Advanced Stage Disease

Management of Disease Progression and Emerging Drug Protocols

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I. Clinical States: A framework for drug development.

The clinical context in which we develop drugs for castration-resistant disease is patients who are not ready for chemotherapy or who don't want to take chemotherapy. There is a first-line standard against which most therapies are being compared and a second line where there is currently no standard. Docetaxel was established as the standard of care based on a survival benefit from two randomized phase III trials with essentially equivalent outcomes.

Thinking about how we move forward, we do define very clear objectives and therapeutic aims, and what is most encouraging is that the drugs that are now being brought to the clinic are in many cases showing efficacy even in phase I, which I think is attributed to our improved understanding of the disease biology.

We have a variety of different drugs that are being tested now. It's not just chemotherapy, and a major focus is targeting the host/tumor interactions. We have made a very intensive effort to get very clear readouts as to whether or not drugs are working so we can move them forward.

The End Points initiative was a response to the FDA challenge, which said if you don't like the way we do business, please change it. We tried to focus on what we do as doctors, which is we make a recommendation and we want to make sure that the drug has had an adequate trial. We're learning that if we can slow the disease or modulate the disease that can be beneficial, and what we're doing now is confirming the bone scan and making a strong effort to worry less about response and focus more on whether it is working and if we should change treatment.

Building on docetaxel as the first-line standard of care, there are a number of agents that are being tested either as monotherapy or in combination, and in some cases you think it's a me-too exercise where every new drug that has any signal is being tested in combination with docetaxel. The Avastin trial is ongoing, and it has proven to be active in breast, colorectal and other tumors. Atrasentan and ZD4054 are designed to affect the prostate cancer in bone and to shut off the growth stimulation that occurs from bone stroma or the support in which the prostate cancer cells reside. The good news is these are agents with very different mechanisms—bone targeting, vessel targeting, specific signally and actually specific drugs that accelerate the death of cells. This is called apoptosis, and two agents that have shown at least additive effects with docetaxel are in phase III.

A trial that we are all awaiting is the CLGB study that is using the vascular inhibitor, Atrasentan. Patients are stratified based on a nomogram, which predicts for outcome, and it is looking for a 25% improvement in survival.

II. Dissecting the lethal phenotype.

When patients are progressing following depletion or blockade of androgens, the PSA goes up. PSA is a signal that the androgen receptor is still functioning, and if we think about it, we knew that for a long time there were patients who respond to secondary hormones. We knew that if you stopped hormones, in some cases patients would respond. What this is telling us is that the androgen receptor is still playing a role in the progression of these tumors despite the fact that we're measuring low levels or castrate levels of testosterone in the blood.

In terms of clinical insights into castration-resistant progression guiding drug development, rising PSA levels are consistent with continued AR signaling. Clinical significance of AR targeting is reinforced by the response to secondary hormone therapies, as well as the "withdrawal" or "discontinuation" of anti-androgens. This suggests the antagonist later functions as an agonist as the disease progresses. Finally, the AR ligand-binding domain is clinically relevant and contributes to progression.

III. Targeting AR Signaling: MDV3100 and Abiraterone Acetate

MDV3100 and Abiraterone acetate target specific alterations in castration-resistant prostate cancer and show promising activity. We then asked why not use hormonal agents in the post-chemotherapy setting, which is not only from a patient benefit point of view but also from an approval standpoint. Four separate phase 1 and phase 2 trials demonstrated the activity of Abiraterone pre- and post-chemotherapy. These have led to a phase III trial where there are two objectives. One is to get the drug approved, and the trial accrued the 1,200 patients in record time. It was finished early and should be reported next year. We also included looking at circulating tumor cells as a potential earlier endpoint to see that the drugs are working. We were able to collect samples on 1,000 patients.

MDV3100 was specifically engineered to be active in tumors with too much of the androgen receptor, and it has been shown to be active against bicalutamide-resistant xenografts with overexpressed AR. It has also been shown to be active in pre- and post-chemotherapy castration-resistant prostate cancer based on PSA, imaging and CTC conversion rates. The phase III registration trial of MDV3100 is ongoing, and it also includes the prospective evaluation of circulating tumor cells as a biomarker.