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How to deal with checkpoint blockade failure in HL

Dr Pavlovsky: It's my honour to introduce Dr Philippe Armand who has become a very important teacher to all of us about checkpoint inhibitors in the use of Hodgkin lymphoma. He's Chief of the Lymphoma Division in Dana-Farber Cancer Institute. So, thank you very much, Philippe, for joining us in this activity.

Prof Armand: Thank you. Thank you, thank you, thank you for inviting me. It's a great pleasure always to see you, and to be here. You can see my screen okay?

Dr Pavlovsky: Yes, yes.

Prof Armand: I spent a lot of time on this slide, so, I'm leaving it up for a long time.

Dr Pavlovsky: Okay, we appreciate it.

Prof Armand: So, I am indeed gonna talk about checkpoint failure in Hodgkin lymphoma, and try to keep it around 30 minutes or so. And as probably whoever's in the audience now knows, checkpoint inhibition has really altered the treatment paradigm in Hodgkin lymphoma over the last decade, by providing at least a new effective drug for patients with relapsed/refractory disease. And now, checkpoint blockade, especially PD-1 blockade is part of most trials in most settings in classical Hodgkin lymphoma. But at this point, it's leading to this fast-moving jumble of both small and large studies, which are, I think, increasingly difficult to make sense of. So, if you stick to on-label use of PD-1 blockade, which is a single agent in relapsed/refractory disease, most of these present a tantalising future of a more effective way or earlier way to use these therapies. If you think about using the drugs off-label then, it's a confusing present because it's not clear where they belong. And so, what I'm gonna try to do in the next half hour or so is to go through some of the data that I've accumulated over the last few years, and looking at it through the lens of checkpoint failure, because I find that, to me, it's a helpful way of organising the information for me. So, I hope it is for you as well. So, we'll talk about three kinds of failure. So, we have progression, pre-emption, and prevention. And to start, just go through the basic foundations, just so we're all on the same page. It was recognised now over a decade ago that classical Hodgkin lymphoma has a very unique relationship to the PD-1 pathway, with these near-universal genetic amplification events at 9p24, that results in over-expression of the PD-1 ligands, PD-L1, PD-L2, on the surface of the tumour cells. And as well, which will become briefly relevant later, activation of JAK-STAT signalling, since JAK2 is on the same 9p24 amplicon. And now, we know for sure that there's strong activity of anti-PD-1 monoclonal antibody in relapsed/refractory disease. So there are five agents that have been tested in phase II which you can see here. Only two of them are approved in the US. The other three have been developed in China so far. And across that experience, the overall response rate is about 65 to 85%, depending on the study and the kind of patient. And the CR rate is 15 to 35%. There's one notable exception, which is tislelizumab, which is now being picked up for development in the US, and which in phase II had a quite a bit higher CR rate of 67%. whether that's real and represents a better antibody is still unclear.

I think it's certainly an intriguing signal, but I hope that we get additional data in this space as the development of this drug proceeds. We also know from the KEYNOTE 204 study, which was a phase III study, that pembrolizumab is more active than brentuximab. So, this was a direct comparison of single agent activity, and as you can see on this graph, the progression-free survival was better with pembro. As well, there seemed to be better quality of life for patients on this study. What that means exactly is not clear. I think at this point, few patients come to us with relapsed/refractory disease, not having seen either of these drugs, and if that's the case, we would either combine them or sequence them. So, this PFS benefit may not be of great clinical significance in terms of how we use a drug, but it is confirming that it's an active agent, and probably, a most active drug, if not the most active drug, in relapsed/refractory Hodgkin lymphoma. But this is the problem. And this is, I think, the foundation for the rest of this talk, that despite this activity, most responders will progress and most of them will do so within two years. So here on the left, are some duration of response curve from CHECKMATE 205, which was a phase II pivotal study of nivolumab. And then, the right is KEYNOTE 87, which is a phase II study of pembrolizumab. On the left, the curve is separated by response-quality, PRCR, we'll come back to that. And on the right just by cohort, but you can see they have basically the same shape. And at two years, there's been a more than 50% on both studies of patients that have lost response. And if you walk far enough out to five years, it's really a minority of patients, maybe 20% or so, who are still in response. So, for the majority of patients, this is a good drug, but the benefit is limited to that time-frame. And so, that's the first way to think about it, is we need to tackle the challenge of checkpoint failure, because in most patients this therapy will fail. And this slide is to remind you to ask questions, and send comments at any time through the Q&A, which should be on the bottom of your Zoom window. And this slide will come up again, forward. So, the first and the most obvious mode of progression, but the one that probably haunts us the most in clinic today is progression. And by which I'm referring to progressive disease on PD-1 blockade. And so, what does that look like today? One option that we have always is treatment beyond progression. And this is a concept that has gained traction in general with checkpoint blockade, not just in lymphoma, and which was adopted in lymphoma. And I think it is a really, it is a useful strategy. It's hard to get definitive data on it, but the study which I'm showing you comes from my colleague, Reid Merryman, which was based on a multicentre retrospective series, that included 20 patients who were treated beyond progression, and those are in the red curve, compared to 44 who weren't, who are on the blue curve. And there's a low objective response rate for the patients who continue beyond progression, but there is really a suggestion of meaningful clinical benefit. And if you look at the top-left panel, this is time-to-next treatment, which was better for those patients treated beyond progression, that's the most obvious, but also the most questionable one, because, of course, if you continue patients on therapy, you might delay their next treatment, but that doesn't mean it's better. So, I think the real value is in the other curves. If you look at the bottom left, this is time to subsequent treatment failure. So, the time from progression until the time that they failed their next line of treatment. And you can see it was better in the patients that were treated beyond progression. And similarly, if you look in the top-right, this is PFS2. So, this is the progression-free survival of patients to their next line of therapy. And the concern would be, you treat them beyond progression, you get some mileage initially, but then, they won't have as longer remission with their next line of therapy. If anything, it seems to be the opposite. They seem to do better with their next line of therapy, if anything. So, all those, I think, are encouraging signals that we can do that, and that we do benefit patients by doing that, but of course, it's very, very important to emphasise that these studies are full of selection bias. So, it's not for everybody, and it is impossible to definitively say that there's a benefit. But I think I certainly do it in clinic all the time. Patients have progression, but they're doing well, you continue therapy and see what happens. The other thing that this alludes to, which I think is much more important, is the concept of chemo-sensitization. And that basically refers to the improved benefit of chemotherapy when given after PD-1 blockade. And there's been a strong signal for that for a long time. And there are actually a couple of publications that have looked at that, both retrospectively. And in both cases, the response rate to subsequent therapy after checkpoint blockade failure was 65%, about 40% CR. That's pretty high when you're considering where those patients typically are. So, typically, by that point, they're like fifth line of therapy,

sixth line of therapy. And we don't expect those kinds of responses. And even more convincingly in both papers, and in our own experience, we've had patients who were sensitive to chemo that they were previously refractory to. That's pretty, in my mind at least, pretty convincing evidence that the drug is resetting something in terms of the chemo-sensitivity of tumour. And if you look at this as a PFS curve from the second paper, from the Carreau study, and stretching pretty far out, it's actually quite a good PFS curve. Of course, it's not stable once you get beyond a thousand days, but a thousand days is a long time, and still, the majority of patients were progression-free. So, I think there really is something to that concept, and it actually drives a lot of what we'll talk about in a bit about considerations around transplant, et cetera. So, I think this is really, really important. So, speaking of transplant, one issue that comes up in this setting is what's the role of allo-transplant, so, again, for patients who progress on PD-1 blockade? And the early signal for that is that prior PD-1 blockade appeared to increase both the toxicity and the efficacy of transplant. But what we've learned in the intervening years is that the increase in toxicity seems to be mitigated by the choice of transplant strategy and in particular by the use of post-transplant cyclophosphamide. And I'm showing here curves from another paper by Reid Merryman, in which was an international cohort of patients, over 200 patients who were allografted after PD-1 blockade, with or without intervening therapy. And you can see on the left, the PFS, which is the red curve, was about almost 70% at two years. That's really good for allo-curve, I think, for Hodgkin. Traditionally, the allo-PFS curve sits more in the 30, 35% range. So, that's quite good. And on top of that, if you use PTCY, which you can see on the right panel, the outcomes are definitely better. So, this particular panel is GRFS, which is GvHD relapse-free survival. And whether it is done with a haplo donor or a non-haplo donor, the PTCY patients did much better for GRFS, which was 60% at two years. Again, for GvHD and relapse-free survival, 60% at two years, I think is quite good, and should definitely alleviate the concerns for doing allo after a checkpoint blockade. We also learned from this study that the outcomes of allo differ by remission depth. So, it's better to go to transplant in CR, but not by whether patients had intervening therapy or not. So, if they're in CR it doesn't matter much whether they were transplanted straight off PD-1 blockade, or in their next remission. And same thing if they're in PR at the time of transplant. Of course, you have to get them back in remission of transplanting. And now, let's switch gears to autologous transplant. We'll come back to allo decisions in a little bit, but auto-transplant is also a bit of a surprising finding here. This is another study of Reid, looking at 78 patients from US centres. Again, retrospective, who got auto after PD-1 blockade. Similarly, they could have had intervening therapy or not. And the 18-month PFS, as you can see here, is 81%. Again, that's quite good for auto in general. Now that's not so different from what we typically expect from auto-transplant, but it's good when you think about who those patients are, because they tended to be pretty refractory. And even if you look at the patients who are triple refractory, so, this is refractory to three lines of chemo before PD-1. Which are patients that I think before we would never have thought about autografting those patients. If they've gone through three lines of chemotherapy, why ever would you give them high-dose chemo? But their PFS was 67% at 18 months, which again is remarkably good. And to go back to that theme, I think what it reflects is chemo-sensitization. So, getting PD-1 before auto-transplant is probably ideal, because you sensitise them to the high-dose chemo. So, that's also demonstrated here in this subgroup analysis, that the outcomes were similar in terms of PFS, even for patients with very refractory disease. It is probably better to do this straight after PD-1 blockade, unlike for allo. And unlike other auto setting, it may not be critical to have patients in metabolic CR. That's generally a theme with checkpoint blockade, that complete metabolic response may not be as meaningful as it is for standard therapies. And that was the case here. So, there was no benefit to being in CR, again, in a retrospective study. So, I think what we can conclude today is that both allo and auto-transplant have very good outcomes after PD-1, or after PD-1 failure. But you have to remember, those are consolidative, not rescue options. So, you have to be able to get your patient back in remission if you're gonna wait for failure. And that concept, now, if we project it in the future, this progression on PD-1 blockade, or PD-1 refractoriness, I think represents the new unmet need in Hodgkin lymphoma. In practise, we're treating patients often with chemo used as a bridge to stem-cell transplant, but that defines a new clinical trial population, and probably, the population that's in the greatest need for novel therapies. So, what's out

there now on the investigational horizon? There's a lot of activity in checkpoint combinations. And then, there are a couple of novel agents that I think are very promising, that we'll talk about briefly. You've seen this before. So, remember to ask questions and make comments. So, this slide summarises the activity of checkpoint combinations in five studies that are listed here. Those are all studies in PD-1 naive patients. So, this is PD-1 plus, when patients haven't received prior PD-1, you can see I'm not gonna go through it in detail, but PD-1 with CTLA4, PD-1 with KIR. So, this is an interesting drug, this AFM13. AFM13 is a bispecific antibody, that's CD3, CD16. So, it's actually trying to bring the NK cell in contact with the Reed-Sternberg cell. And it's interesting, because as we've realised now over the last 10 years, in terms of studying the biology of this, there really might be an important role to NK cell activity in mediating the effect of checkpoint blockade. And without going too far into it, because that would take us beyond the time-range of this talk, but if you think about it, Hodgkin is a disease that often lacks MHC, both MHC Class I and MHC Class II. The majority of tumours are negative for one or the other. They say, well, if that's the case, how do people ever respond to checkpoint blockade? And perhaps, it's because some of it depends on NK cells. So, we might see more NK-based therapy in the future. I think it's very interesting. And then the last two studies are with brentuximab, which is not really immunotherapy, but I list them here, either brentux-nivo, which has been done a few times, or the triplet of nivo, brentux and ipilimumab. And if you look at the table, in general, you see that the response rates are high, the CR rates are good. They seem to be best with BV-nivo. We know by now that this is really an active therapy, but it makes sense because they're two active drugs. And the PFS for the doublet combinations that are not BV-based, are not clearly better than single agent PD-1 blockade. Of course, when you add brentuximab, you get something that does look better. Here, the three-year PFS of 77%, in second line, a one-year PFS of 70% beyond the second line which is better than what we expect with single agent blockade. But the point is it's hard for this to pick a winner. It's hard to look at these data and say, "Oh, this is obviously the doublet of choice". And part of that reflects the fact that PD-1 by itself is active. So, when it's studied in PD-1 naive patients, it's hard to know even what endpoint to look at. Should we look at CR, should we look at PFS? And that's made, I think, moving these combinations forward a little bit challenging. But a way round that is to study PD-1 refractory patients. So, there are four trials in this space that I wanted to mention. The first one, the one that has the most data, is PD-1 plus HMA. And the combination in particular is this combination of camrelizumab plus decitabine that's been published by a Chinese group now in a couple of papers. So, they have accumulated a sizeable experience, both of PD-1 naive and PD-1 refractory patients. Camrelizumab is not available to us in the United States. And we assume that this is portable to other PD-1 antibodies like nivolumab and pembrolizumab that are available. Of course, we don't know that for sure. There is a trial that is ramping up that is studying a similar combination in US patients with pembrolizumab or nivolumab. One of the two, I can't remember. But here, if you look at the response rate in the PD-1 refractory patient, 60% with a CR rate of 30%, and two-year duration of remission of 50%. That's really good for PD-1 refractory. That's about as good as I think we've seen. And that does suggest that there is a good synergy between those drugs. Alex Herrera just presented at ASH, the combination of pembro-vorinostat, and again, like with HMA, there is some preclinical rationale for studying these combinations. Also, with a PD-1 refractory cohort, also, with good response rates, 61%, their CR rate was 11%, and the one-year duration remission was 50%. So, not quite as good as what was published with cam and decitabine, but still pretty good. The other interesting trial was presented by Veronika Bachanova of nivo plus ruxolitinib. So, a JAK2 inhibition, only in PD-1 refractory patients. Here, the response rates were a little bit lower, but still, the median duration of response of a little over a year. And of course, the reason, this is interesting, because the biology is so compelling of this, that we know JAK-STAT is amplified, and so, to go after it makes sense. Unfortunately, the response rates don't seem be quite as good as the other ones. And then there are a couple of trials that will probably be reported soon of PD-1 plus LAG3 blockade. So here, I think, those trials, unlike the first ones I mentioned, because they describe the activity in PD-1 refractory patients, where single agent PD-1 is not likely to be very good, probably, provide an easier to assess guide to the activity of the combination drugs. It's always difficult to know what is truly PD-1 refractory. So, when evaluating those trials, it's important to look at what that means. And typically, it's not that clearly defined.

Having said that, and based on comparison of small studies, the winner seems to be camrelizumab-decitabine, or PD-1 plus HMA, which really has very promising activity, I think, but needs validation. So, what about non-checkpoint? The first drug I want to mention is this CD25-targeting antibody drug conjugate, camidanlumab tesirine, or Cami-T. And this is an antibody that's conjugated to PBD. And in a single agent study, it had a high-response rate, 66%, CR rate of 28%. Basically, all the patients had prior PD-1 blockade. A good duration of response as well. One of the issues with this drug is the toxicity. There's a risk of Guillain-Barre Syndrome, which is not super frequent. It's about 6%, but still, it's a worrisome enough complication that it makes the development of the drug a little more challenging, especially, its use in earlier lines. That might be a little bit dicey, but it's an active drug for sure. The other one is CAR-T, specifically CD30 CAR-T. So, in phase I, the trial included 32 patients who received fludarabine lymphodepletion, which we now know is important. A good response rate again, 72%, 59% CR, median PFS of about 10 months. And now, this is being studied in international phase.

Dr Pavlovsky: I think we lost Dr Armand, so, we'll just hold on a few minutes to see if he can join us again.

Prof Armand: Can you hear me okay?

Dr Pavlovsky: Yes, we lost you for a couple of minutes, but now we can hear you.

Prof Armand: Oh my, okay.

Dr Pavlovsky: Okay.

Prof Armand: Do you want me to go back?

Dr Pavlovsky: No, that's okay. Just talking about the response to CAR-T.

Prof Armand: Yes. I just wanna say about CAR that it's not clear how durable those responses are, I think was the main point. But it seems very active. And CAR like Cami-T, I think, is one of these quite powerful non-checkpoint inhibitor agents. Right now, what it looks like is all of these will provide future options for disease control for patients with PD-1 relapse or PD-1 refractory. So far, based on what we've seen, it seems like it's gonna be temporary control for most patients, but that already can change the way we think about our patients today, as we'll talk about in a moment. And here's a slide again, encouraging you to ask questions. I wish my internet connection had gone down during this point today. All right, so this is part II, which is pre-emption. So, the idea is we know patients on PD-1 blockade are going to progress, most of them are gonna progress. So, can we do anything about that? And so, we can think about it in two ways. Patients who achieve a complete remission on PD-1 blockade, or patients who achieve a partial remission. If they achieve a complete remission, they're on this blue curve here, and based on long-term follow-up of both nivo and pembro phase II, as you can see here, there's actually probably a 40 to 50% chance that those patients will remain in remission at five years. That's quite good, and if you look at the shape of the curve, there's even the suggestion that maybe some of these patients will be cured. And in the case of pembro patients, came off therapy after two years. So, it doesn't require continued therapy. So, it's possible that we're curing what would be a minority of patients, but that makes attempting to continue therapy if you have a patient in CR, rather than take them to something else, your options are still there. You can take those patients straight to allo-transplant. And pulling the numbers from that retrospective series I quoted earlier, the two-year PFS is about 80% for patients who go to transplant and CR. Or you could go to auto, where the 18-month PFS is about 80%. And in both cases, the PFS numbers are better than what you expect if you just continue on the single agent drug. So, for auto candidates, I think it's a pretty easy decision. If a patient hasn't had an auto-transplant, they achieve a CR, you could continue treatment for a little, and then autograft them, and hope that you convert more of them to a cure. For allo candidates it's a very hard decision because you take patients who are feeling well, often they're working, they're living their life, and you expose them to the hassle, and the toxicity, and the mortality risk of allo. It's a very hard sell, especially if half of them might not

even be cured. So, I can tell you, personally, I don't allograph those patients in CR. This is a very individual decision, but it's too hard of a hill to climb for me. However, things get harder when you talk about PR patients. So here, their chance of durable remission is low. It's probably less than 20%. And that's harder, that impending failure is harder to ignore. Again, the options are the same. You can take them to allo, in which case the two-year PFS seems to be about 60% if you believe that study, or to auto, where you have about the same PFS as if they were in CR, about 80% at 18 months. And here, by the numbers, transplant is quite attractive. And I would say for patients who haven't had a prior auto, it's almost a no brainer. It looks much better than just continuing PD-1 blockade. And remember for auto that's a population where the data suggest that they don't do as well if you wait and autograft them in their next remission. So, I think that's an easy sell. Allo, it's still hard, but it is something that at least we should consider and discuss with our patients. It's not an easy decision, but I'll tell you, sort of think through the pros and cons with you. The pro is that it probably maximises PFS. It probably maximises overall survival too, because otherwise you have to get the patient back in remission to get to transplant. But you incur significant toxicity earlier than you would otherwise. And also, it precludes the use of other therapies after PD-1 blockade. So, all the novel agents, et cetera, much harder to use if the patient has had a prior allograft. So, I'll stick my neck out and tell you what I typically do in this setting. And I think the first thing that is the most important And I think the first thing that is the most important I think, is to avoid the one-size-fits-all approach. I would be leery of people who say you absolutely should allograft all these patients, or you should never do an allo. I think it's patient-dependent. And I think it's worth with an individual patient thinking about what the allo toxicity is gonna be for them. So, what's their comorbid burden, their age, et cetera? And then what are their remaining options? So, once they progress on PD-1 blockade, what's left for them? Have they been, have they seen already... Oh, can you hear me okay? Okay, good.

Dr Pavlovsky: Yes.

Prof Armand: Have they seen all the useful chemotherapies? Have they seen GND, have they seen bendamustine? If you have nothing left, you have to worry that you may not be able to get them back in remission. Now, on the other hand, if they've gone to PD-1 blockade relatively early, and they have other chemos left, then you might hope they're chemo-sensitized, and you can get them to transplant. And also, that's where the upcoming developments, I think, are important. If you're in a centre where you're likely to have access to new drugs or to clinical trials, I think it's an argument to wait. If you're in a place where you don't have easy access to those, or if new drugs become available, it takes a long time to get them available to you, then, it's harder to wait. So, I think for me, again, personally, because of where I practise, we tend to have good access to trials, et cetera. So, it's easy to wait, and that's generally what I do. But that's not right for everyone and everywhere, for sure. And also, this is a good space for clinical trials, I think. So, what we need here, we need new salvage options, better getting some and then, we need better biomarkers, for sure. We need to be able to look at the tumour or the tumour microenvironment, or maybe dynamic markers like ctDNA, and be able to tell who's gonna stay on the curve. Who are those patients who are gonna derive continued benefit, who are the ones who are destined to progress? Because I think that's the kind of information that we could use to refine our decisions in this setting. All right, please ask questions. Last part is about prevention. And so that basically recapitulates a story that we know well in oncology. We develop drugs that are active in very advanced settings, so, in patients who've had many prior lines of therapy, where they're not curative. Probably, the best place to use them is earlier in the treatment course when we are trying to cure patients. And now is, of course, the story of brentuximab, which moved from relapsed/refractory sort of inexorably up the chain to now be part of frontline therapy for some patients. So, I'll go quickly through these data, but it's been the same with PD-1 blockade. It's been investigated as consolidation, post auto. This is a study for pembro post auto with a 19-month PFS of 81%, including patients who are high-risk by their criteria. That 81% is pretty good and better than what we typically expect, but not so much better that it clearly is a winner. The other one is BV-nivo, which Alex Herrera did as an IST. And here, the 19-month PFS is 92%, and that's getting to a place where you really, it seems likely that this is a

useful place to be. But these are non-comparative results. They're required phase III studies, and as we'll talk about in a second, it's probably already too late. I think that ship has sailed. And so, we may not end up seeing those studies. And that's because of this, because of the use of PD-1 blockade, pre-transplant for salvage. And here, we're seeing really some outstanding results. Although non-comparative still. The curves here are for BV-nivo, the study I alluded to earlier. And there were 91 patients treated in second line. And the response rates, CR rate, were quite good, 85, 67%. But what was particularly impressive is the PFS, 77% at three years for all comers. And the patients that went straight to auto after BV-nivo, they weren't all in CR, they had a three-year PFS of 91%, that's the green curve. That's pretty darn good. And even better is this curve. This is from the pembro-GVD trial that Alison Moskowitz published in JCO last year. So, 38 patients, a little bit of a smaller study, who got pembro-GVD up to four cycles, then up to auto. A hundred percent response rate, 95% CR, and a PFS curve like this. And you can't really do better than this. So, of course, it can't be that good. Nothing's a hundred percent, but if it's anywhere close, that is a really an extremely powerful therapy, I think. And if you think about everything that we've talked about, I think this is really an ideal place for PD-1 blockade, because we're chemo-sensitizing patients, then, we take them to auto. We have good response rate, so, we can take a lot of patients to auto, and the data that we have so far looks really phenomenal. So, I like those studies, and I like this place for PD-1, and that has implications for what we do distally, because it means, as I was alluding to, maintenance is probably less interesting if this is the outcome from just salvage. And also, it means we may not need to so aggressive about putting those drugs in the frontline setting, if we can salvage so many patients in second line by the use of PD-1, and that would save cost and toxicity. But still, it requires phase III data, of course, to confirm that it's that good. And then, lastly, in frontline. So, here, there are a bunch of studies. Most of them, actually, all of them so far are non-comparative. The top four are PD-1 plus chemo. And without going through individually for lack of time, but you can see the response rates, the CR rates are very good, the PFS is very good. It does look better than straight up ABVD, maybe even better than AAVD. So, they look like a very promising combination. Without chemo, not so good. BV-nivo by itself is not great in elderly patients. The latest one was nivo by itself, with or without vinblastine. That was just presented at ASH, that looked quite disappointing. So, what I take these to mean is, for now, what they support is adding PD-1 blockade to chemo, as opposed to using PD-1 blockade instead of chemo in frontline. And there is this ongoing intergroup study of brentuximab-AVD versus nivo-AVD in advanced stage patients, which I think will be very interesting in terms of thinking about the toxicity, the benefit, how to select patients through qualitative studies, et cetera. So, I look forward to those results. And in concluding, the future of checkpoint blockade is gonna look probably very different from what it looks like today. If you're pessimistic, you would say, well, we're gonna win now, we're gonna cure more patients, or treat more patients, but then those that relapse are gonna be very hard to treat, because we already require chemo to cure patients with PD-1 blockade, and maybe we'll spend out those chemo-sensitization credits. So, there'll be fewer failures, but harder to rescue. More optimistically, you could say checkpoint blockade seems to be reusable. So, here, this is a brief parenthesis on re-treating patients who achieve CR with pembro, and the response rates are quite good. So, it may not be a one-time deal. Maybe even chemo-sensitization can remain, and we have novel agents on the way. So probably, the truth is somewhere in the middle. There'll be fewer failures, because I think we're gonna cure more patients if we use those drugs in second or first line. It probably will be a little bit harder to salvage those patients, but we'll have better options. So, on balance, I think it'll be, I hope, a clear net win. And to finish up, the use of checkpoint blockade is really a rapidly changing paradigm in checkpoint. I think, the earlier use, so, before single agent relapsed/refractory disease is both inevitable and desirable. We have to remember toxicity, because toxicity concerns have been foundational through our approach to classical Hodgkin lymphoma. And I think because we have a shiny new toy, we tend to forget it now. We don't focus as much on what the cost is of adding, let's say, nivolumab or pembrolizumab to AVD. There is a cost, both a financial cost, there's also a toxicity cost. And it's not nothing, and we shouldn't ignore it just because the drugs are cool. And so, in thinking beyond failure, I think we have to remember to ask the right questions. So, what's the role of chemo with PD-1 blockade? Is it always important to combine, or in some cases is it better to sequence? For example, is it better to reserve PD-1 for second line therapy, and

then, still work on biomarkers of sensitivity, which I think will be so important to targeting those drugs to the patients most likely to benefit from them. Obviously, we need phase III studies, but all in all, I think, I hope that thinking about this helps us all in our clinic today, prepare now for the world of tomorrow. And with that, I will be quiet. And thank you. And I'm happy to take any questions or comments.

Dr Pavlovsky: Okay, thank you. Thank you very much, Philippe, I think you've gone all over all publications on the topic. So, we thank you for this excellent review, and we do have some questions, some very practical questions, maybe clinical and everyday questions. And one is going back to the beginning of your lecture when you talk about progression of disease in patients with checkpoint inhibitors. So, how much do you rely on PET scan? And when do you ask for a PET scan in a patient who you're treating with monotherapy with checkpoint inhibitors?

Prof Armand: That's a great question. So, I do rely on PET scan and that's what I use to follow patients, at least until they achieve CR. You don't want to scan too early. So, generally, if the patient's doing okay, I don't think there's a need to re-scan them before 12 weeks. And then, after that, it depends. It depends on what their early scan looks like, it depends on how they're doing. At the early, very, very, most frequent, would be every three months. But I think in many patients you can go beyond that, especially if they achieve a CR, you can lengthen that, but I do tend to use PET.

Dr Pavlovsky: And also, as you mentioned, many refractory patients are now using checkpoint inhibitors even before autologous stem cell transplantation, and complete response is not mandatory before we think about doing it. So, in a patient who does not have a CR by PET scan, and you plan to do autologous stem cell transplantation, do you think more cycles of checkpoint inhibitors are useful and are beneficial?

Prof Armand: We don't know. And in the series that I mentioned, there's no clear signal for that. I think, in general, and this is not really, this is more extrapolation of evidence than hard evidence, but I would say you probably want to get it at least 8 to 10 doses of PD-1 blockade. So, depending on the interval that you're using, that's probably six to eight months of treatment, to know that you loaded the patient enough, probably with PD-1 blockade.

Dr Pavlovsky: And now, another question regarding these patients monotherapy, but in whom you are going to do allotransplantation. There has been a lot written and different discussions about the toxicity and the benefit of using, as you mentioned, checkpoint before allo, and the different time points with different experts defining how many months or what to do between the last dose of checkpoint inhibitors and allo-transplant. So, what do you do in your centre?

Prof Armand: So again, there's not convincing data that I'm aware of to say it has to be X, but typically, I aim for six weeks. Now, truthfully, as I mentioned, in my practise, I tend not to autograft the patients who are responding to checkpoint blockade. I tend to wait until their next remission, and that's even truer now, because we're starting to use it so much earlier. We're basically using it in third line in almost everybody, right? So, for us, if they've gone through two lines of therapy and they didn't respond, they're getting a PD-1 blockade. So, by the time they get it, they have often a lot of options left. And so, between that and clinical trial, I feel like it's likely we can get them back in remission. So, that question of how much time to give between PD-1 and allo-transplant doesn't come up a lot for me for that reason. But when it does, I use six weeks as sort of a guide. And definitely, definitely, what cannot be over-emphasised, what we do have data for, is that we should be using PTCY based GvHD prophylaxis, regardless of donor. That I think is really important to remember. If there's anything that I said about allo-transplant, that I would suggest, that I would wanna emphasise, it's that.

Dr Pavlovsky: Okay, and following your thought and your practise, that you're not doing allo-transplants in patients who are in CR. When they relapse, do you consider using the same drug is good enough? You

mentioned the results, or should we do chemotherapy plus checkpoint inhibitors, or considering chemo-sensitization?

Prof Armand: So, the data is still pretty limited because it comes from clinical trials, which built that into the trial, both the nivo and pembro trials built in the ability to re-treat patients in CR. But we're just starting to see the data, and I alluded to it quickly, so, the response rate looked quite good with pembro, but it's not that many patients. And it certainly could be better to use PD-1 plus chemo. So, if you're just thinking at that point, okay, you want to bridge the patient to transplant, let's say to allo-transplant, and you really want to get him in response, I think, you can use PD-1 plus chemo, it's fine. Or you could probably start PD-1, and if you don't have a good response, add chemo or something like that. But it is probably a better response with PD-1 chemo than chemo alone. And if you think about the question from another standpoint, so, when we are talking about chemo-sensitization, and looking at chemo after PD-1 failure, in the French study that I briefly cited, the patients who got continued PD-1 with chemo did better than the patients who just went on the chemo. It's completely selected as well, it's not a randomised data, so it may not be real, but it does mean from both sides of that question, if you can do it, it's probably not crazy to do PD-1 plus chemo.

Dr Pavlovsky: So, there was also a next question, a patient whom you have clear diagnosis of progression while on PD-1 monotherapy, whether to just switch to chemotherapy or to add chemotherapy?

Prof Armand: The only thing, so we've historically in our centre, we've always switched, not added, but part of that was that there was no data for chemo plus PD-1, and now we have it. Now we have the pembro-GVD data. There's some nivo-ICE data that's making its way through. And so, it's easier to justify doing it now because we know the drugs can be combined. But whether it's better or not, the only data that I'm aware of is from that French study, which is really a small number of patients. It's not randomised, so it's hard to be dogmatic. And I think it's hard to know. Probably, if you can do it, if you have the drug available, it's off-label, you have to be getting it off label. You have to tolerate the financial cost, and the extra toxicity. I think for example, the mucositis is most more pronounced with pembro-GVD, but if all that is tolerable, you say, probably why not?

Dr Pavlovsky: Okay, so I think we still have many open questions and also another one regarding consolidation after the allo-transplant, or after autologous stem cell transplantation with either a checkpoint inhibitor or a combination with brentuximab. And we see these great curves, but we also know that these drugs are very useful in a relapse setting. So, my question is, are we doing early treatment to some patients who are quickly relapsing after transplant, or is it really a consolidation treatment with a better outcome?

Prof Armand: I'm not sure that I understood the question, Astrid. Are you asking is it better to use the drugs before transplant or after transplant?

Dr Pavlovsky: No, just the use of consolidation after transplant, with these curves that you showed. How do you see the future of this?

Prof Armand: Right, so I think I understand. So, it's very different for allo and auto, because as you well know, you don't want to use PD-1 after allo, if you can avoid it. Those patients can get quite sick from GvH, and fatal GvH. So that's something which I only use as a last resort. Now of course, last resort comes quickly when you relapse after allo. So, everybody basically ends up getting it, but that's not a good place to be, PD-1 after allo. So, if you're thinking about allo, definitely, definitely, definitely need PD-1 before allo, right? Not after. So, that one, I think to me is very clear. BV is different. You can use BV after allo, maybe even prevent some GvH, but you might as well maximise its benefit earlier, in earlier lines of therapy, like for first or second line, I think. Auto is different, but the answer to that is I think that the data for consolidation are promising, but if it's that good at second line, we probably don't need to consolidate patients. And it makes more sense to use PD-1 before high-dose chemo than after high-dose chemo because of this chemo-sensitization. So, if you look at this PFS curve, if the truth is anywhere near that, we'll never be able to demonstrate a benefit to

maintenance after that, right? So, I think basically in both cases, that means for different reasons, probably better to use before than after is my sense.

Dr Pavlovsky: Okay, so we have, I think in the last years, or the last decades, we have had so many new options while before the big debate was ABVD or BEACOPP. So, how do you see the future? Do you think this is the end of chemotherapy for Hodgkin lymphoma? Maybe, in 10 years, we will not be using chemotherapy?

Prof Armand: Oh, in 10 years, I'm trying to predict 1 year.

Dr Pavlovsky: Okay.

Prof Armand: I can't even predict inflation for one year, so, 10 years, I don't know. But in the short-term, I don't think we're done with chemo, because if you, and of course I present it with my own bias, but if you look at the totality of what we talked about, really what it suggests is that PD-1 plus chemo, or PD-1 then chemo, that kind of stuff is what's best. And we haven't shown that we can effectively replace chemo in a disease where chemo is so curative. So, I think for a while, I suspect, it'll be still with chemo. Now you have to consider also BV as being chemo-like, which I think it is.

Dr Pavlovsky: Yes.

Prof Armand: So yeah, I think we're stuck with chemo for a little while longer, but maybe 10 years.

Dr Pavlovsky: I hope we're still discussing this in 10 years.

Prof Armand: I'll be retired at best.

Dr Pavlovsky: Thank you, Philippe, I think we're in time. Thank you very much. It has been great to just go over all these very interesting publications. And hope to have you again, maybe in our e-grants.

Prof Armand: Pleasure, pleasure, thank you, thank you for inviting me.

Dr Pavlovsky: Okay. Thank you, and thank you for all the participants.

Prof Armand: Thank you, bye-bye.