Interviews

EMJ had the pleasure of speaking with Pieter Sonneveld, Erasmus University Medical Center, Rotterdam, the Netherlands; Nicola Conran, State University of Campinas (UNICAMP), Brazil; and Simona Pagliuca, Nancy University Hospital, Vandoeuvre-lès-Nancy, France, about the latest advances in haematology, spanning multiple myeloma, sickle cell disease, bone marrow failure syndromes, and cellular therapies. They discussed how innovations in immunotherapy, gene editing, immunogenetics, immune monitoring, and minimal residual disease assessment are driving more personalised treatment approaches and improving outcomes for patients.

Featuring: Pieter Sonneveld, Nicola Conran, and Simona Pagliuca.

Pieter Sonneveld

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Q1 Can you tell us a little bit about your career journey, your background, and what initially inspired you to get into haematology?

I started to gain an interest in haematology during my medical studies, specifically why patients with leukaemia did so poorly on any therapy, and why other patients with other diseases, like lymphoma, did relatively better. So, I developed an interest in haematology in general, and then specifically in acute leukaemia.

When I graduated, I started a PhD project on the role of doxorubicin, which was discovered a couple of years before, but at the time, there was no experience with the drug in leukaemia. I did a PhD investigation on the Pharmacokinetics of Doxorubicin at the University of Leiden, the Netherlands, and, following that, I moved to the USA for a fellowship at the National Cancer Institute, Bethesda, Maryland, USA, again, working on anthracyclines, like daunorubicin and Idarubicin. Then, I had to do my clinical training for internal medicine, but I also got a grant for a laboratory study on methotrexate, which was another anti-leukaemia drug, especially used in childhood leukaemia.

Later, I got a position in a haematology department in Rotterdam, where I built my career, both clinically and in research, focusing on acute leukaemia. After a couple of years, I discovered that myeloma was a disease area where the treatment results were very poor. There was nothing, in fact, for those patients, so I decided to move from leukaemia to multiple myeloma in the late 90s. Shortly after, we introduced high-dose melphalan and autologous transplant as a way to treat younger patients with multiple myeloma. This is how I

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got more and more interested in multiple myeloma, with the help of the late Brian Durie, Co-Founder, International Myeloma Foundation (IMF), who was at the University of London in the UK at the time.

We worked together on several research topics, and then, we developed a laboratory dedicated to multiple myeloma diagnostics and also better prognostic models in multiple myeloma. We developed clinical trials in multiple myeloma and later, with Hans Johnson from Aarhus University, Denmark; Hartmut Goldschmidt, University of Heidelberg, Germany; and Antonio Palumbo, University of Torino, Italy, we founded the European Myeloma Network (EMN), which is now a large organisation for clinical trials in Europe and abroad.

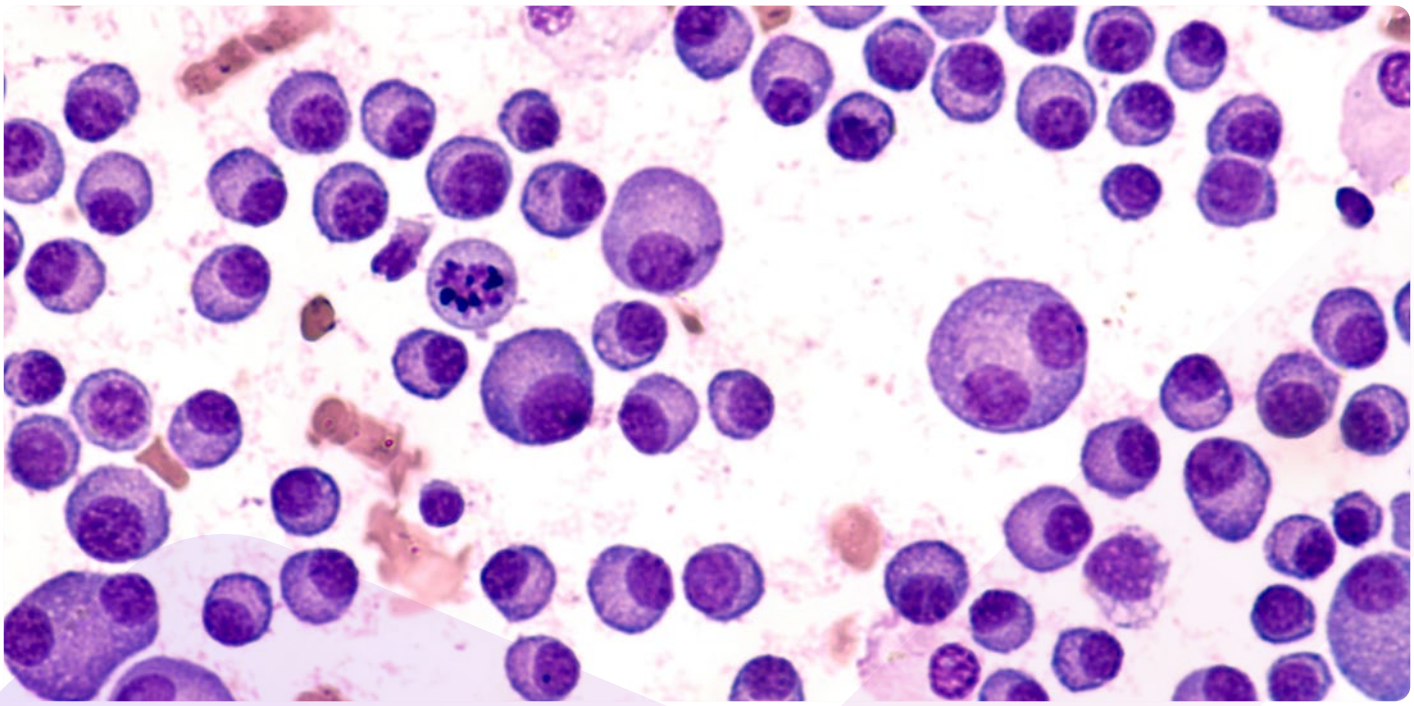
> **The FDA in the USA has approved MRD as a surrogate endpoint for PFS**

Q2 As a leading expert in multiple myeloma, can you give me an overview of what the current treatment and diagnostic landscape is like for multiple myeloma? What kind of barriers do you think still persist in this area?

I think we are in an exciting era of multiple myeloma, and that's because of the many novel drugs and treatment modalities that have been developed for this disease. I think it's one of the diseases within haematology with the most approvals for new drugs and the most successful trials. Many trials have focused on these new agents in combination with traditional treatment schedules, but also challenged some of the dogmas that we accepted in the disease for a long time, for example, high-dose melphalan and autologous transplant, which I already mentioned, was the standard in younger patients from the 1990s.

Over the past couple of years, we have started to challenge that role. Can we do better with less side effects? One of these attempts is with CAR-T cell therapy, for example. Another one was the introduction of quadruplet therapy for induction and consolidation, combined with autologous transplant or with other approaches. The third major attempt was by improving maintenance therapy, like we have done in the PERSEUS trial, adding daratumumab to the standard maintenance of lenalidomide. From now on, I think most people will focus on the new bispecific antibodies and even trispecific antibodies that are on the horizon. That will enable us to treat patients without toxic chemotherapy, using immunologic approaches only.

This will be a great turnaround for myeloma. For the first time, we will be able to treat patients without the adverse events associated with chemotherapy, with very good and long-lasting results, maybe even leading to a cure. This is what I think we are going to see in the next 10 years or so.



Q3 What promise do you think minimal residual disease (MRD) holds? And do you think we could be using it as a decision-making tool in daily practice in the future?

There is a real need for response evaluation, which is more sensitive and earlier than the traditional progression-free survival (PFS) and overall survival. The reason is that the results of treatment have improved so much in this disease, especially in younger patients, that it may take many years before we see if PFS will be better than the traditional treatment. One such trial that clearly indicates the need for MRD is the PERSEUS trial, where daratumumab in combination with VRD (velcade, revlimid, and dexamethasone) was compared to VRD alone for induction and consolidation therapy. Then, in the maintenance phase, the treatment was daratumumab plus lenalidomide compared with lenalidomide alone in the control arm.

The trial has been published with a 4-year follow-up. Now, we are at a 6-year follow-up. We will do an updated MRD analysis later this year. We know, from calculations based on the NICE methodology used in the UK, that the predicted PFS for patients treated with daratumumab plus VRD and autologous transplants and daratumumab/lenalidomide maintenance will be up to 12–13 years.

For current and future trials, with this great efficacy of the treatments, we will not be able to evaluate the outcome of trials, the comparison with the control arm, for 10 or more years, which makes it really impossible to introduce and approve new treatments and to introduce them into daily practice. That's where MRD comes in, because, by using MRD, we can look with great sensitivity into the marrow to see if there are still malignant cells, and this can be followed over time in the patient. We know now that MRD negativity, and especially sustained MRD negativity for more than 6–12 months, is a good predictor for PFS and for overall survival.

The FDA in the USA has approved MRD as a surrogate endpoint for PFS, which means that it can be used for earlier approval of new drugs, which is in the interest of many patients. In Europe, it is different. The European Medicines Agency (EMA) has not yet approved MRD as a surrogate endpoint, but discussions are ongoing with many experts from the field and EMA staff to see how we can reach a conclusion on this and introduce MRD in European countries. I think now is the time to get approval for that, because it's CAR-T, the bispecific antibodies, the trispecific antibodies, other immunotherapy techniques, and other conventional drug combinations that are waiting for approval, and the lives of many patients in Europe will depend on their approval, so they can receive the best, newest treatment in time for them to have a longer survival.

Q4 How do you see immunotherapies being integrated into earlier lines of treatment in the future? What promise do they hold?

They have been developed for later lines of treatment, but some of these new drugs, such as bispecifics, are already moving into first-line therapy. In the European Myeloma Network (EMN), we have just concluded the accrual of patients in a trial evaluating CAR-T cell therapy as an alternative to autologous transplant in the first-line setting.

The CARTITUDE-6 trial included more than 700 patients. We now have to wait for the data of the first evaluation, but many patients have already received CAR-T cells as part of first-line treatment. The same is true for the bispecific antibodies, where patients receive teclistamab, elranatamab, or other bispecific antibodies in first-line, now, in the context of clinical studies, in particular for maintenance, but also, increasingly, for combining with standard treatment or even replacing standard treatments in first-line.

All this data will come in the next couple of years. The data need to mature, so we will be sure that the results observed with high MRD negativity rates and other good response criteria are durable, and that these stay considerably better than what we have seen with traditional treatment. I trust that this will be the case.

The overall response rates, the complete remission rates, and the MRD negativity rates are all so good that this most probably will translate into longer PFS and overall survival. The only way to be sure is by consistently performing MRD studies in the trials, but also observing individual patients in our daily practice, which is occurring right now.

Many clinicians already do MRD analysis in routine clinical practice for their patients. The point is that, over the next few years, we have to develop algorithms on how to use MRD data for designing further treatments, to guide patients' treatment decisions (yes or no), or maybe stopping

treatment early, if a patient is consistently MRD negative. These are important clinical questions because, by doing this, we might reduce the treatment burden on patients when they already have a deep remission.

Q5 Moving on to congress, we have the European Hematology Association (EHA) Congress approaching, held in June this year. How do you feel meetings like EHA, American Society for Clinical Oncology (ASCO), and American Society of Hematology (ASH), for example, influence global treatment guidelines and generally clinical practice in haematology?

These are the three big, traditional meetings: EHA, ASCO, and ASH. More recently, we have had other meetings organised by EMN and also by the International Myeloma Society (IMS).

Therefore, there is a lot of information available, and a lot of data sharing is possible in these meetings between the investigators, and also focusing on practising clinicians. I think the guidelines are an area that should be developed in more detail. The reason is that, because there are so many new developments, the guidelines can change almost every year, or maybe more often. The EMN, together with EHA, has developed an updated guideline, which was published last year. If I compare that with the previous guideline from 2021, it's completely different.

There are hardly any similarities left in the treatment, so that's an indicator of how fast the clinical treatment landscape is changing. It also means that for the general practising physician, it is increasingly difficult to recognise what the benefits of all these treatments are? Where do they differ? How should I make my choice for the older patient or the younger patients? There's a lot of new options, but also a lot of new choices to make, and guidelines may help the general physicians in the hospitals to make the right decision, but also to help to understand the disease, to understand why some agents are more effective, how they work, how you can measure the treatment effect, and also how to prevent adverse events, to give the right prophylaxis to prevent infections, for example, or other adverse events.

All of this is increasingly complex. The academia, the myeloma experts, and the researchers should make the biggest effort to get this information, in the right format, to both the patients and treating physicians. The guidelines were important, but they are becoming increasingly relevant. Regulatory bodies in Europe may use the guidelines to base their approval decisions on. We know this from the past, but we also know now that this is increasingly done. The regulators read the guidelines, and they include the conclusions of the guidelines in their decision-making process.

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