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LETTER TO THE EDITOR

Comments on "Abiraterone acetate plus prednisolone for metastatic patients starting hormone therapy: 5-year follow-up results from the STAMPEDE randomised trial (NCT00268476)"

Dear editor

Several systemic agents showed significant prolongation of overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC), and these drugs have been initially approved in that setting.[1] Subsequently, combinations of androgen-deprivation therapy (ADT) with chemotherapy or novel androgen-receptor signaling inhibitors (ARSi) demonstrated efficacy in the earlier setting of metastatic hormone-sensitive prostate cancer (mHSPC). The clinical validity of early treatment intensification has been recently confirmed by trials involving triplets with ADT, chemotherapy and ARSi in mHSPC,[2,3] and by the use of ADT plus ARSi in nonmetastatic castration-resistant prostate cancer (nmCRPC).

James and colleagues recently reported updated results regarding the use of abiraterone acetate in patients with mHSPC enrolled in the STAMPEDE platform.[4] Adjusted hazard ratio (HR) favored abiraterone (0.60; 95% CI: 0.50-0.71) and 5-years survival improved from 41% of standard-of-care (SOC) alone to 60% of SOC plus abiraterone. Of note, estimated median survival was 46 months in the SOC-alone group and 79 months in the SOC plus abiraterone group (median gain in OS of 33 months).

HRs are the most widely used parameter to design and interpret survival benefit in clinical trials. However, they are a relative measure. Median absolute gain in OS can be used to indirectly compare the overall impact of treatments in different settings, and represents a good indicator of clinical benefit.[5] The same HR translates in greater OS prolongation if the median OS of control arm is longer. In the present correspondence, we highlight that the median gain in OS (calculated as the difference in median OS between study arms) better represents clinical benefit that is provided by approved drugs in patients with prostate cancer. Systemic agents demonstrated median gains in OS ranging from 2.4 to 5 months in mCRPC setting, whereas the magnitude of OS prolongation was significantly stronger in trials that investigated these drugs at earlier disease stages, including mHSPC and nmCRPC settings (Figure 1). Consequently, clinicians should be aware that the same drug can result in a different clinical impact when used at earlier stages.

In the case of abiraterone acetate, a mCRPC patient who receives this drug, in addition to ADT, is expected to live about 4 months longer compared to another one who receives ADT alone. However, based on recent results from STAMPEDE trial, we know that this survival improvement can increase up to 33 months if we move to a patient treated in the mHSPC setting.[4]

Our observation supports the notion that HRs are not a sufficient measure of clinical effect when comparing drugs in different patient's populations or settings. Data on median gain in OS clearly show that early treatment intensification is a prerequisite to improve the survival of prostate cancer patients, and later use of chemotherapy or ARSi is associated with less impactful clinical benefit.

CONFLICT OF INTEREST

Carlo Cattrini: expenses from Novartis, Pfizer, Janssen, BMS and Ipsen; advisory board from Janssen. **Carlo Messina**: expenses from Pfizer, Janssen, Astellas and Ipsen; advisory board from Janssen, MSD and Ipsen. **David Olmos**: honoraria from Astellas Pharma (Inst), Bayer, Janssen; consulting or advisory role from AstraZeneca (Inst), Bayer, Bayer (Inst), Clovis Oncology, Janssen, Janssen (Inst); research funding from Astellas Medivation (Inst), AstraZeneca (Inst), Bayer (Inst), Genentech/Roche (Inst), Janssen (Inst), Pfizer (Inst), Tokai Pharmaceuticals (Inst); travel, accommodations, expenses from Astellas Pharma, Bayer, Ipsen, Janssen. **Alessandra Gennari**: consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, EISAI, Daichii Sankyo; Speakers Bureau Eisai, Novartis, Eli Lilly, Roche, Teva, Gen-tili, Pfizer, Astra Zeneca, Celgene, Daichii Sankyo, Research Funds: EISAI, Eli Lilly, Roche. **Massimo Di Maio**: Invited Speaker for Boehringer Ingelheim, Advisory Board for AstraZeneca, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Institutional Financial interest for Beigene, Exelixis, Merck Sharp & Dohme, Pfizer, Roche, Tesaro—GlaxoSmithKline. The other authors have no conflicts of interest to declare.

Abbreviations: ADT, androgen-deprivation therapy; ARSi, androgen-receptor signaling inhibitors; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; SOC, standard-of-care.

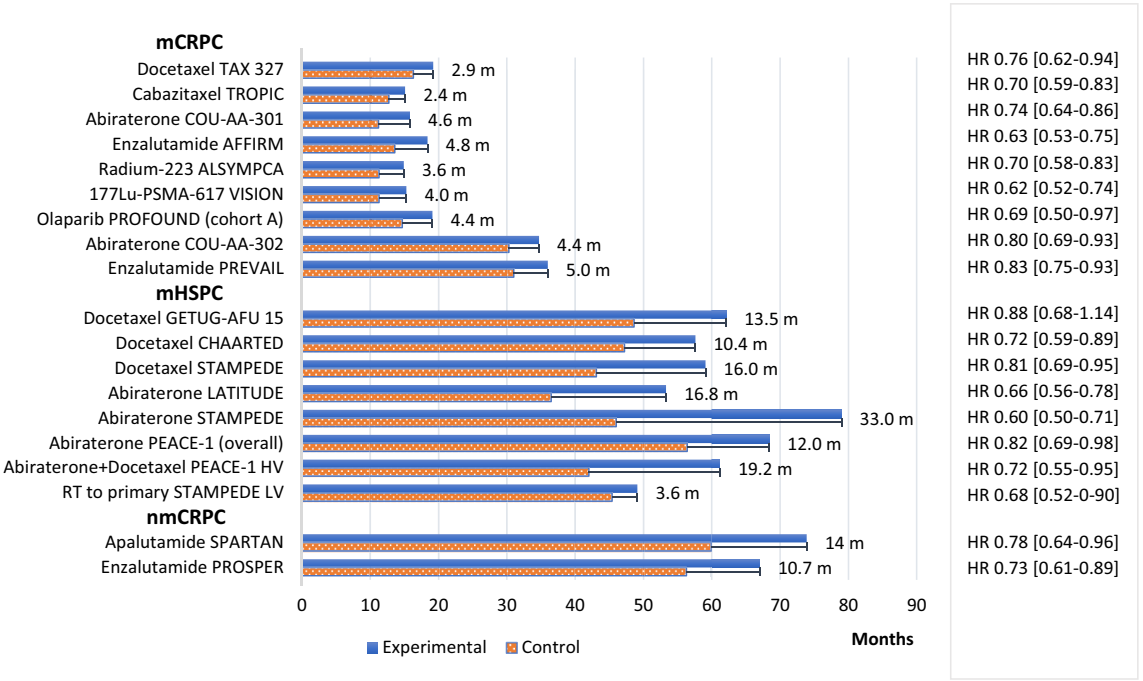

FIGURE 1 Median gain in overall survival in Phase 3 pivotal trials involving patients with advanced prostate cancer. Data about drugs and corresponding trials are updated to latest results available on overall survival (OS). Labels report median gain in OS, as expressed in months. On the right, HRs of pivotal trials are shown. Results from ARAMIS, ARASENS, ARCHES, ENZAMET and TITAN trials were not included because median OS was not estimable. HV, high-volume; LV, low-volume; m, months; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer [Color figure can be viewed at wileyonlinelibrary.com]

Carlo Cattrini[1,2]
Carlo Messina[3]
Alessia Mennitto[1]
Massimo Di Maio[4]
Alessandra Gennari[1]
David Olmos[5]

[1]*Medical Oncology—Department of Translational Medicine (DIMET), Università del Piemonte Orientale (UPO), "Maggiore della Carità" University Hospital, Novara, Italy*
[2]*Department of Internal Medicine and Medical Specialties (DIMI), University of Genoa, Genoa, Italy*
[3]*Oncology Unit, A.R.N.A.S. Civico, Palermo, Italy*
[4]*Department of Oncology, University of Turin, Ordine Mauriziano Hospital, Turin, Italy*
[5]*Medical Oncology Department, I+12 Biomedical Research Institute, Hospital Universitario 12 de Octubre, Madrid, Spain*

Correspondence
Carlo Cattrini, Medical Oncology-A.O.U. "Maggiore della Carità", Corso Mazzini 18, 28100 Novara, Italy.
Email: carlo.cattrini@maggioreosp.novara.it

ORCID

Carlo Cattrini https://orcid.org/0000-0003-4785-9480

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