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EDITORIAL

Phase III Trials With Docetaxel-Based Combinations for Metastatic Castration-Resistant Prostate Cancer: Time to Learn From Past Experiences

Emmanuel S. Antonarakis and Mario A. Eisenberger, *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

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Ever since docetaxel was shown to be the first known agent to extend survival in men with metastatic castration-resistant prostate cancer (mCRPC),[1] drug development efforts have focused on docetaxel as a pivot point for trial design and regulatory approval. To this end, the majority of phase III clinical trials conducted in the postdocetaxel era have investigated the use of novel agents either before docetaxel administration, combined with docetaxel, or after docetaxel exposure.[2] Although this divide is an artificial one biologically, it has been embraced by regulatory agencies for the approval of several new drugs for mCRPC in the past 3 years. However, although new agents have been approved both in the predocetaxel setting (eg, sipuleucel-T, abiraterone) and in the postdocetaxel setting (eg, cabazitaxel, abiraterone, enzalutamide) on the basis of improvements in overall survival, no drug has yet demonstrated a survival benefit (or gained regulatory approval) when combined with docetaxel.

In the article that accompanies this editorial, Fizazi et al[3] report the final results of the ENTHUSE (Endothelin A Use) -M1C study, a randomized phase III trial of docetaxel plus zibotentan (an oral endothelin A receptor antagonist) versus docetaxel plus placebo. Despite the random assignment of 1,052 patients, this study failed to demonstrate a survival improvement in the docetaxel-zibotentan arm (hazard ratio, 1.00; 95% CI, 0.84 to 1.18), the primary end point of the trial. In addition, the combination arm was not associated with improvements in any of the secondary end points: prostate-specific antigen (PSA) response rate, time to PSA progression, progression-free survival, time to new bone metastases, time to new skeletal-related events, pain response, or time to pain progression.[3] Could these negative findings have been predicted before conducting a large phase III study? We sought to examine the evidence arguing for or against proceeding with a phase III trial.

Before the design of the ENTHUSE-M1C study, a single phase I/II trial had been conducted examining the safety and efficacy of the docetaxel-zibotentan combination.[4] In this trial, six patients were enrolled onto two dose-escalation cohorts followed by an expansion phase in which 31 additional patients were randomly assigned (2:1) to receive docetaxel-zibotentan (n = 20) or docetaxel-placebo (n = 11). The prespecified primary end points for the phase II expansion component were overall response rate and PSA response rate. There were no differences observed between arms in either of these end points. Objective response rates in the docetaxel-zibotentan and docetaxel-placebo groups were 22.2% and 16.7% respectively (difference, 5.5%; 80% CI, −23% to 30%; $P > .05$); PSA response rates were 85.0% and 72.7% respectively (difference, 12.3%; 80% CI, −6% to 33%; $P > .05$). Despite these findings and perhaps encouraged by a separate randomized phase II trial of single-agent zibotentan versus placebo in asymptomatic patients with mCRPC, which showed a trend ($P > .10$) toward improved survival with zibotentan (a secondary end point in that study),[5] the authors of the phase I/II trial commented that "sufficient preliminary activity was seen with this combination to merit continued development." On the basis of the available clinical data, we do not believe that compelling evidence existed to justify proceeding with a phase III trial.

In addition to this particular docetaxel-based combination, eight other decisive phase III trials have been designed in an attempt to improve on the efficacy of docetaxel in men with mCRPC. These trials are summarized in Table 1.[6-18] Of the nine total trials (examining a range of agents including antiangiogenic drugs, bone microenvironment agents, immune modulators, and others), eight have been completed, and one is still awaiting final results. Discouragingly, all eight of the studies with mature results failed to meet the primary end point of improving overall survival. Indeed, no docetaxel-based combination reported to date, to our knowledge, has been shown to extend survival compared with docetaxel alone. Notable as well is that a trial evaluating another endothelin A receptor antagonist (atrasentan) also failed to improve survival beyond docetaxel alone.

A more careful examination of this table reveals some sobering truths. Of the nine docetaxel-based combinations examined in the phase III setting, only three agents (bevacizumab, calcitriol, custirsen) had previously been tested in combination with docetaxel in dedicated phase II trials, whereas four agents (atrasentan, zibotentan, dasatinib, lenalidomide) were tested in expansion cohorts of phase I/II trials, and two agents (aflibercept, GVAX) were never tested in combination with docetaxel at all in the phase II setting. Moreover, of the seven docetaxel-based combinations that did have phase II data available, these phase II trials either did not define the metric for success that would prompt phase III development (dasatinib, lenalidomide) or did define the metric for success but did not achieve it (bevacizumab, atrasentan, zibotentan, calcitriol, custirsen). Therefore, it

Table 1. Completed or Ongoing Phase III Studies Examining Docetaxel-Based Combinations in the First-Line Treatment of Metastatic Castration-Resistant Prostate Cancer

Agent	Sample Size	Phase III Trial		Prior Phase II Trial(s)	
		Primary End Point	Primary Result	Description, Including Primary End Point(s) Used	Was Primary End Point Met?
Antiangiogenic drugs					
Docetaxel ± bevacizumab (NCT00110214)	1,050	OS	OS not improved in combination arm[6]; HR, 0.91; 95% CI, 0.78 to 1.05	Single-arm phase II study (n = 77) using PFS as primary end point	Primary end point not met[7]
Docetaxel ± aflibercept (NCT00519285)	1,224	OS	OS not improved in combination arm[8]; HR, 0.94; 95% CI, 0.82 to 1.08	No phase II combination studies conducted	—
Bone microenvironment agents					
Docetaxel ± atrasentan (NCT00134056)	991	OS and PFS	OS not improved in combination arm[9]; HR, 1.01; 95% CI, 0.87 to 1.18	Single-arm phase II study (n = 23; expansion of phase I/II trial) using PSA response rate as primary end point	Primary end point not met[10]
Docetaxel ± zibotentan (NCT00617669)	1,052	OS	OS not improved in combination arm[3]; HR, 1.00; 95% CI, 0.84 to 1.18	Randomized phase II study (n = 31; expansion of phase I/II trial) using overall response rate and PSA response rate as primary end points	Primary end points not met[4]
Docetaxel ± dasatinib (NCT00744497)	1,380	OS	OS not improved in combination arm[11]; HR, 0.99; 95% CI, 0.87 to 1.13	Single-arm phase II study (n = 30; expansion of phase I/II trial) using PSA response rate as primary end point	Metric for success not defined[12]
Immune modulators					
Docetaxel ± GVAX (NCT00133224)	408	OS	OS inferior in combination arm[13]; HR, 1.70; 95% CI, 1.15 to 2.53	No phase II combination studies conducted	—
Docetaxel ± lenalidomide (NCT00988208)	1,059	OS	OS inferior in combination arm[14]; HR, 1.53; 95% CI, 1.17 to 2.00	Single-arm phase II study (n = 20; expansion of phase I/II trial) using PSA response rate as primary end point	Metric for success not defined[15]
Miscellaneous agents					
Docetaxel ± calcitriol (NCT00273338)	953	OS	OS inferior in combination arm[16]; HR, 1.42; 95% CI, 1.13 to 1.86	Randomized phase II study (n = 250) using PSA response rate as primary end point	Primary end point not met[17]
Docetaxel ± custirsen (NCT01188187)	800	OS	Study is ongoing	Randomized phase II study (n = 82) using PSA response rate as primary end point	Primary end point not met[18]

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

could be argued that none of the nine docetaxel-based combination strategies shown in Table 1 had sufficient phase II data to warrant additional development.

The decision-making process to proceed from phase II to phase III trials in oncology remains challenging. Oncologic clinical trials are becoming increasingly complex with the recognition of the molecular heterogeneity of tumors, even ones that originate from the same primary site. In addition, anticancer drugs are frequently designed to target specific cellular pathways and metastatic sites, which indicates a need for personalized treatment planning. Although accurate prediction of a positive phase III study is an impossible endeavor, there are several logical steps that can be taken in early-phase drug development to enhance our ability to identify potentially active treatments worthy of additional study in the phase III setting. First, and most simplistically, phase III trials should not be pursued without the prior conduct of at least one phase II study that has met a prespecified rationally selected primary end point and its predefined metric for success (signal for efficacy) in a safe manner. Our experience in phase III trials using docetaxel-based regimens in mCRPC in the past several years demonstrates that it is not appropriate to conclude that a regimen has sufficient activity to warrant phase III testing if the primary end point has not been met and the decision to proceed is based on whether a secondary end point has been achieved or on other post hoc considerations. Second, the most appropriate end point for defining a success in phase II trials should ideally be agent specific or at least class specific. For example, the choice of PSA response rate as the primary end point for phase II development of an androgen receptor–directed therapy (eg, abiraterone, enzalutamide) may be reasonable, whereas this might not be appropriate for a bone-targeting agent (eg, zibotentan, dasatinib). Third and most relevant to targeted therapies, early-phase studies should seek to confirm that the drug in question reaches its target, engages its target, and inhibits its target and that target inhibition produces a clinical effect. Fourth, phase II trials should use enrichment strategies to narrow down the target population to those patients who are most likely to benefit from a particular agent, on the basis of either clinical characteristics or molecular information. Along these lines, phase II trials should be designed with prospectively defined predictive biomarkers (ie, biomarker-stratified studies) in place; these trials would have the ability to investigate clinical outcomes to an experimental agent in patients both with and without a given biologic marker. Finally, because there are currently no established surrogate end points for overall survival in men with mCRPC,[19] new efforts should focus on identification and validation of alternative intermediate biomarkers of clinical benefit (eg, change in circulating tumor cell counts at 12 weeks after initiation of therapy), potentially shortening the duration of phase III trials and allowing for an earlier signal of efficacy.

In conclusion, Fizazi et al[3] report that the results of the phase III ENTHUSE-M1C study "contradict earlier promising clinical data on the combination of zibotentan with chemotherapy."[3] On the basis of the information presented here, we would argue that the results of ENTHUSE-M1C confirm the phase II data that the combination of docetaxel and zibotentan has little clinical activity in men with mCRPC. We should be careful not to redefine our failures as successes.

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