



## Going towards a precise definition of the therapeutic management of de-novo metastatic castration sensitive prostate cancer patients: How prognostic classification impact treatment decisions

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### ABSTRACT

De-novo metastatic castration sensitive prostate cancer (mCSPC) is a subgroup of prostate cancer associated with poor prognosis. Recently, the treatment of mCSPC has been enriched by new life-prolonging options, including the combination of docetaxel or abiraterone acetate with androgen deprivation therapy (ADT). Of note, the advantage of chemohormonal therapy was more relevant in the subgroup of high-volume disease compared to low-volume, while the survival prolongation of abiraterone was observed only in high-risk patients. Choosing the most appropriate therapy is one of the most debated issues. This review describes the latest news on de-novo mCSPC to better outline patients' management. At the ESMO 2018 Congress two novel studies focused on this setting have been presented, trying to define the role of radiotherapy to the primary tumour and the efficacy of abiraterone acetate in the subset of low-risk patients. We have analysed these results in light of the evidence already available.

### 1. Introduction

A small (approximately 4% in Western Countries) but clinically significant subset of prostate cancer (PC) patients presents with metastatic disease at the time of diagnosis, outlining a condition known as de-novo metastatic castration sensitive PC (de-novo mCSPC). De-novo mCSPC is an aggressive disease characterized by shorter time of development of castration resistance and worse overall survival (OS) compared to PC with metachronous metastases after curative treatments (Mosillo et al., 2018). This subgroup includes a wide heterogeneous spectrum of different biological and clinical patterns, ranging from indolent conditions (asymptomatic patients with low tumor burden) to more aggressive forms (high Gleason score, low PSA values, symptomatic patients with extensive bone involvement and/or visceral metastases) (Mosillo et al., 2018; Iacovelli et al., 2018a).

The recent interest towards this peculiar metastatic castration-sensitive disease setting comes from the demonstration of a survival

advantage of two therapeutic approaches (the early combination of docetaxel or abiraterone acetate plus androgen deprivation therapy – ADT –), which have modified the historical treatment algorithm and dramatically improved the patients' prognosis (Kyriakopoulos et al., 2018; Fizazi et al., 2017; James et al., 2016, 2017). Unfortunately, these two strategies have not been directly compared. Moreover, the prognostic classifications used for stratifying mCSPC patients and guide treatment selection are different. Indeed, the CHARTED criteria classified patients based on the disease volume; the high-volume (HV) was defined by the presence of visceral metastases or  $\geq 4$  bone lesions with  $\geq 1$  beyond the vertebral bodies and pelvis, while low-volume (LV) included patients that did not meet the above criteria. The LATITUDE classification included only patient with high-risk (HR) disease based on the presence of at least two criteria among presence of visceral metastases, number of bone lesions  $\geq 3$  or Gleason score  $\geq 8$  (Fig. 1).

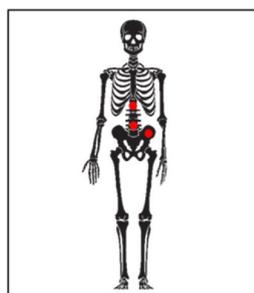
To further confirm the scientific relevance of outlying the proper management of de-novo mCSPC, at the ESMO 2018 Congress two novel

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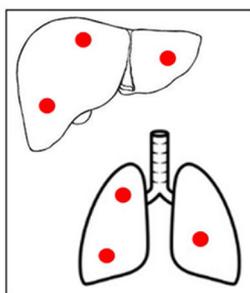
E-mail addresses: [roberto.iacovelli@alice.it](mailto:roberto.iacovelli@alice.it), [roberto.iacovelli@policlinicogemelli.it](mailto:roberto.iacovelli@policlinicogemelli.it) (R. Iacovelli).

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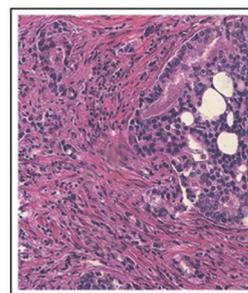
Definition of **High-Risk** disease according to LATITUDE study  
(At least two of the following criteria)



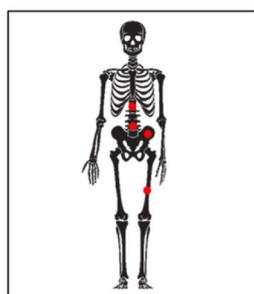
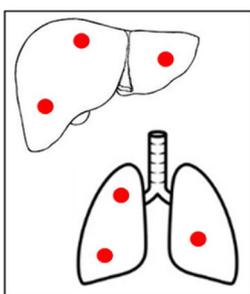
3 or more bone mets



Visceral mets

Gleason score  $\geq 8$ 

Definition of **High-Volume** disease according to CHAARTED study  
(At least one of the following criteria)

4 or more bone mets  
(with at least one outside  
the pelvis/column)

Visceral mets

Fig. 1. Prognostic classification criteria of de-novo mCSPC according to CHAARTED and LATITUDE trials.

studies focused on this setting have been presented, trying to define the role of local treatments to the primary tumour and the efficacy of abiraterone acetate in the subset of low-risk patients (Hoyle et al., 2018; Parker et al., 2018). This review aims at delineating the recent news regarding the management of patients with de-novo mCSPC.

### 1.1. The efficacy of abiraterone acetate in the subset of low-risk mCSPC patients

ADT has been considered for long time the cornerstone of mCSPC treatment, with median OS of about 42 months. Recently, two new life-prolonging options – docetaxel and abiraterone acetate concurrent to ADT – have enriched the therapeutic armamentarium for this disease, by demonstrating to enhance the antitumor activity, delay the development of resistance, and improve the patients' prognosis (Kyriakopoulos et al., 2018; Fizazi et al., 2017; James et al., 2016, 2017).

In particular, the CHAARTED trial demonstrated a statistically significant and clinically relevant survival benefit of more than 13 months for the early combination of docetaxel plus ADT compared to ADT alone (mOS 57.6 vs. 44 months; HR 0.61;  $p < 0.001$ ). Of note, when stratifying patients based on the disease volume, the superiority of early chemo-hormonal therapy was even more marked in the subgroup of HV disease (mOS 51.2 versus 34.4 months; HR, 0.63;  $p < 0.001$ ). On the contrary, median OS did not differ significantly for low-volume (LV) patients (HR 1.04;  $p = 0.86$ ) (Kyriakopoulos et al., 2018). The benefit of adding docetaxel to ADT was then confirmed in the multi-arm and multi-stage design STAMPEDE study, which demonstrated a survival advantage of about 15 months compared to ADT alone (mOS 60 versus 45 months; HR 0.76;  $p = 0.005$ ) in metastatic CSPC patients (James

et al., 2016).

As concern the efficacy of abiraterone acetate in addition to ADT in de-novo mCSPC patients, the phase 3 LATITUDE trial showed a statistically significant survival prolongation (mOS not reached vs. 34.7 months; HR 0.62;  $p < 0.001$ ) in HR (Fizazi et al., 2017). Of note, patients that did not satisfy the definition of HR disease were excluded from this study. Once again, the STAMPEDE study corroborated the OS benefit of combining abiraterone/prednisone plus ADT compared to ADT alone in mCSPC (HR 0.61, 95% CI 0.49 - 0.75) (James et al., 2017). Furthermore, when the LATITUDE study population was respectively stratified according to CHAARTED criteria, the survival prolongation of abiraterone acetate plus ADT compared to ADT alone was confirmed in the HV subgroup (HR 0.57,  $p < 0.0001$ ) (Fizazi et al., 2018).

Choosing the most appropriate treatment available (ADT monotherapy, ADT plus chemotherapy, ADT plus abiraterone acetate) is today one of the most debated issue of daily clinical practice. Direct comparisons of the two combination strategies (ADT plus docetaxel and ADT plus abiraterone) still lack. No difference in survival (HR for the OS of 1.16,  $p 0.40$ ) was observed in an indirect comparison between the two combination treatment cohorts evaluated in the STAMPEDE trial (abiraterone acetate plus ADT versus docetaxel plus ADT), while abiraterone demonstrated a statistically significant advantage in terms of biochemical relapse and disease progression compared to docetaxel (Sydes et al., 2018). However, these data do not allow drawing definitive conclusions. Moreover, ADT monotherapy still preserves a role for selected de-novo mCSPC patients, with a more indolent behaviour.

A unique validated prognostic classification that encompasses clinical and histopathological features with the aim of predicting clinical outcomes could help clinicians in the decision-making process, but at

the moment has yet to be identified (Iacovelli et al., 2018b). Apart from the difficulty related to the choice between chemotherapy and second-generation hormonal agents in HV and HR patients, conclusive data about the benefit (or the lack of benefit) from docetaxel in the LV patients are needed and concerns about the best treatment for the LR population - excluded from the LATITUDE trial – have to be solved.

At the ESMO 2018 Congress, Ali presented the results of a retrospective evaluation of the cohort of metastatic patients included in the STAMPEDE trial treated with abiraterone/prednisone plus ADT compared to ADT alone and retrospectively stratified for the disease risk (high versus low risk) according to the LATITUDE trial definition (Hoyle et al., 2018). The main hypothesis tested was to evaluate if LR mCSPC patients could benefit from the addition of abiraterone/prednisone to ADT. Almost 990 patients were included in this analysis, 452 received standard of care (SOC) and 449 SOC plus abiraterone/prednisone; 428 patients met the LR LATITUDE criteria, while 473 were defined as HR patients. After a median follow-up of 41.5 months, abiraterone/prednisone plus ADT confirmed the OS benefit over ADT in the HR subgroup (HR 0.54,  $p < 0.001$ ) and demonstrated an OS prolongation (despite of less magnitude) also in the LR subgroup (HR of 0.66,  $p = 0.041$ ).

Besides overall survival, the combination of abiraterone/prednisone plus ADT improved all the other survival endpoints (failure free survival, skeletal related events, progression free survival, and prostate cancer specific deaths) in both HR and LR groups. Indeed, P values for interaction were all non-significant, therefore suggesting that the benefit of abiraterone/prednisone plus SOC was consistent throughout all subgroups between high and low risk disease. Moreover, the same cohort of patients was stratified as per CHAARTED volume criteria. This exploratory analysis revealed the benefit of abiraterone over placebo in all survival endpoints irrespective of the disease volume (HV and LV).

Interestingly, when the CHAARTED and LATITUDE classifications were matched, discordance between these two stratifications was noticed in 18.2% of all patients. This data is in line to what previously observed (about 13% of patients with HV or HR disease in a cohort of 106 PC patients) (Iacovelli et al., 2018b), and underline the urgent necessity of a unique prognostic score system (Table 1).

These results – albeit retrospective – further complicate the selection of the best treatment for mCSPC patients. Should all de-novo mCSPC patients be considered for ADT plus abiraterone upfront, irrespective of disease risk and/or volume classification? Which patients are then the best candidates for early docetaxel? Does ADT alone preserve a place in the treatment algorithm of metastatic PC patients?

### 1.2. The role of Radiotherapy to the primary tumour in de-novo mCSPS

Local therapy of the primary tumor (external-beam-radiotherapy [EBRT] or radical prostatectomy [RP]) in patients with metastatic PC cancer - except when strictly required for symptoms palliation - is usually not recommended. However, strong preclinical evidence

support the local treatment of the primary tumour not only to inhibit the development of distant disease by avoiding the dissemination of tumour cells into the circulation, but also to avoid the progression of existing metastases by impairing the premetastatic niche proliferation through the inhibition of compounds secreted by the primary tumour into the circulation (Kaplan et al., 2005).

Emerging clinical data have shed the light about the advantage of definitive treatment of the primary tumor for men diagnosed with metastatic PC (Culp et al., 2014; Fossati et al., 2015; Rusthoven et al., 2016; Boevé et al., 2018). Retrospective analyses identified an association between prostate EBRT and improved overall survival, especially in patients with a better prognosis (Culp et al., 2014; Fossati et al., 2015; Rusthoven et al., 2016). Prospective data came from the HORRAD trial, which randomized patients with CSPC and metastasis to the bone at diagnosis to ADT with or without prostate EBRT. No overall survival advantage was observed in favor of additional radiotherapy (HR 0.90, 95% CI 0.70–1.14). However, the subgroup of patients with fewer than five bone metastases seemed to benefit from this strategy (0.68, 0.42–1.10) (Boevé et al., 2018).

The lack of a survival improvement for unselected de-novo mCSPC patients was recently confirmed by the results of STAMPEDE study, which randomized more than 2000 men with newly diagnosed PC to SOC (ADT alone or combined with early docetaxel) or SOC plus EBRT (36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over 4 weeks). Local radiotherapy to the prostate did not improve overall survival compared to SOC in the overall population (HR 0.92, 95% CI 0.80–1.06;  $p = 0.266$ ). Interestingly, the prespecified subgroup analysis by metastatic burden (as per CHAARTED definition) showed an OS advantage with radiotherapy in patients with low metastatic burden at baseline (HR 0.68, 95% CI 0.52–0.90;  $p = 0.007$ ; 3-year survival 81% versus 73%), while no evidence of a treatment effect was observed in patients with a high metastatic burden (HR 1.07, 95% CI 0.90–1.28;  $p = 0.420$ ). The interaction p value ( $p = 0.0098$ ) gave clear evidence that the magnitude of prostate radiotherapy effect differed by disease burden (Parker et al., 2018).

One of the main concerns about these results, besides the retrospective determination of disease volume from patients' baseline scans, regards the ideal definition of low metastatic volume and the optimal technique for the disease volume assessment. Indeed, as previously explained, the CHAARTED and LATITUDE definitions of disease burden are different and not completely overlapping. Moreover, the concept of LV according to CHAARTED cannot be considered superimposable to that of oligometastatic disease, including patients with unlimited number of metastases confined to lymph nodes and the axial skeleton; on the contrary, LR disease as per LATITUDE definition includes only patients with no more than 3 bone metastases but unlimited number of metastatic lymph nodes. In addition, all current definitions of disease volume are based on conventional imaging with CT and bone scans, but the use of more sensitive techniques (eg. PSMA PET) and the subsequent identification of additional lesions could reduce the proportion

**Table 1**  
Efficacy of docetaxel or abiraterone in terms of overall survival based on disease volume and disease risk: evidence available.

		Prognostic Classification			
		DISEASE VOLUME		DISEASE RISK	
		High Volume	Low Volume	High Risk	Low Risk
Docetaxel plus ADT	CHAARTED (Kyriakopoulos et al., 2018)	YES	NO	NA	NA
	STAMPEDE (James et al., 2016)	NA	NA	NA	NA
	GETUG (Gravis et al., 2016)	NO	NO	NA	NA
Abiraterone Acetate/prednisone plus ADT	LATITUDE (Fizazi et al., 2017, 2018, 2019)	YES	NO	YES	NA
	STAMPEDE (Hoyle et al., 2018)	YES	YES	YES	YES
Radiotherapy to the primary tumor plus SOC	STAMPEDE (Parker et al., 2018)	NO	YES	NA	NA

YES = available evidence of efficacy, NO = available evidence of no efficacy; NA = evidence not available.  
ADT = androgen deprivation therapy; SOC = standard of care; NA = evidence not available.

of low-volume patients defined with conventional imaging, and therefore resize the amount of patients that could benefit from prostate EBRT.

Several questions about the role of a local treatment in the metastatic PC setting remain unsolved. The value of prostate radiotherapy in de-novo mCSPC patients treated with abiraterone is being tested in the PEACE1 trial (NCT01957436), which compares ADT alone, ADT + Abiraterone/prednisone, ADT + local radiotherapy, and ADT + local radiotherapy + Abiraterone/prednisone. The role of another local approach in this setting (prostate surgery) is being tested in the g-RAMMP trial (NCT02454543). Furthermore, the benefit of radiotherapy to the oligometastases themselves in addition to the primary tumour could be investigated.

### 1.3. Conclusions and future prospective

In recent years, many efforts have been made in an attempt to improve the prognosis of patients with de-novo mCSPC. The therapeutic scenario has been enriched with new options (docetaxel and abiraterone, in addition to ADT) for selected categories of patients (chemotherapy for HV disease, abiraterone for HR but also LR patients). Local EBRT in addition to systemic therapy can be considered for LV PC. However, a unique patients stratification system has yet to be identified, and therefore the proper treatment management still needs the recognition of prognostic and predictive markers to be clearly outlined.

Perhaps a prognostic system based on clinical (tumor burden and site of disease) and pathological factors (Gleason score) is not sufficiently accurate to stratify a tumour characterized by a marked heterogeneity. The genomic profiling of PC revealed a higher mutational load (more copy-number alterations and mutations) in metastatic castration resistant prostate cancer (mCRPC) compared to localized PC. Moreover, the AR and PI3K/Akt/mTOR signaling pathways, and somatic or germline aberrations of DNA repair genes, are the most frequently mutated in mCRPC with a higher incidence compared to primary PCa (Cancer Genome Atlas Research Network, 2015; Robinson et al., 2015). Therefore, tumor progression can be considered as an incremental increase in the somatic mutational tumor burden that gives a proliferative advantage going from localized to mCRPC disease. On the contrary, data regarding the molecular characterization of a PC that presents with metastatic disease at the time of diagnosis are missing, and represent an urgent need. It is of fundamental importance to identify specific biomarkers that allow a prompt identification of a defined molecular subtype of de-novo mCSPC, to guide treatment decisions by integrating clinical and molecular information.

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