What Is the Purpose of the DETERMINATION Trial in Myeloma?

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Jack Aiello:
New drugs that have been approved by the FDA in the last 10 years like bortezomib (Velcade) and lenalidomide (Revlimid) have gotten there, because patients have signed up and gone through clinical trials. These new treatments coming down the road also need patients in clinical trials. Can you talk about the importance of patients investigating clinical trials?

Dr. Richardson:
Oh, hugely. I mean, I think it goes beyond just new agents. I think the participation in clinical trials has been the lifeblood of progress in myeloma. If patients had not been brave enough to participate 15 years ago, we wouldn't have Velcade. We wouldn't have Revlimid. We wouldn't have thalidomide (Thalomid). We wouldn't have carfilzomib (Kyprolis). We wouldn't have pomalidomide (Pomalyst). And we wouldn't have elo. And we wouldn't have dara. We wouldn't have SAR. I mean, none of these agents would be here without participation in clinical trials.

And what I think is terribly important for patients to understand is of course it's—what I love about clinical trials now is it's truly a win-win. The best drugs, best options, ahead of the curve, and also high quality control. I mean, these are the essentials of good clinical trials. So patients get the benefit of the best quality control, and at the same time they help patients in the future. So it's a true win-win.

Jack Aiello:
And one last question. Sometimes trials aren't for new drugs, but they're to look at existing treatments. And I know you're very close to one that's called DETERMINATION to try to determine the timing of transplants. Can you talk more about that trial?

Dr. Richardson:
That's a great question, and I think it's beautifully framed by what you've just said. The field is moving so quickly, and we have so many new and exciting drugs, and we have the ability now to unleash the immune system in a totally different way than we did before. What then is the role of transplant? Now, to date, high-dose therapy with stem cell rescue has been effective in younger patients most of the time, and clinical benefit has been shown in terms of progression-free survival advantage. Interestingly, even in the old days, as it were, there was no survival difference that was obvious to early versus late transplant.

If you did a transplant late, the survival was the same as it was if you did it early. That was in the old days of chemotherapy. And the question is now even more pressing than before. If you've got these fantastic new drugs that are deriving really

exciting clinical benefit and doing so in a very nontoxic fashion, what is the relative gain of transplant? I personally think transplant has a definite role for younger patients—but not in everyone—and not necessarily all at the same time.

So the question then belongs—to be where do you do it, in whom and when? And the DETERMINATION trial seeks to really provide a sort of starting point to answering those questions. So it's a tremendously important study. And I think it's very important that people understand it's a U.S. trial, because what we've also learned in our clinical trials is that care differs between countries. So what happens in Europe and the options available to European patients is not necessarily the same as what we have here, and that has an impact on outcome.

So, therefore, just simply saying, well, if it works in Europe it's got to work here, is not actually true, that in fact there may be important differences between countries that mean that you tailor therapy appropriately to what you have available. And so I think the DETERMINATION trial provides an incredibly important platform for future progress.

I think for our patients who are part of it now—and we are over 77—70 percent enrolled now, so there's still plenty of scope for more patients, but we're really getting there—what it provides for patients now is quality control because they are part of a very highly organized treatment plan. Two, as you mentioned, Jack, it's not a randomized trial in the sense of any placebos or experimental agents. It's standards of care, and it retains a wonderful degree of control I think for patients and their caregivers in both arms of the study.

Because what it offers is early transplant in half, later in the other half, but if you're in the later transplant group and your disease tells you need to be treated sooner, you can be.

And, conversely, if you're in the early transplant group and there's any safety worry or concern that this may not be the best option for you it can be generally pushed back. So from a clinical trials perspective, we feel very comfortable with its design in the modern era as a means of offering patients really best choices.

And you may say, well, do you have evidence for that? And actually we do, because what we've shown is that in—to date, the event rate, in other words, the outcomes for both arms of the study with our French partners have taken a very long time to mature, which tells us that our patients are doing much better than expected.

Jack Aiello:
It's good, yeah.

Dr. Richardson:
So this tells us also that in that context the treatment is benefitting growth groups.

And one last comment I'd make is that in striking contrast to the French trial our study offers maintenance continuously…

Jack Aiello:
Right.

Dr. Richardson:
…for as long as it's helping the patient. Unfortunately, in France for regulatory reasons and probably cost reasons as well the maintenance was stopped at one year, so our expectation is that that event rate in the French study, unfortunately, will click up because, of course, patients are no longer on treatment. In contrast, the U.S. study is quite different in that regard.