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## Where are we in first line therapy for Hodgkin Lymphoma?

**Prof Johnson:** So, thank you very much for the automated introduction. It's a great pleasure to be with you this afternoon and to talk a bit about the latest data in the first line treatment of Hodgkin Lymphoma with my friend and colleague, Dr Pavlovsky. So, I'm going to start by illustrating the question that we have with a case that we've seen at our centre in Southampton. This is a 20-year-old female who presented to us because she felt a swelling in the right-hand side of her neck, and on questioning in the clinic, she told us that she had been breathless on exertion but in other respects had been quite well without any systemic symptoms. We did some tests, she had a normal blood count, her ESR was 10 millimetres per hour, and the biopsy from the right supraclavicular fascia showed Nodular sclerosing Hodgkin lymphoma. And this is her PET scan which shows quite extensive, but all super diaphragmatic Hodgkin lymphoma. So, this was Stage II AXE with unfavourable characteristics. So, the question for us was what would be the best approach to treatment in this particular case? And I think the range of options which we have for somebody in this situation really illustrates both the historical data about how we treated this illness and some of the cutting points of potential treatment for the future. So, the traditional approach, and we'll come back to this data in a minute, would be to give four cycles of ABVD and 30 Gy of involved-field radiotherapy. A number of trials have been conducted looking at the reduction of radiation exposure, which suggests that you might be able to give two cycles of ABVD, and if the PET scan was negative after two cycles, avoid the radiotherapy and give four cycles of de-escalated treatment with AVD. Similarly, the H-10 study carried out by the European group in this group of patients suggested that you could give two cycles of ABVD and then four ABVD, again, avoiding radiotherapy if the PET scan was negative. The German Hodgkin study group HD-17 study, and will come back to all these different trials in a minute, suggested that giving two cycles of escalated BEACOPP and two cycles of ABVD would allow you to avoid the radiotherapy if the PET scan was negative after this treatment. So, all of these have reasonably good evidence-base and a good rationale for taking that approach. More recently, we've seen the introduction of neuro-antibody treatments, Brentuximab vedotin or BV for short, combined with ABVD chemotherapy and a case series from Memorial Sloan Catching Hospital, which suggested that if the PET scan was negative after four cycles of that, in a case like this, it might be possible to avoid radiotherapy. And finally, another series from the United States has suggested that three cycles of the anti-PD-1 antibody pembrolizumab, followed by four cycles of AVD, again, might allow you to omit radiotherapy if the PET was negative after that treatment. And what I think this illustrates is how the treatment paradigm for Hodgkin lymphoma has shifted over the last decade or so away from what we would regard as the conventional combined modality treatment increasingly to modulated treatment according to response adapted approaches and now, starting to incorporate some of these new agents. And I think it's a way of negotiating through this landscape of new opportunities that we need. So, just to return to the overall results of therapy, if we look at how patients with Hodgkin lymphoma can expect to be treated and their expectation of survival, we know that we cure around 90% of people with the first line treatment that we give because this is of course a disease predominantly of the younger age group. The cure rate is higher in early-stage disease than it is in advanced-stage disease, and if you look overall, the around 80% of people are alive 10 years from the time of their diagnosis. And these data from the UK illustrates the progressive increase in net-

survival 10-year survival, age standardised in the UK, starting in the 1970s and ending in the first decade of the current century. Whereas I say we're up to about 80% 10-year survival. So, this has already been a very significant success story for modern oncology. It's important to note however that this is not homogeneous across the age ranges. And what this diagram shows you here from a paper that was in the Journal of Clinical Oncology a couple of years ago, is that if you compare the life expectancy or rather the cumulative mortality for the general population, which is down here at the bottom, the black lines, which you can hardly see, versus the likelihood of dying from lymphoma, which are the red lines, or the likelihood of dying from other causes such as secondary malignancy or cardiovascular disease, you can see that if you look in the younger age group, there's a relatively low cumulative mortality, certainly from lymphoma and from secondary effects, which is somewhat higher obviously in advanced-stage disease, but if we look in the older age group, we can see a significant excess mortality still from both the lymphoma and very importantly from other causes, as I say, such as cardiovascular disease and second cancers. So, what this illustrates is that we still have significant work to do, particularly in the older age populations. The competing risks are notable and it's worth making the point that some of our recent trials have shown more deaths from other causes than Hodgkin lymphoma. That's not the case in the population studies on the right here, but it isn't the case in some of our clinical trials. And really important to emphasise that this control of the lymphoma and overall survival are not the same thing. So, we can have treatments which are slightly less effective at controlling lymphoma, but still, have the same overall survival because we have in many cases effective salvage treatment, and again, we'll come back to that point. So, obviously, the primary focus of our ongoing research efforts is firstly to continue improving the results. And secondly, and very importantly in this group of predominantly younger patients with a long life expectancy to minimise the toxicity, particularly in the longer term, and thinking about competing risks and the things which we would like to avoid for the patients that we are looking after, clearly, we want as far as possible to avoid the short-term toxicity of myelosuppression, the risk of hospitalisation, infection, and of course, recently during the pandemic, susceptibility to respiratory viruses, which are undoubtedly worse with more intensive chemotherapy. We'd like to avoid inducing second cancers, either myelodysplasia and AML, as illustrated in the top panel on the right here, from exposure to alkylating agents or cardiac disease or breast or lung cancers from exposure within a radiotherapy field. In many cases, we want to make sure we preserve future fertility, which again means restricting the amount of alkylating agent chemotherapy people are subjected to. And we'd like to avoid pulmonary fibrosis, which is why we've gone to some trouble to see if we can drop Bleomycin if people have had a good response to initial treatment. We'd like to avoid cardiac muscle damage from excessive use of anthracycline and we'd like to avoid neuropathy from the effects of alkaloids, also including the antibody drug conjugates, which include vedotin, which again is a spindle poison, and of course, very importantly we want to avoid initial treatment failure and as far as possible to avoid the need for second line therapy, if at all, if at all possible. So, the first question is, in thinking about these competing risks and then thinking about the optimal approach to treatment, can we distinguish worse from less-bad disease at the baseline at the time of presentation? And there's a very long-established international prognostic score originally described by Derek Hasenclever. So, it's sometimes called the Hasenclever score, which uses seven different characteristics to segment patients into different risk categories. And this was updated recently from the same group, well not 10 years ago by the same group. And you can see the survival curves on the right there. The progression free survival curves segregated according to the number of adverse prognostic factors. And this still to this day is a useful in prognostic index for separating out the different risk categories. A variety of baseline biological assessments have been made of things like circulating cytokine levels or the tumour micro-environment or indeed circulating DNA levels, all of which are interesting and have given us some data, but none of which has been fully validated as a baseline prognostic variable. The dominant prognostic variable that we see is how well the treatment responds to therapy. And these two PET scans at the bottom of the screen here show in one case a patient who's had an extremely good response in the mediastinal lymphoma with no sign of any FDG uptake within the residual abnormal mass. And on the right hand-side, somebody who's had a very poor response to treatment with persistent FDG-avid disease within the mediastinum, and we know from

historical data and of course from the more recent studies that we've done that there's a big segregation in progression-free survival according to the responsiveness to treatment and the original paper, which has been very well-cited, is on the bottom right here, showing that patients who became PET negative had an extremely good prognosis, even if they had bad baseline characteristics. And conversely, people who remained PET positive had a very poor outlook, even if they had a low-risk characteristics of baseline. We've subsequently found that this is not entirely the case and that that there is some interaction between the two. But nonetheless, the point is the important one that responsiveness to therapy remains the dominant driver of expectation of outcome. So, at this point, I just wanted to pause and say that it's very important for you to feedback and to ask questions and to send comments at any time. We are very happy to pick these up as we go along and, and Dr Pavlovsky is going to be keeping an eye on the chat box, but I perhaps pause there and see if there's any burning questions anyone wanted to ask.

**Dr Pavlovsky:** Okay, thank you, Dr Johnson. Thank you very much for this introduction, we have some questions here. You said something that is very important and that is the difference between control of lymphoma and survival, which are not the same thing. So, when we are about to start first line treatment in our patients, which studies do you think are mandatory to decide upon treatment before we start treatment?

**Prof Johnson:** So, I think in terms of baseline assessment, we need to be able to calculate the prognostic index. And we always these days if we can do a baseline PET scan in order to define the anatomical extent. Now, there is a move towards using, radiomics, to using calculated volumes and levels of activity measurements such as the metabolic tumour volume or total lesion or glycolysis, which are potential alternatives to the conventional prognostic index. I'm not sure they're hugely better, but one of the ways in which you can segment the prognosis even at the baseline is to measure the so-called MTW that's the extent of the lymphoma and how avidly it takes up FDG which is one means of making an assessment of that prognosis. It's also, of course, important if you can, to get one of these scans at the baseline because it gives you something to measure against when you're doing your response assessment.

**Dr Pavlovsky:** So, we just see a lot of information about MTV and other baseline facts and getting some PET CT at diagnosis. Do you think we are ready to incorporate this into clinical practise to decide which patients to get more or less aggressive treatment?

**Prof Johnson:** I think it's fair to say that we are still trying to work out the optimal way in which to calculate the MTV. There are a variety of different algorithms which draw around the areas of increased uptake on scans and different ways of calculating this. And this is still a subject of a good deal of discussion and work. So, a number of groups internationally are thinking about how we can standardise these kinds of measurements. One of the other issues is that PET scanning reconstruction algorithms continue to evolve. So, the ways in which we determined PET positive and PET negative areas a few years ago have changed with differential sensitivity and software which makes it easier to spot the areas of abnormal uptake. So, I think it is still an evolving field.

**Dr Pavlovsky:** So, we still have more to learn about this, and what about there have been some numerous very important papers on the value of CT DNA.

**Prof Johnson:** Yeah, so, CT DNA, looking at circulating free DNA in the plasma of patients is one way to potentially pick up, and it's mainly based on the mutational signature that you can pick up in Hodgkin lymphoma. And there have been some important studies carried out which show that the levels of circulated DNA correlates to some extent with tumour burden. And very importantly that the changes in these with treatment may be prognostic. Now, at the moment it's quite a laborious and time-consuming process and it's difficult to do this in real-time when the advantages of using PET scanning to investigate responsiveness as you can get a PET scan done one day and you can have a report very soon afterwards. Circulating tumour DNA is a still relatively technically complex and time-consuming process, so we have a lot of retrospective analyses of the utility of CF DNA but as yet we haven't managed to apply it in real time to modulate treatment.

**Dr Pavlovsky:** Okay, thank you.

**Prof Johnson:** Okay, so thank you for that. What I'll do is I will move on to talk about some of the emerging options for systemic therapy. And I've already mentioned these in my introduction in the discussion of the different therapeutic options for the case I described. And I think the two most important molecules to draw attention to in this are both antibody-based treatments. Firstly, the anti-CD30, the CD30 targeting antibody drug conjugate Brentuximab vedotin which targets a spindle poison to CD30 on the cell surface, which is then endocytosed, liberated in the lysosomes and interrupts tumoral formation. So, it's a kind of highly-targeted version of a vinca alkaloid essentially. And then, the other approach is the anti-PD-1 antibodies, which, of course, have been very widely used in solid tumour oncology in order to modulate T-cell responsiveness and to disinhibit T-cell reactions to tumour antigens. In Hodgkin lymphoma, they seem to act by a somewhat different mechanism. We know that Hodgkin lymphoma very often has amplified PD ligands in the Reed-Sternberg cells and the fish diagram at the top illustrates the ways in which this occurs either by polysomic copy gain or amplification. And a very important paper by the German group cited at the bottom here looked into the mechanisms by which anti PD-1 is targeting and effectively treating Hodgkin lymphoma. And they did biopsies prior to treatment and then a few days after the first anti PD-1 treatment and very strikingly what they saw was a very rapid reduction in both Hodgkin Reed-Sternberg cells, but also, in tissue resident T-cell and tissue associated macrophages, suggesting that this antibody ligation is interrupting cell-cell signalling between PD-1 and PD-L1 which is sustaining the Hodgkin Reed-Sternberg cells in the micro-environment. So, there wasn't any evidence of a stimulation and you wouldn't expect it so soon after the first treatment of an active T-Cell mediated immune response, what there was a depletion of the micro-environment which was sustaining the lymphoma cells. And it looks as though these agents were acting directly by their effect on inhibition of cell signalling in the micro environment, which of course explains the very rapid responses that we see to their use in the clinic. So, those two classes of agent working by very different mechanisms are potentially I think going to be very exciting for the future approaches to treatment. And I'll talk a bit about that. So, firstly to return to early-stage lymphoma and what we would regard of being the standard of care, two very important trials published some time ago now by the German Hodgkin study group looking on the left hand- side at early-favourable disease, that's to say non-bulky disease, stage 1 or 2A without adverse factors such as multiple sites of involvement or race sedimentation rate. And the experiment, there was to compare two versus four cycles of ABVD with 20 versus 30 Gy involved-field radiotherapy and showed equivalence and extremely good results for any of those approaches suggesting that the lowest approach to treatments, so two cycles of ABVD and 20 Gy radiotherapy would be your standard and favoured approach. In unfavourable disease of the type which I showed you in the diagram there, the randomization was between ABVD and BEACOPP chemotherapy and again, 20 versus 30 Gy of radiation. And what the finding was in this study was that disease control was slightly lower if you used the less intensive chemotherapy ABVD and the lower-dose of radiation. So, you could choose between either having four BEACOPP's and 20 Gy or four ABVD and 30 Gy to get your optimum results. But again, important to emphasise as we've already said, that overall survival is not the same thing as feeling from treatment failure. And in all of these groups the overall survival was extremely good because patients could be readily salvaged even if they recurred after this approach. But this really set the standard for what would be regarded as a standard combined modality approach for early-stage disease. And we've done a series of trials over the last decade looking at whether we could use interim PET to determine who had had a good enough response to treatment to be able to de-escalate the therapy and in this case, in the case of early-stage disease to leave out radiation. So, the RAPID study which was published back in 2015 took patients who were treated with three cycles of ABVD, and this was favourable and unfavourable groups, but provided they had non-bulk disease, if they were PET positive, they completed four cycles with involved radiotherapy as well. And if they were PET negative, they were randomised to either receive the radiotherapy or no further treatment. The European H-10 study segmented the population into favourable and unfavourable. They were randomised at the baseline between a standard approach, which were favourable with three cycles of ABVD, and involve

node radiotherapy. So, two cycles before a PET scan and then, one cycle in radiation afterwards, or in the unfavourable group, four cycles of ABVD and involve-node radiotherapy in the standard arm. And then, in the experimental arm, the PET result was acted upon so that those who were negative, who had favourable disease had two more cycles. Those who were unfavourable with PET negative disease had four more cycles but no radiotherapy. And those who stayed PET positive had their treatment escalated to BEACOPP chemotherapy and had the radiotherapy as well. And then, the German Hodgkin study group did two studies, one HT-16 unfavourable disease and one HT-17 in unfavourable disease. Again, patients were randomised at the baseline to either a standard approach or a PET-mediated approach, the favourable ones got two ABVD, the unfavourable ones got two BEACOPP and two ABVD, before the PET scan; in the standard arm, they all then went on to receive involved-node radiotherapy. And in the PET-driven arm, those who were PET negative had no further treatment and those who were PET positive had the radiation. So, in this group, favourable disease could result in simply two cycles of ABVD. So, this was the lowest intensity of treatment of all. So, these trials had very complimentary design and yielded complimentary information. And I've summarised them very briefly on this slide here. And in the top row you can see the results in predominantly favourable disease. These are progression-free or event-free survivals. And what you can see is there's a small but definite reduction in lymphoma control in the groups in which the radiotherapy was omitted, whether it was in the RAPID, the HD-16 study where they only had two cycles of ABVD or the H-10 study where they would have four cycles of ABVD if they were PET negative. And you can see there's a small but definite reduction in progression-free survival. Interestingly in the unfavourable group where the control arms got rather more chemotherapy, six cycles of ABVD in the case of H-10 or two BEACOPP escalated in two ABVD in the case of HD-17, the results were much closer together and there was a much smaller difference in progression-free survival. Finally, what I've put on the right here are the results of a non-randomized single arm studies. This is the Memorial Sloan Kettering experiment giving brentuximab vedotin in class ABVD, different cohorts who received different dwindling amounts of radiotherapy and cohort four, in fact, received no- radiotherapy at all if they were PET negative showing excellent two-year progression-free survival. But it is important to emphasise this is only two years, and finally, a study from the US, and we'll come back to this study a bit later, looking at pembrolizumab given before AVD where there were no relapses at all in this group of patients, none of whom received radiotherapy. So, it looks as though omitting radiotherapy is at least a potential option, but in favourable disease with conventional chemotherapy based on ABVD, it looks as though there may be a small reduction in disease control. Of course, that may be worth it if the radiation field was going to be potentially damaging, causing coronary artery disease or second malignancies in later life. The other important point to make once again, is that overall survival is extremely good in all of these cases. And even where there was a slight diminution of lymphoma control with the first line treatment in these studies where the radiotherapy was omitted after a negative PET scan, you can see that the overall survival figures are all extremely favourable in all of these groups suggesting that whatever the approach it's taken, the outlook is very good for this group of patients. So, if I can try pull the evidence together for early-stage disease and say where I think we've got to in this, I think we have to acknowledge that combined modality treatment remains our standard of care, but the PET driven response adapted studies have shown that you can modulate treatment according to an interim PET scan and that it's certainly worth considering chemotherapy only approaches for people with low-risk disease, something like a low MTV at presentation and if the PET is negative after two ABVD for people if they have unfavourable disease, if they have a negative PET scan after two BEACOPP and two ABVD, as in the German study. And most importantly for people at high-risk of a second cancer or cardiac damage if the radiotherapy field is going to cover organs that are sensitive to those. So, I think that's where we've got to at the moment. And I think for the future, I'm hoping this will become an increasingly academic question because particularly I think the results of the anti PD-1 followed by chemotherapy where they have had no relapses with just under three years follow-up, are highly suggestive that this may be the optimal approach for the future provided there's no signs of untoward long-term toxicity or late relapses. So, I think we are gradually moving away from the use of radiotherapy in early-stage disease. I don't think it's completely gone and certainly, there are still groups of patients for whom we

would consider it as standard, particularly, if the radiotherapy field is in a non-damaging site. But nonetheless, I think that this is very much an evolving field. So, I think we'll pause briefly there and again, see if there are any questions.

**Dr Pavlovsky:** So, Peter, I think this question has been going on ever since the presentation or the publication of the RAPID trial. Whether we should look further into this small reduction in PFS if we radiate our PET negative patients or should we give more importance to the same overall survival for all patients avoiding radiotherapy in most of our patients? And you mentioned which patients you think in which we should consider avoiding radiotherapy, but what about young patients with no other comorbidities in your everyday clinical practise? And regarding these results you just showed, you think we should take into account this small difference in reduction in PFS and go on with radiation or should we consider that the overall survival is the same and we can avoid radiotherapy in most of our patients?

**Prof Johnson:** So, this is a discussion we have every week in our clinic with the patients and the important thing is to share this kind of information with the patients. It's relatively straightforward to explain we can use chemotherapy alone as a slightly higher-risk disease might come back, but we avoid some of the long-term risks of radiation or we can use combined modality treatment if what we want to do is absolutely optimised the chances of first-time cure, and different people will come at that in different ways. If you are an old person like me who's got lymph nodes in a radiotherapy field where involved field radio therapy is very unlikely to give you long-term consequences, then, I think the combined modality treatment on the optimised chance of first-time cure is dominant. If on the other hand you are a young woman with extensive disease in the mediastinum maybe around the base of the aorta and the coronary Ostia or involving a significant amount of breast tissue, then, it seems the balance is really tipped in favour of a chemotherapy-only approach and avoiding the potential long- term consequences of radiation. So, I think it's what we have now is a useful body of information which tells us how well these approaches work and what the relative risks are in these and we can have those conversations with our patients on that basis.

**Dr Pavlovsky:** And also, do you think considering this result you just showed that if a patient is in favourable or unfavourable group achieves the negative PET CT the risk for that patient is the same, meaning that after achieving a negative PET CT, basal prognostic factors are no longer relevant?

**Prof Johnson:** Now, you make a really important point and that is that we know that the negative predictive value of a PET scan after, as an interim point in treatment, is determined by two things. Importantly, it's determined by how bad the disease was before you started. The risks of recurrence in people who had bad disease before they started are actually higher after a negative PET scan than they are if the disease was of low-risk beforehand. And also, the intensity of the treatment you use to get there. We know that the negative predictive value of an interim PET scan after escalated BEACOPP is higher than the negative predictive value of a PET negative PET scan after ABVD. So, there's an interaction between how bad the disease is, how intensive the treatment is, and what the predictive value of your PET scan is. And I think that's really important for people to appreciate. A negative PET scan is not the same thing in all cases. It depends how bad the disease was and how much treatment you had beforehand.

**Dr Pavlovsky:** And another confusing thing is these trials defined a negative PET CT in a different way, right? Every trial has different definition?

**Prof Johnson:** Yeah, just to be confusing, different thresholds for what was called PET negative. The more stringent trials, the RAPID trial and the German Hodgkin trial used Deauville scores of 1 and 2 as negative. Whereas in some of the other trials and the advanced disease trials, with 1, 2 and 3 is negative. And I think that speaks to our lack of knowledge at the outset of these studies about exactly where the cut-off would fall. I think these days, most people accept the fact that a Deauville score of 1, 2 or 3 can reasonably be regarded as a negative PET scan, 4 and 5 are positive. There is still debate about the significance and importance of a Deauville score of 4, and we know that even with a score of 4, in some cases, people will still

go on to have a relatively good prognosis with continued low-intensity treatment. What we do know is the PET score of 5 is a very bad sign if you have that in the middle of treatment.

**Dr Pavlovsky:** Okay, thank you.

**Prof Johnson:** Okay, so, I'm now going to talk a little bit about some of the studies which we've done in advanced Hodgkin lymphoma trial and again, define what we could do about modulating treatment and how we might change our approaches. And again, three sets of trials to draw your attention to firstly the raffle trial, again, some years ago, now, where we gave people two cycles of ABVD and did an interim PET and if the PET scan was negative, they were randomised between continuing ABVD or omitting the bleomycin and just receiving four cycles of ABD, they didn't have radiotherapy. If the PET scan was positive, they were either escalated BEACOPP or BEACOPP-14. And again, if they became PET negative after three or four cycles of that, they went on to complete chemotherapy-only and didn't have radiation. The German Hodgkin study group looked at a similar approach, but using BEACOPP as the initial therapy, patients had a PET scan, if they were negative, they were randomised between fewer or the normal number of cycles of BEACOPP which started out being 8 and went down to 6 during the course of the trial. And if they were PET negative, they were randomised to have rituximab added to their treatment or not. And finally, the trial in the middle of these two was the group run by the French trial, AHL-2011 where patients were randomised between a standard approach of 6 cycles of escalated BEACOPP or a PET modulated approach where they had 2 BEACOPPs and if the PET scan was negative, they went down to receiving ABVD, and if it stayed positive, they carried on and had the BEACOPP as originally planned. And these are, to get a long story short, the progression-free survival curves for those groups who became PET negative after ABVD in the case of the RATHL study, after BEACOPP in the case of the LYSA and the HD-18 studies and what you can see in all of these cases is the de-escalation of treatment after a negative interim PET scan with whatever chemotherapy you started with, resulted in overlapping curves, whether it was dropping bleomycin, whether it was going down from BEACOPP to ABVD or whether it was reducing the number of cycles of BEACOPP, the results were overlapping in all of these trials indicating that in this case a negative interim PET scan is a very good sign that you can de-escalate the treatment in the way anticipated. What you'll also see from the figures here is that the progression-free survival overall is lower in patients with advanced Hodgkin lymphoma, if you start with ABVD, it's about 82%, compared to if you start with BEACOPP where it's up at around 90% in both the LYSA and the HD-18 studies. So, you can push up your progression-free survival by starting with more intensive chemotherapy, but you can then de-escalate or reduce the amount of chemotherapy subsequently. Another trial which was important in this context looked at the use of consolidation radiotherapy. And again, this is from an Italian group where patients had two cycles of ABVD and if the PET scan was negative, they completed six cycles of treatment but were randomised to whether or not they had radiotherapy, if they had a residual mass. And what this group showed was that that made no difference at all if it was a PET negative mass, whether you irradiated it or not. So, this was really good evidence that we don't need to give consolidation radiotherapy if people have a negative interim PET scan. Of course, the most recent trial which has gone a lot of attention was the ECHELON-1 study, which took a slightly different approach. So, patients with stage 3 or 4 disease were randomised between ABVD or AVD with brentuximab vedotin so-called AAVD. They then had an interim PET scan and the great majority of patients would carry on with their protocol treatment. So, if they had a Deauville score of 1 to 4, they carried on with whatever they'd been allocated, either AAVD or ABVD. And only those who had a Deauville score of 5 were suggested to come off protocol, although, they were in this case allowed to continue with the protocol described treatment as well. And the results of this have been published on a couple of occasions. Firstly, in 2020, the study which showed a difference in progression-free survival on the top left here between 76% with ABVD and 83% with AAVD. And then, more recently, this is in the New England Journal of Medicine this year, this is the overall survival figures showing a small but definite difference between AAVD and ABVD. And you can see there that there's a difference in the overall numbers of deaths between 39 in the AAVD arm and 64 in the ABVD arm. Interestingly, quite a significant number of deaths from second malignancy in the ABVD arm. Slightly unusual finding because most studies of ABVD

show very low-rates of second malignancy. So, slightly difficult to know how to interpret that data. But nonetheless, because the number of events in even the control arm is very low, the hazard ratio for death it now reaches significance at 0.59 indicating that there is a small but definite difference in overall survival. And this is the subgroup analysis from that same paper in the New England Journal of Medicine, looking to see which groups are most likely to benefit from using Brentuximab vedotin. What we can see here is that it's men, in whom the effect is dominant and it's those with a significant amount of extra nodal disease. So, stage 4 disease does better than stage 3 disease with Brentuximab vedotin. And the number of extra nodal sites also appears to have an influence on this. So, overall, it appears to be men with worse prognostic disease who stand to benefit most from the addition of brentuximab vedotin and in some respects, as we can see that doesn't appear to be anything like as large and effective, in effect at all in women of those with low-risk disease. Finally, very importantly, as I said at the beginning, treating the over sixties remains a challenging problem in Hodgkin lymphoma. And there was hope that using brentuximab vedotin might allow us to give more effective intensive treatment to this group for whom it's difficult to give neomycin for example because of the risks of pulmonary toxicity. But you can see from this analysis that was published again this year looking in the over 60 group, that this doesn't appear to be the case unfortunate in this group. And if we look at the overall survival figures here, we can see that the group that for over 60 appears to be close to the line of unity. So, unfortunately, brentuximab vedotin doesn't appear to be a fantastic answer for older patients, although the study that Andrew Evans also reported of using it sequentially with chemotherapy did show a very good response rate. So, I think the jury is still very much out on how best we manage older patients with Hodgkin lymphoma. One of the other analyses which is important is to look at the potential cost and Brentuximab vedotin remains unfortunately quite a costly drug and if you have to give 12 doses of it as part of a course of chemotherapy, that adds very significantly to the bill. And so, this analysis published in Lancet Haematology a couple of years ago now, looked at cost-effectiveness modelled according to the, qualities that were gained by giving these different treatments. And in fact found that probably the AHL-2011 programme was the most cost-effective. So, starting with BEACOPP and de-escalating to ABVD seems to be the most cost-effective approach closely followed by the RATHL approach, starting with ABVD and going down to AVD. The ABVD starting approach becomes more attractive in cost- benefit if there are concerns about fertility, which is obviously a concern with starting with more intensive treatment. But as you can see, brentuximab with AVD remains a relatively expensive option and the changing costs shown in this diagram here if you use the list price is extremely striking. So, I think we're still waiting to see how best to use something like brentuximab vedotin and particularly given the subgroup analysis that we've seen and the suggestion that there may be more benefit in some subgroups than others. The study to which I want to return having already mentioned it in the context of early stage disease, is this small study of 30 patients given three doses of pembrolizumab, anti PDD one antibodies is sole therapy prior to going on to have a PET scan and then, going on to AVD chemotherapy for six cycles following this, if there was a good response, and what the PET scan on the right shows you is a really very striking response in somebody with very extensive supradiaphragmatic disease of the same sort that I showed you in our case at the beginning with an extraordinarily good response to three doses of antibody treatment with this very rapid reduction of both the anatomical extent and the FTG uptake. And this was a combined study of both patients with early unfavourable and advanced stage disease and I've already showed you the progression-free survival curve, which at the time that this was published in Blood was at 24 months and has now been extended and it is in a pre-print at 33 months. So that I think is a potentially very striking initial observation. The follow-up is short and the numbers are small, but I think if that holds up, that may well transform the way we approach this illness. So, trying to summarise where we've got to in thinking about our initial therapy, I think combining risk-adapted approaches based on prognostic factors and response-adapted approaches using PET to modulate our approach probably offers the optimal approach, optimal strategy. I think our antibody-based therapies seem likely to be coming in to replace chemotherapy-alone regimens in the first line, certainly, in those with worse prognosis disease and of course providing the costs are manageable and something like a PET-adapted approach may help in this respect because although there's absolutely no trial data to support

this, you could consider starting with AAVD and then de-escalating to AVD if the PET scan was negative after two cycles. We can see from the data in the ECHELON-1 study that AAVD results in a higher progression-free survival and a small increment in overall survival compared to non-PET adapted ABVD and it also appears importantly to be less toxic although more costly than starting with escalated BEACOPP. So, I think overall using an interim PET scan to determine de-escalation of treatment is a good approach. It allows us to decide not to use radiotherapy. If you're using bleomycin, it allows you to drop the bleomycin or to reduce from BEACOPP to ABVD, or to give fewer cycles of BEACOPP and all of these are legitimate strategies based on the evidence we have. So, to conclude finally on this illness, I think we can see and I said at the beginning that Hodgkin lymphoma is generally a curable illness but there remains scope to improve the outcomes particularly for those with very bad disease at presentation or whose interim PET scans are positive or of course for the older patients for whom our conventional approaches are still struggling to cut through. And again, it will be interesting to see whether something like the anti PD-1 approach gives us a better level of efficacy in the older group. I think that adapting according to baseline risk and response as measured by FDG-uptake still gives us our best combined approach to the way we treat these patients. And as I've said already, I think the antibody targeted treatments with the impressive results we are seeing in the early studies are going to continue evolving our model of treatment. And finally, up on the top-right there is a picture of our friend Kairos and this is a nod towards Folkadeal who really started out with the idea of the most effective initial treatment being the place you'd want start in this illness. So, I will stop there and again thank you very much. And invite any questions or comments.

**Dr Pavlovsky:** Thank you very much and I think a lot of questions have been coming up and a lot of discussion on this, I think the new debate is whether we really should be incorporating first line and we have some questions regarding this and maybe, the questions are regarding what importance should we give to subgroup analyses because some statisticians say that subgroup analyses are not worth doing or worth taking into account. So, one of the questions is from one of my colleagues here, in Argentina, Fernando [Audio Not Clear] is why do you think ECHELON-1 showed such difference between men and women, can this be a confounder or is it possible that men have more advanced disease with more extra nodal and higher RPF? And also, together with this, my first comment, do you think we should rely on subgroup analyses in order to decide which patients will benefit from BV in first line?

**Prof Johnson:** I will give you my personal view. I think the benefit from BV is, as you can see from the curves, a relatively small degree, it does appear to be skewed towards particular populations. And I think we have to bear that in mind when we are thinking particularly in cost-constrained healthcare systems about where you are likely to derive most benefit. We've known for a very long time that men generally speaking have a poorer prognosis than women with Hodgkin lymphoma, particularly advanced disease, it's part of the prognostic index. So, it's perhaps not surprising that a more active agent is more striking in its effect in a worse prognosis group, whether that's men or people with more advanced disease. So, I, whilst I completely understand the caveats about subgroup analyses and the fact that we really should be looking at multi-variable regression rather than simple subgroup analyses to make sure that we don't have confounding variables, I think we do need to look very carefully, particularly, when we are thinking about the best use of resource about which groups are likely to derive most benefit from these types of treatment.

**Dr Pavlovsky:** And also, regarding the results of this trial, some patients use BEACOPP for advanced stage CT. So, the question is there any data regarding projection of ABVD versus BEACOPP in first line Hodgkin lymphoma? And how should these groups that usually choose BEACOPP incorporate this new information?

**Prof Johnson:** Yeah, so, the German Hodgkin study group have been studying BREKAD which incorporates brentuximab vedotin into their first line regimen and they're doing a trial which I hope will give us some information about that. But at the moment there is no head-to-head comparative data between AAVD and escalated BEACOPP which is a shame. We had tried to incorporate that into the RATHL study for our escalation arm, but we didn't manage to get that done.

**Dr Pavlovsky:** Okay, I think we have time for one more question regarding the stuff you showed about a bulky disease with a negative PET CT doesn't necessarily need radiotherapy. Are we ready to incorporate that in our clinical practise regarding these trials and can we extrapolate this to localised stage disease?

**Prof Johnson:** So, it's important to emphasise this is about advanced disease and we are very confident now that if you have a negative interim PET scan you can omit consolidation radiotherapy for a small residual masse at the end of treatment, and there's data from the Italian study and there's also very good data from the German Hodgkin study group as well. So, I think we are very confident about omitting consolidation radiotherapy in that group of patients. I think it's a different story in early-stage disease as we've already seen and you need to take into account the different risk profiles and the anti-seeding treatment. So, advanced disease, I think we are confident.

**Dr Pavlovsky:** And maybe just one last minute to let you and share with us, which way do you think we're going, what's the future of first line treatment of Hodgkin lymphoma?

**Prof Johnson:** I'm optimistic that these antibody-based treatments are going to change the way we approach first line treatments and I, whilst the data with the antibody drug conjugate is interesting, in the end it's a form of targeted chemotherapy. I think the ability of the anti PD-1 antibodies to block the cell-cell signalling in the micro-environment seems to have such a dramatic effect on the lymphoma that it feels to me as though this is the kind of rituximab moment for Hodgkin lymphoma in a way, and that seems, feels to me as though we're on the cusp of a shift in the way we approach the treatment.

**Dr Pavlovsky:** Okay, thank you very much. So, hopefully, we'll soon cure more people with less chemotherapy. Hopefully.

**Prof Johnson:** Indeed.

**Dr Pavlovsky:** Okay, thank you very-very much, for this very interesting review, and I want to thank also all the viewers in different countries and we hope to keep on going on with this educational moment. Thank you very much.

**Prof Johnson:** Thank you.