Good afternoon, my name is Volker Diehl. I was professor at the University here in Cologne of the Department of Internal Medicine especially working with cancer patients and here mainly with lymphoma and leukemia patients, I am Emeritus since 2004, and I am now living in Berlin.

My interest in Hodgkin’s disease at this time, what we call it today Hodgkin lymphoma because we know that it is a B-cell lymphoma different from the other non-Hodgkin lymphomas because this Hodgkin lymphoma has one special cell that makes it to Hodgkin lymphoma. This cell is a Reed-Sternberg cell, and this cell was for 160 years an enigma, and the whole disease was a puzzle. When I started to get to know this disease in Sweden in 1968, we did not know is it an infection, is it an inflammation, or is it a real tumor disease?

So, we did not know until about 1992 when I worked here in Cologne. We found out that with Ralf Küppers and Martin Hansmann, and Klaus Rajewsky that this disease is malignant lymphoma. It is compromising of monoclonal B cells. The Reed Sternberg cells are germinal center derived B-cells, monoclonal and have IgG rearrangement and every patient himself has a special IgG rearrangement that is different from other patient’s lymphoma cells. So, when we started these symposia here in Cologne in 1987, we did not know is it a monoclonal disease or a polyclonal disease? And I, at this time, when I started these meetings here in Cologne, I asked the four groups working on this disease to come at the podium and tell us, is it a monoclonal or polyclonal disease, and three groups said it is polyclonal, and only one, our group here in Cologne, Ralf Küppers, said yes it is a monoclonal disease and he was right.

If we first elude on the basic biology and molecular biology, then here is the question, what are the factors that make a normal B-cell in the germinal center to a malignant cell that is rather fragile, and we have only 14 cell lines that are grown out of biopsies in vitro. We have thousands of leukemia and lymphoma cell lines, but only 14 Hodgkin cell
lines, and these Hodgkin cell lines, five of them that I have cultured in Hanover and here in Cologne are the ones that gave us the insight of the molecular biology of this disease.

So here, we discussed now factors that stop the B-cell differentiation and act as drivers to the malignant process, and these are factors that are now well known, and we are looking for the scenario that makes these normal B-cell to a malignant cell, and we want to know why the T-cells that normally kill the tumor cells in our body are inhibited to kill this Reed-Sternberg cell, and all these discussions are going on now on a completely different level than we discussed in 1987. Is it B-cell lymphoma, is it an infection, or an inflammation? So, the big questions today, when we can cure in the early stages with very little tumor in one area of the body with one lymph node. We can cure 97%. And in stage III-IV in the advanced stages with more than two-three lymph node areas and organ involvement like lung or liver or bone involvement, we can cure it in about 90% of these advanced stages.

But the question is today and we go in detail in big discussions at this meeting, and we have sometimes opposing opinions about that. What is the right treatment? Should we give only chemotherapy or should we use combined modality in early stages? Do we need radiotherapy that gives us late effects like secondary tumors, cardio, or pulmonary problems after 10, 15, 20 years, avoids breast cancer in young girls when we treat them with radiotherapy over the mediastinum with radiotherapy, and therefore, we discussed do we need radiotherapy?

We have a new instrument that is discussed intensively here, and this is the PET, the fluoro-deoxyglucose-guided PET that lights up the tumor sites at the beginning and also intermittent after two courses of chemotherapy and at the end of therapy, and we know that if we still have morphological CT-guided residual tumor, is that still Hodgkin’s or is it not Hodgkin lymphoma just fibrosis or residual non-malignant rest? And this PET is now one of the most important instruments guiding our intensity of therapy. For the advanced stages, there is a big question here discussed at this meeting, should we aggressively start with the therapy, for instance like in Europe, we use two escalated BEACOPP, then make the PET; if the PET is negative, we go to ABVD, and this is done in many studies here in Europe. Or, we in the German Hodgkin Study Group, start with two escalated BEACOPP. If the PET is negative in these patients, we just give another two escalated BEACOPP and stop, do another PET; and if it is negative, then we do not give radiation, and we come down from 90% to 70% radiation in these stages and go down to about 10%.
We have now the Ninth International Hodgkin Symposium here in Cologne. At the fourth, the fifth, and the sixth, we had chemotherapy and radiotherapy. We had no PET, and we had no risk markers, and we had no other help for our treatment strategies than chemotherapy with the very toxic drugs like cyclophosphamide, Adriamycin, etoposide, procarbazine, and we had radiation; but since about 2 years, there is an advent of many new molecules and drugs that help us to target therapy to very specific targets in the tumor cell and in the microenvironment around the tumor cells, and this is a great new impact here in the discussions that we now have a new drug that is an antibody drug construct with a little bump on this antibody.

Thirty years ago, Harald Stein and I detected the CD30 on my Hodgkin cell line L428 here in Cologne and in Berlin, and it took us 30 years until we have an instrument with this antibody, and a very intelligent chemist in Seattle, Peter Senter, put a bump a little in our statin, a drug that inhibits the mitosis. It is a tubulin inhibitor, and with this antibody drug component and construct, we can, in relapsing and refractory patients, cure even patients and have about 70% responses with 37% complete responders in far advanced and resistant tumors that were resistant against chemo and radiotherapy.

So, we have moved forward from the biology of the disease to new drugs, and we are discussing here in the milestones of this meeting what are the milestones in hematology/oncology, and my task is here to talk about clinical trials, and I wrote I would elude on these milestones in hematology/oncology that is for me that we went from micropathology to molecular pathology. We came from eminence-based medicine that a professor said “what I say is right” to evidence-based medicine, and this is based on clinical trials with thousands of patients, and we are bridging basic and clinical research, and we have a liaison between biostatisticians, clinicians, biologists, and epidemiologists, and we all work together as a group of people to help our patients to get the higher cure rates, and it is from one-man-shows expanding to a cooperative clinical trials, and we are switching from the domain radiation therapy, chemotherapy, now to molecular targeted therapy, and hopefully, we start to integrate the third-world because it is very, very needed that we get instruments to help these people in Southern America and in Africa that they get the blessings of our progress in managing Hodgkin lymphoma.

So, we started in 1902 with anecdotal case studies. We came up to 20% cure rate. We came to local studies. Then, we came to regional studies in America or in Europe to 50%. Then, we had tumor-free survival in the cooperative groups in Stanford, in Boston, and in Europe of about 60%, and then we had national studies up to 70%, tumor-free survival, and then we started the studies in the EORTC in Europe and the German Hodgkin Study Group and finally became, even advanced stages up to 70-80%, and
today, in all stages of Hodgkin, we are up to 90%. First until 1960, it was the domain the radiotherapy curing localized stages and then in the 1965 to 1970, the Stanford Group started with randomized trials with combined local irrigation and prophylactic chemotherapy. And then, the turn came in 1965 to chemotherapy as a domain; and when we started our Hodgkin Study Group, and I like to elude a little bit on this when we started that in 1978.

Our data had 20% to 40% overall survival of our Hodgkin patients here at the University in Cologne. Then came a call from the Ministry of Health in Germany, and they gave 15 million Deutschemark to improve the clinical research in Germany, to develop and improve German clinical research, standardize and improve the care of cancer patients and foster corporation between disciplines and between clinics and private doctors. And here in Germany, we have now about 450 centers cooperating in our study, and from 2,000 new patients, we put in our studies about 80% of our patients, that means 1,600 to 1,800. This means also that we include the private hematologists because in 80%, the patients are seen by the private oncologists. Then, we activate the translational research by bridging clinical basic research, and the government wanted to enforce European cooperation and building a basis for economical research on cost effectiveness. All that had to be guaranteed by sufficient financial support.

So, in 1978, I started this with my friend and old radiotherapist. He became 99 years and died last year, Carl Musshoff, and we started, at this time, it was eminence-based medicine, not evidence-based medicine. There were no clinical trials, and 25% refused law of randomization. The doctor said no we do not take these American funny things because this is medicine for rabbits. So, I was not allowed to start with the studies, but my friend Carl Musshoff helped me, and at the first studies, we had about 5 patients in 2 years, and today, we have about 1,800 per year, and in the last 5 years, we recruited more than 5,000 patients in our studies.

Which factors were instrumental for the success of the German Hodgkin Study Group over the last 35 years? It is the continuity of leadership through all trial generations. It is a mutual translational exchange, laboratory to clinics. It is the quality assurance through panels. We have a radiotherapy panel. We have a pathology panel. We have a nuclear medicine panel and radiology panel. Every CT, every PET is seen here in Cologne of every patient in the study. Therefore, we have a very high quality, and we have workshops for the diagnostic people. We have workshops for the radiotherapists and for the medical people. Therefore, the average of the quality in the different centers even in the private practice is very high. We have an integration of all health providers and this means all private hematologists, and we have high recruitment of nearly 80% of all newly diagnosed Hodgkin patients, and we have an adequate financial support,
thanks to the German Cancer Aid, a private enterprise that gave us the money to do these studies.

So, in the last years, there was a big interaction of the basic research groups here in Cologne and the German Hodgkin study group. We described the first Hodgkin cell lines. We described the CD30 and the Ki-67 in our group. We started the research that Hodgkin is a monoclonal B-cell lymphoma, and we produced the international prognostic index with Dirk Hasenclever, and we started the European taskforce on lymphoma, and we defined nodular lymphocyte predominant and lymphocyte-rich classical Hodgkin. We tried to reduce radiotherapy from 70% to 10%, and we stayed up with cure rates up to 90%. Most importantly, since now our young patients live a normal life for 30 or 40 years, we look for the quality of life, fertility, survivorship, heart, and lung problems of these patients, and we developed in the Hodgkin Study Group the BEACOPP regimen that is competing with ABVD transatlantically in the United States. Here in Europe, most of the large cooperative groups use now BEACOPP as the induction therapy and go to ABVD if the PET is negative after two ABVDs.

So, we have come from about 0 survival to about 90% survival in 40 years, and this is a great success not withstanding that this is due to our clinical studies that we have done and thanks to our patients that were able and willing to agree to come to our protocols. It was not easy to convince them to be randomized by chance.

And also, I would like to thank all the doctors, and I would like to thank the nurses and everybody, who worked with us. With this, I would like to thank you for your attention.