIST response) and toxicity outcomes- also see Excel spreadsheet attached with requested variables. The variables evaluated in the analysis will include prednisone intake status (yes vs. no), setting of therapy (pre vs. post-docetaxel) and pre-defined candidate prognostic factors will be based on recently described prognostic factors derived from patients receiving docetaxel: Eastern Cooperative Oncology Group performance status, disease site (visceral, bone +/-LN, LN only), lactate dehydrogenase, opioid analgesic use, albumin, hemoglobin, prostate-specific antigen, and alkaline phosphatase [29]. Additionally, neutrophil and lymphocyte counts at baseline will be obtained based on recent data showing its independent impact on OS [30, 31]. Toxicities of all grades and grade ≥3 toxicities will be collected, as well as data for hyperglycemia, hypertension, hypokalemia, skeletal related events and edema. Time from The Kaplan-Meier method will be used for to estimate overall survival within selected subgroups. Validation of factors previously hypothesized to be prognostic will be performed using the entire dataset. All analyses will be two-sided and statistical significance will be defined at the α=0.05 level.

References

- List references, studies, and sources that support the study design.


[21] Scher HI FK, Saad F, Chi K, Taplin M, Stemberg CN et al. ASSOCIATION OF BASELINE CORTICOSTEROID WITH OUTCOMES IN A MULTIVARIATE ANALYSIS OF THE PHASE 3 AFFIRM STUDY OF ENZALUTAMIDE (ENZA), AN ANDROGEN RECEPTOR SIGNALING INHIBITOR (ARSI. ESMO Congress September-October 2012, Vienna, Austria, abstract 899PD.


Other Important Information / Consideration
- Please be as descriptive as possible.

Approvals have been obtained from the respective sponsors to receive the other 3 non-BMS trial datasets

Supplemental/Supporting Information attached  X  Yes  No