



## Platinum Priority – Editorial

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# The Balancing Act: Assessing Treatment Burden Versus Treatment Benefit with Evolving Metastatic Hormone-sensitive Prostate Cancer Data

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In this issue of *European Urology*, the STAMPEDE investigators report results from the arduous and very worthy task of retrospectively annotating the risk status of the patients treated with testosterone suppression with or without abiraterone using existing clinical categorizations [1]. The team was motivated to provide regulatory bodies with the requisite data to determine whether to extend the approval of abiraterone to also include patients with low-risk metastatic hormone-sensitive prostate cancer (mHSPC).

In the absence of precise biomarkers to identify who and by how much an individual patient would benefit from a given treatment, decision-making relies on (1) the treatment burden including treatment-related death for a given patient with given comorbidities, and (2) the absolute benefit for a given treatment. While robust efforts to define biological prognostic and predictive biomarkers of benefit are ongoing, we are left with clinical features as criteria. The LATITUDE [2] and CHAARTED [3] risk categorizations were based on prognostic factors from prior phase 3 trials. As with any classification and biomarker work, there is some inherent misclassification and neither definition accounts for important differences between patients who present with metastatic disease and those who develop metachronous metastases after prior local therapy (prostatectomy or radiation). Recent analyses of GETUG15 and CHAARTED and a Dana Farber Cancer Institute hospital registry revealed three distinct groups [4,5]:

1 Patients with high-volume de novo metastatic prostate cancer have median overall survival (OS) of ~3 yr. This is

basically the same median OS as for patients on testosterone suppression alone (and possibly with prednisone or weak nonsteroidal anti-androgens [NSAA)s) in LATITUDE, GETUG, CHAARTED, and ENZAMET patients with high-volume disease.

- 2 Patients with de novo low-volume disease or prior local therapy and high-volume disease have median OS of ~4.5 yr.
- 3 Patients with prior local therapy and starting hormonal therapy for low-volume metastatic disease have median OS of ~8 yr.

The authors clearly state that their results only apply to patients with de novo low-risk disease, as patients with prior local therapy were not accrued to LATITUDE and accounted for approximately 5% of STAMPEDE patients. There is no doubt that there is a need for consensus on risk categorization and harmonization of clinical trial conduct so that the whole disease spectrum is represented. This would mean that results would be more informative for routine clinical care. One aspect that may also need to be taken into account is patients who relapse with metastatic disease after prior adjuvant hormonal therapy (and not “hormone-naïve” and possibly less “sensitive” to testosterone suppression). Moreover, the LATITUDE classification also requires Gleason score and some patients may not have undergone prostate biopsy if they were treated on the basis of clinical criteria or underwent metastasis biopsy.

Let us consider two extremes in light of all the new data and therapies. At one end is a fit 55-yr-old man with no comorbidities who presents with high-volume disease. In

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this setting, docetaxel, abiraterone, enzalutamide, and apalutamide have all been proven to be beneficial in combination with testosterone suppression. At the other extreme is a 78-yr-old man with congestive heart failure who underwent prostatectomy for Gleason 8 prostate cancer 8 yr previously and now has two bone metastases. In this setting it is not clear whether he would benefit from anything more than testosterone suppression alone. In short, in routine clinical care, clinicians and patients make decisions that balance the treatment burden against the treatment benefit. It is for this reason that OS is such an important endpoint as it takes into account the totality of the treatment burden (including treatment-related deaths) and benefit (including the impact of salvage systemic therapy for a rising prostate-specific antigen with castrate levels of testosterone) when choosing first-line therapy on starting testosterone suppression. It is interesting to observe that a 5-yr OS benefit of 2.9% on adding nilutamide or flutamide (weak NSAA with a low cost and side-effect profile) to testosterone suppression was not considered a standard of care as evidenced by only one (ENZAMET) of the seven studies that included a weaker NSAA as the control arm in phase 3 trials.

The data for abiraterone in the current paper further document the approximate 20% absolute improvement in 3-yr OS, with a hazard ratio (HR) of approximately 0.65 for addition of docetaxel, abiraterone, apalutamide, or enzalutamide to testosterone suppression for patients with “high-risk/volume” disease. This is very clear evidence of a high likelihood of benefit for patients who are able to tolerate the additional agent. By contrast, the 5% absolute OS benefit, albeit with a HR of 0.66, requires more patient-specific deliberation. The observation that the 7% absolute improvement in prostate cancer–specific mortality suggests that the OS benefit may be diluted by deaths from other causes because of the longer OS for patients with low-volume disease managed with testosterone suppression alone,

which may or not be compounded by long-term co-administration of prednisone and the insidious metabolic and cardiac impact of long-term CYP17A1 inhibition and low-dose prednisone. To address this, the authors reported that the number need to treat (NNT) to prevent one death by 3 yr is five patients for de novo high-risk disease and 20 patients for de novo low-risk disease. It is also clear that trial data represent patients enrolled in and closely monitored on clinical trials. In many cases clinical trial data over-represent the benefits and underestimate the adverse event profile (including treatment-related deaths) in routine practice. This is especially relevant for cytotoxics such as docetaxel [6].

In addition, these new abiraterone data should be considered in the light of results from the other studies that have reported OS outcomes in high- and low-volume disease. We currently have two trials with direct evidence of a benefit from docetaxel in high-volume but not low-volume disease [4]. The long-term OS results for patients with low-volume mHSPC in the STAMPEDE docetaxel arm, which will be presented after this editorial is written, will need to be interpreted in light of (1) the fact that the patients will nearly all have presented with de novo metastatic disease, and (2) the clear direct documentation of OS benefits among patients with low-volume disease on the oral hormonal therapies (abiraterone, enzalutamide [7], and apalutamide [8]) and those undergoing radiation to the primary tumor if presenting with de novo disease [9]. Moreover, these therapies all have less acute life-threatening adverse events. It is also of note that although the event rates are still low among patients who did not present with de novo metastatic disease in TITAN (18 of 144 died) and ENZAMET (88 of 473 died), and most of these patients had low-volume disease, the OS HRs are 0.40 (95% confidence interval [CI] 0.15–1.03) and 0.72 (95% CI 0.47–1.09) on the respective forest plots.

**Table 1 – Summary of data with some direct evidence of an overall survival benefit as of August 2019.<sup>a</sup>**

Patient comorbidity	Metastatic burden <sup>b</sup>	Agent to add to testosterone suppression
Chemofit <sup>c</sup>	High volume	Docetaxel
		Abiraterone
		Apalutamide
		Enzalutamide
Not chemofit	High volume	Abiraterone
		Apalutamide
		Enzalutamide
Chemofit and not chemofit De novo metastatic disease	Low volume	Abiraterone
		Apalutamide
		Enzalutamide
		Or radiation of the primary tumor <sup>d</sup> (Docetaxel: to be decided) <sup>e</sup>
Chemofit and not chemofit Prior local therapy <sup>f</sup>	Low volume	Apalutamide <sup>g</sup>
		Enzalutamide <sup>g</sup>

<sup>a</sup> These are not treatment recommendations; choices should be based on patient-physician discussion and availability/affordability.

<sup>b</sup> CHAARTED definition.

<sup>c</sup> Able to tolerate docetaxel at 75 mg/m<sup>2</sup> every 3 wk.

<sup>d</sup> Unknown if docetaxel or new hormonal therapies add to radiation or if radiation adds to docetaxel or new hormonal therapies.

<sup>e</sup> Data to be presented at the European Society for Medical Oncology 2019 congress.

<sup>f</sup> Prior prostatectomy or radiation with curative intent.

<sup>g</sup> Data very immature and incomplete.

In conclusion, clinicians and patients need to make treatment decisions based on rapidly evolving data showing improvement in OS with the judicious early use of docetaxel or the new oral hormonal therapies or radiation to the prostate in low-volume de novo mHSPC. It should be noted that although resistance mechanisms will probably evolve with the use of systemic therapies, there is no clinical evidence that earlier use of these agents in mHSPC results in earlier induction of the neuroendocrine or anaplastic disease that shortens OS. We are actually seeing the opposite, as longevity increased with earlier use. Moreover, it is incumbent on the research community to harmonize patient risk categorization and identify biomarkers (and efforts are under way for both) so that we have more accurate information when balancing treatment burden against treatment benefit for an individual patient. **Table 1** summarizes the direct OS benefit documented by drug and patient subgroup as of August 2019, recognizing the inherent limitations because of incomplete and/or immature data and/or subgroup analyses and could well be out of date at the time of publication. Moreover, the table is agnostic to cost of and access to the new agents and does not address the issue of revisiting treatment breaks for patients experiencing deep remissions and destined to be on therapy for many years. Nor does it address the potential benefits of oligometastatic radiation, which is now being addressed in clinical trials. Nonetheless, it is a proposed framework for the current state of the art and can be updated as new data emerge.

**Conflicts of interest:** Christopher J. Sweeney has stock or other ownership interest in Leuchemix; has acted in a consulting or advisory role for Sanofi, Janssen, Astellas Pharma, Bayer, Genentech, AstraZeneca, Pfizer, Tolmar, Celgene, and Eli Lilly; has received institutional research

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