# Transcript

Paul:

Hello, my name is Paul Klenerman. I'm a professor at Oxford and I'm the host of this podcast on immunology called To Immunity and Beyond. So this is just to say that what we're putting forward with the podcast is a scientific discussion, and it's really just for information. And it isn't in any way medical advice. So if it's medical advice you're after, please go and talk to your doctor or some other medical professional. Meanwhile, enjoy the podcast.

Hello and welcome to another episode of two Immunity and beyond. And today I've got with me Ben Fairfax, and Ben's gonna introduce himself.

Ben

Hi Paul, thanks for asking me along. Yeah. My name is Ben Fairfax and I'm a medical oncologist and Professor of Cancer Immunogenetics in Oxford.

Paul

Thanks very much. So we're going to talk about your paper that you've just published in Nature. It's on the impact of CMV on melanoma and its treatment. First up I, for full disclosure, I'm an author on the paper, but I thought it's such a great paper and there's so many interesting components to it I thought everybody should hear about it. First up, maybe Ben, you could just explain to everybody your sort of background about how you got into this. You know, as you develop your career in academic medicine.

Ben

Great. Yeah. So thanks very much, Paul. My background is not really in immunology. So I feel a little bit of a fish out of water on this podcast, but my background is as you alluded to, I'm a medic and during training I got very much interested in the immune response and why some people were susceptible to infectious diseases, and other people weren't. And so I did a postdoctoral fellowship with Julian Knight, at the Wellcome Centre for Human Genetics and we described a lot of eQTL, these are Expression Quantitative Trait Loci, polymorphisms that regulate gene expression, and we looked across these in different immune contexts and different cell types. And this is interesting because it demonstrates how genetics links to immune function. Having done that work, I actually went off on a slight tangent and specialised in medical oncology. And I was in a very fortunate time during medical oncology in the development of therapeutics in as much as when I started my training as a registrar in medical oncology, checkpoint immunotherapy was not in the clinic, but over that period of time it was introduced and now we're in a stage where the main backbone of many cancer treatments is checkpoint immunotherapy and this is typically anti-PD1 or anti-CTLA-4 or combinations of those treatments. And this introduction of immunotherapy sort of nicely correlated with my background interest in genetics of immunity. And so this study has sort of stemmed from those observations.

Paul

So you've got yourself in a good position with all that training and it's really great I think for the immunology field to have people coming in from all sorts of different backgrounds. I would say you are for sure an immunologist and there are lots of different ways to be one based on this paper alone, that's pretty good evidence. So what we're looking at in this paper then is this cohort that you've set up with these interests in mind. So tell us about maybe some of the nuts and bolts of setting that up and what you had in mind when you did that.

Ben

Yeah. So the cohort we're talking about, we've given it a title, OxCITE, which is the Oxford Cancer Immunotherapy Toxicity and Efficacy Cohort and this was established back in 2015 and it consists of blood samples taken from patients immediately prior to and whilst undergoing checkpoint immunotherapy, and it's primarily composed of patients with a background history of melanoma. But we are also looking at other cancers. So mesothelioma, renal cell carcinoma and mismatch repair deficient colorectal cancer. And we have built up the cohort so it’s almost now 500 individuals and the real aim of this is to try and understand why some patients do have a very good clinical outcome with respect to immunotherapy and other patients don't, but also the determinants of toxicity. So why some patients get autoimmune toxicities or so-called immune related adverse events secondary to immunotherapy, we're really focusing on the blood, and the reason behind that is that immunotherapy actually acts on the immune cells within the blood, the T cells, et cetera. And so we feel that it's potentially a good approach to developing novel peripheral biomarkers. So in the end, we can better stratify treatment. So give the patients who are going to do better with certain treatments, targeted in the right manner, and in treatments which potentially are going to cause patients problems, potentially we will be able to look at different alternative therapies, but also an underlying aspect is to try and see if we can explore other factors such as germline genetics because we know the cancer genetics, that are mutations within the cancer, play a big role as to whether a cancer is sensitive or not to immunotherapy, but it's much less clear how germline genetics relates to that. So that was the other key aim.

Paul

Brilliant. So I mean, I'd encourage people to look up some of the other papers on the host genetics, cause they're all fascinating, but just focusing on this one then. So you've ended up looking at CMV. It's not the most obvious thing to look at if you've got a patient with melanoma, so how did you sort of get to that point? Maybe just walk us through that.

Ben

We had a study back in 2020 where what we were trying to look at was how we could predict whether patients did well or not. And what we found was that just looking in the peripheral blood, we could look at the CD8 T cells. And we could determine that, or a proxy for, the number of clones in their blood. But basically we mapped the TCR. So we were looking at CD8 T cell transcriptomics and from those transcriptomics we used packages to map the different TCR and from those T cell receptors, TCRs, we were able to determine the clonality of different patients and one observation from this study was that after immunotherapy, we found that patients with more large clones, what we defined as a large clone as being a clone that's greater than .5% of the total peripheral circulating CD8 population that we tested. Those patients with the higher number of large clones after immunotherapy, it being either anti-PD1 or combination anti-PD1 and anti-CTLA-4, and this was in the context of melanoma, those patients had a better outcome and so tended to have improved overall survival. And so from that observation, this got us thinking - a lot of questions from that paper where people say, well, so what, you know, and quite reasonably, what are these large clones reacting to, are they just a correlate? And I think that's a really good point. And we're not entirely sure. But the other aspect, if you think about it is, well, what are the other determinants of large clones? Are these large clones a proxy for reacting to the tumour, or could other factors that increased number of large clones have an effect, and this really, to answer your question, specifically led us to CMV because CMV or cytomegalovirus, has been known to have very profound effects for a long time on the immune system, some of the earliest papers described changes in clonality secondary to patients who had CMV.

Paul

Brilliant. OK. Well, that's a very good background. And so at this point then you kind of really ready to, you've got a great cohort, you got a good question. And so why don’t you just maybe explain for people who haven't read the paper in any detail, hopefully they'll pore over it once they've listened to the podcast. But what the kind of key elements that you found were when you compared the different components of your cohort together?

Ben

Yeah. So. At this point, so this paper, we really put it together last year in 2024. And so our cohort had very much grown in size and we looked at 341 prospectively recruited patients receiving checkpoint immunotherapy for melanoma, and we made three different observations really with respect to CMV. And these were, patients with CMV had different clinical outcomes determined by the treatment type they had. In addition, we made observations with respect to the toxicities that patients may or may not develop secondary to immunotherapy if or they weren't CMV seropositive. And then finally we looked at the epidemiology of CMV and melanoma in the ages at which people were developing melanoma in our cohort. And so the first real observation was that, actually we were just looking quite simply at hospital blood, so we looked at patients with CMV and without CMV, at their baseline hospital bloods before they started checkpoint immunotherapy therapy. So it's the full blood count that they have before starting treatment and we found that patients with CMV tended to have more lymphocytes before they even started treatment, which was an interesting observation. And this led to the secondary observation that if you looked at the ratio of neutrophil to lymphocytes, which is a known prognostic and predictive marker across many cancers actually, patients with CMV tended to have a lower neutrophil to lymphocyte ratio, so a higher neutrophil lymphocyte ratio is typically associated with a poorer outcome. And actually we could look in our cohort and we could see that independent of every other observation the neutrophil to lymphocyte ratio prior to starting checkpoint immunotherapy was associated with survival. So then we went on, I should say, and we looked at flow cytometry. So these were the hospital bloods, and looking at flow cytometry, we sort of replicated the same observations, many other papers have done over the years, looking at many other groups, I should say, performed over the years looking at the changes in different T cell subsets. So we looked at CD4 and CD8 T cell subsets. We saw that patients with CMV had fewer naive T cells, typically fewer central memory T cells, but expanded effector memory populations and greatly expanded TEMRA populations. The other observation, which I think is less well described in the literature, was that we found patients before they started checkpoint immunotherapy, the CMV positive patients had a significantly lower number of circulating CD25+ FOXP3+ T Regs, which was an interesting observation as well, so. Already we're at this point that we could see that patients with CMV tended to have a slightly different immunological and haematological set up to patients without, prior to them starting checkpoint immunotherapy.

Paul

That's great. So that I mean that, you know, concurs as you say with other data in non melanoma patients, there's a kind of a massive impact of CMV. And it's actually quite interesting whether in some of those other papers with the neutrophil to lymphocyte ratio where they haven't looked at CMV, then maybe there's a CMV effect in there as well. But we'll maybe come back to that. But I guess maybe you could talk a bit about the treatment effect, cause that's really important.

Ben

Focusing on immunotherapy, the three main options for treating patients with checkpoint immunotherapy in the clinic today with metastatic melanoma… at the time that we were collecting patients for this cohort, there were two main options, which I'll focus on. Which is either anti-PD1 alone, which is pembrolizumab or nivolumab, or alternatively anti-PD1 and anti-CTLA-4. So nivolumab and ipilimumab and more recently nivolumab has been introduced in conjunction with anti-LAG-3. But this data set was focusing on either anti-CTLA-4 anti-PD1 combination immunotherapy, or single agent anti-PD1. And a seminal study called Checkmate 67, several years ago now, demonstrated that patients who were given combination immunotherapy tend to have to have better overall survival. But it wasn't really powered to explore differences with anti-PD1 alone actually, but it tends to be our standard treatment. The problem with combination immunotherapy though is it's highly toxic; about 60% of patients will develop an immune related adverse event which is grade 3 or above, so typically requiring them to stop treatment and go on to an immunosuppressant such as steroids or even going to hospital. Whereas if you just give one agent, anti-PD1, the toxicity rate is much lower, 10 to 15% and the overall survival difference between these two groups is maybe 8% difference. So you can see why there's a meaningful difference, but there's a significant subset of patients who probably will get just as good a benefit from anti-PD1 and what we found is that when we looked in patients given combination immunotherapy in our cohort, actually it didn't matter what their CMV status was. If they were CMV positive or CMV negative, they had the same clinical outcome, so there was really no difference in overall survival. Conversely, when we looked at those patients just given anti-PD1 alone, it seemed to be that those patients who were CMV positive had improved overall survival versus those who were CMV negative and this held up when we performed multivariable analysis. So when we control for factors such as age and sex. And then in a subset of patients, and I would say this is a small cohort, so it's very early data, but it was the data that we had in the cohort. We had 28 patients who'd also been given anti-PD1 - separate to the original observations of metastatic disease - we had 28 patients being given anti-PD1 to reduce the risk of relapse of resected stage two or three melanoma. And it seemed to be that in the patients who were CMV positive, they had reduced likelihood of recurrence in the CMV positive. So, all in all, this added up to a picture that if you were given two drugs, didn't seem to matter if you were CMV positive or not, whereas if you were just given anti-PD1 alone without the anti-CTLA-4, those who had CMV tended to have well, had significantly improved outcomes over those that didn't.

Paul

So, for those of us who not prescribing these drugs, maybe you could just explain why some people, it's not a randomised trial or anything, so maybe you could just explain why some people are getting two drugs and some people are getting one drug. What's the sort of thinking?

Ben

Yeah, it's about performance status. So what does that mean? It's relatively it's a very crude way of saying, how fit a patient is. And so to be able to be given combination immunotherapy, a patient has to actually theoretically be a performance status of one or above. So able to lead a pretty active normal life, whereas there's no control, no limitation on performance status really for patients just given anti-PD1 alone. So that's one aspect. The second aspect is sometimes about the nature of the disease. If a patient has brain metastasis that requires treatment with steroids then, we have to fill a form in to say whether they can have combination therapy, and they're excluded from combination immunotherapy as well. So there are some nuances, some subtle differences between the two groups, and in general in our cohorts, patients given combination immunotherapy were slightly younger than patients with the single agent, although we did do multivariable analysis to adjust for these. We don't think that this was specifically an age effect or an effect of other factors such as performance status.

Paul

Great. So before we get to the question of like, well, how on Earth does that work? Perhaps you could continue with the clinical observations then. So what about the toxicity, that's perhaps the next one to address?

Ben

Yeah. So previously, multiple groups, including our own, have made an observation that patients who get toxicity - so what do I mean by toxicity? I mean, autoimmune complications secondary to immunotherapy, and these can involve any organ in the body. They're typically after several cycles of immunotherapy, but they can occur at any time. And interestingly, sometimes they can occur when the patients have, many months after finishing immunotherapy. Most commonly, the skin is affected. But also, endocrine organs. So, thyroid gland… hypophysitis is a common complication. So inflammation of the pituitary gland. When I say common - less than 5%, but it's an observation which you don't see with any other cancer treatments, with anti-CTLA-4 treatment. And really problematically for patients, development frequently of colitis. And the colitis itself can be really debilitating. And very occasionally, you know, can require colectomy, very unusually. But so it's a real complication that can be difficult to get on top of, but actually checkpoint immunotherapy can cause just weird complications in as much as any organ of the body can be involved. So. Pneumonitis is another complication. And autoimmune hepatitis. Those are pretty common, relatively speaking, complications secondary to checkpoint immunotherapy. So these are the autoimmune toxicities.

Paul

Great. So yeah, so you've got this kind of panel of things that you've been measuring carefully in your cohort, as you said at the beginning, that was one of the reasons you set it up. So you presumably had enough power even though they're rare to kind of make some pretty clear conclusions about this.

Ben

Yeah. So when we looked at our cohort, so previously we've made some observations that toxicity tended to have a subtlely better effect. And when we looked at this much extended cohort from our previous publications, what we found is that in patients who developed a lower grade, i.e. grade one or two immune related adverse event, they tended to have reduced hazard ratio for death and actually the toxicities themselves that seem most associated with having better outcomes were arthritis, when the patient developed arthritis, and also dermatitis, so skin rash. Now that might be related to the way that we treat those toxicities or it might be related to the nature of those toxicities themselves, we don't know, but it tends to be that dermatitis is treated with topical creams and topical steroids. So it's unusual to require systemic steroids or systemic or immunosuppression. And that's often the same with arthritis. It tends to be responsive to low doses of steroids and sometimes interarticular steroids. So it may be that these toxicities require less immunosuppressants. So when we looked in the cohort beforehand, we thought, well, hang on, CMV seems to have better outcomes. And we've previously noted that toxicity tends to be associated with potentially better outcomes. So I would anticipate that CMV might also be associated with increased rates of toxicity. But that's not actually what we found. We found quite the opposite. We found that patients with CMV seemed to be overall much less likely to get a severe toxicity. It didn't seem to affect a mild toxicity. But the mild toxicities tend to be skin rash. And so when we looked across the different toxicities, what we found was that CMV specifically was associated with a lower risk of colitis and that was most obvious in patients who've been given combination anti-CTLA-4 and anti-PD1 who are much higher risk of colitis. And being CMV seropositive significantly reduced their risk of colitis, I think by about half, which is a very marked reduction. We also saw a reduction in the risk of pneumonitis and a reduction in the risk of myalgia, which wasn't myositis. So non-specific muscle pain. But the confidence interval on the myalgia was pretty big, so small numbers. Conversely, we observed that patients with CMV were more likely to develop a skin rash, which is interesting. So, it wasn't an overall protection from every toxicity going. Potentially it was a shift in the nature of the toxicities being prevented, reduction in those such as colitis, a shift towards dermatological toxicities. So that was the observation and we could also see that patients who were CMV positive were less likely to require steroids at anytime over their treatment, and also less likely to require second line immunosuppressants.

Paul

Great. So that's all really clear, although still, you know plenty to be explained. And then what about the last bit of the paper with the observations about the kind of population risk - perhaps you could just take us through that because that's a bit nuanced.

Ben

So we looked at the ages which patients presented in our cohort for treatment with metastatic melanoma, and what we found was that patients with CMV positivity were presenting at a later age, several years older than patients who are CMV negative. Now, it’s slightly confounded because there's an increased rate of CMV positivity in older populations. But when we looked in patients with non-melanoma cancer that were also receiving checkpoint immunotherapy, we didn't see this age effect. So this could be, this was interesting, but what we thought was potentially the real informative observation here is that maybe 40 to 45% of melanomas carry mutation in the gene BRAF, and so BRAF mutated melanomas are those, they're typically more commonly on the trunk. They're very strongly associated with sun exposure. But not chronic skin damage. So it's a marker of a specific melanoma. It's not seen in mucosal melanoma, for example, BRAF. And BRAF mutated melanomas are associated with slightly younger metastatic disease, age of metastatic disease. And what we found is that when we looked in patients with BRAF mutated melanoma, there is no difference in CMV positive and CMV negative at the age at which they started treatment for metastatic disease. So this age effect wasn't there. Conversely, when we looked at the 60% or so of patients who were wild type, so didn't carry a BRAF mutation in their melanoma, actually, the age effect was really quite pronounced at this point, and patients presenting with metastatic disease were about nine years older on average than their seronegative counterparts. So that's kind of weird because you have a mutation in a cancer which potentially interacts with an environmental factor. And we still quite can't get our head around it, but we're pretty confident in that observation. The second aspect is that when we looked in the patients with BRAF, so in BRAF mutated melanoma, there seem to be fewer of those with CMV than there should be by chance. And so it appears to be that if you're CMV seropositive, it reduces the likelihood of BRAF mutated melanoma becoming metastatic. That's an inference. That's what we infer. We don't know that for sure. That's what we infer. But the second observation was that if you had metastatic melanoma BRAF mutation, it didn't really matter, your CMV status at the age you presented. Conversely, in those patients without the BRAF mutation, there was this age effect. So that was interesting.

Paul

Great. Well, I'm sure that anybody listening to the podcast is wondering, you know, how are you gonna explain this? So in the paper you've made a good stab at trying to kind of come up with a model for how this might work based on your studies in peripheral blood. So maybe just sort of summarise what you think, how the two things connect.

Ben

Yeah, well, I think one of the observations we made was in patients with CMV they tended to have much higher gene expression of cytotoxic genes which we've separately associated with a better response to checkpoint immunotherapy. And we tried to understand the drivers of cytotoxicity within our cohort and we used a number of different approaches, but mainly bioinformatic approaches to identify potentially driving transcription factors behind the cytotoxic module. And we found that TBX21 encoding T-bet was really strongly associated with the cytotoxicity of the CD8 T cells in these patients and also granzyme B production and other markers of cytotoxicity. And so patients with CMV seropositivity tended to have higher baseline TBX21 overall and greater induced TBX21 after treatment, if they were CMV seropositive. And what we could do, going back to our combination versus single agent, was that when you gave patients combination immunotherapy, it seemed to be that in the patients who are CMV negative, there was induction of TBX21 by anti-CTLA-4 and anti-PD1. So it brought up their levels of TBX21 and cytotoxicity whereas in the CMV negative patients if you gave them anti-PD1 alone, actually we saw a reduction in the TBX21 expression whereas in the CMV positive there is a much higher level of TBX21 in the baseline and that remained induced just after anti-PD1. So it was like a rescue effect: giving combination immunotherapy seemed to rescue the effect of CMV. I'm sure it's much more complicated than that, but the second observation potentially where we think that this may be playing a role is going back a few steps and saying, well, we've made this observation with respect to fewer T regs and if you look at data from Sergio Quezada and other groups suggesting that actually anti-CTLA-4 is depleting T Reg numbers and one of the mechanisms of anti-CTLA-4 and anti-CD25, for example, directed drugs, is that they're depleting T regs, you might make an inference that if you already had lower T reg numbers because of CMV in the first place, then that depletion maybe is less important. So we think that's maybe explaining some of the interactions, but we're not there yet because we know for example, TBX21 is extremely important, for example, in ILCs, ILC1 development, etc. And maybe that also has an effect with respect to the toxicity. So those are the key observations that we could see transcriptomic effects. And actually we do believe TBX21 to be a driver of this. Because we could just look, we could forget CMV, forget everything and just look at TBX21 expression in the CD8 T cells in patients after they had received treatment and those with a higher TBX21 expression had a better overall survival as well.

Paul

Excellent. So I guess one question would be, is this melanoma-specific, do you think, or is there any data elsewhere in biggish cohorts that that would make you think it was more generally relevant?

Ben

Yeah, so, I mean, this is one of the things that people say, well, why has this not been described before? I'm slightly unsure why it's not been described before, but I do actually think that CMV is something that is a bit neglected in the oncology field and maybe this is sort of a bugbear of mine. But if we have lots of immuno-oncology papers describing different immune cell subsets, potentially associated with different outcomes, the number one or one of the most important variables in peripheral immunity, and I suspect in tissue immunity, is whether a patient has CMV. Coming from the background of population genetics, it's a bit like doing GWAS and forgetting to control, in my opinion, for population stratification, ignoring that different alleles are at different frequencies in different populations. Actually, when we look at a lot of immuno-oncology, it could be that some of our observations may be being driven by CMV. And of course we don't know that. So there's a bit of a plea to, actually, I think it's something we should be measuring. So back to your specific question - is this only in melanoma? I don't know. And we don't have any other evidence that it's any other cancers at the moment. I would hesitate, I think we think that this is potentially a skin effect. So I think it may be of importance with cutaneous squamous cell cancer, for example, but I don't know about other, for example, immunosensitive tumours, so mismatch repair deficient colorectal cancer. So these things need to be explored. At the moment we don't know, but these observations are on the back of other observations going on. For example, the observation with respect to Shingrix shingles vaccination being potentially associated with a reduced development rate of dementia from Paul Harrison, and other groups have similarly replicated these observations. So, this feeling that, you know, people have been obsessed with the microbiome for the last 10 years and you know that obsession isn't misplaced obviously. But I do think that chronic viral infections may be playing a bigger role than we’d anticipated. Maybe not in the outcomes of metastatic disease, but actually in the development of cancers in the first place. And I'm not necessarily talking about directly through mutational effects of the of the virus themselves, but potentially secondary to the driver effects on the peripheral immunity and mucosal or tissue immunity.

Paul

Excellent. So just a couple more I think just to round off. So I think hopefully anybody listening has just got a really clear idea of what you found. When you were trying to bring this to publication, obviously you get critiques. Was there anything that you sort of had to overcome to convince people that it was a genuine finding that, you know, that that you can think of? Obviously, lots of small critiques, but what's the kind of major criticism?

Ben

The review process was very helpful in many ways. People asked for replication. It's very difficult to get a replication cohort. But we were able to, so they wanted to see could our anti-PD1 metastatic affect be replicated. We did not have access to other data sets to see if that was the case but we then turned to our adjuvant cohort. And interestingly we found exactly the same observation. So that was one aspect. The second aspect was the immunological drivers. And we worked with you, for example, to demonstrate that murine CMV was associated with open chromatin over the TBX21 to demonstrate this is probably a CMV-specific effect, this upregulation of TBX21. And so those were the main aspects. I think some of the difficulties with the reviewers is that we were trying to go across quite different fields because essentially you're talking about oncological, you know, immuno-oncology. But also we had, I suspect some of our reviewers were from the CMV world. And so there are some aspects which are a little bit unanswered because we're just looking at the UK and different populations have different seropositivity levels and so if our epidemiology is correct, potentially you might expect to see different rates of BRAF mutated melanoma in different countries. Actually, you possibly do see that in South America, rates of BRAF mutated melanomas seem to be lower, for example, whereas CMV seropositivity is much higher. And this is also seen in some Middle Eastern countries. But there are massive confounders because the population genetics are different and the determinants of getting a melanoma different. So that's an aspect, and our work didn't have any animal work involved to see can we functionally dissect these observations, and that's something that we would like to try and do going forward.

Paul

Great. And I think CMV epidemiology is sort of plagued, a lot of it's been done looking at sort of outcomes from cardiovascular disease and it's kind of plagued by this correlation between CMV serostatus and social deprivation.

Ben

Yeah. And that's a really good point. There's quite a bit of literature in terms of CMV potentially being associated with developing certain cancers. But it's not particularly strong and certainly actually when you look at the epidemiology, so the best studies of that are in patients who've had solid organ transplant, and it does seem to be that CMV isn't associated with developing, in fact it's potentially protective, it's protective against lymphomas. And a trend in some of the studies to protection against melanoma in patients who've had a solid organ transplant. So it certainly doesn't look like CMV’s increasing the rate.

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Paul

Great. And just maybe one last question. So apart from celebrating having kind of brought this to light and hoping that people take notice and replicate it, what are you gonna do next to kind of really crack this?

Ben

Probably work with you. Hopefully work with you Paul to try and dissect it further, but there are a lot of questions we want to ask and what we don't understand. So you know, why is this BRAF effect going on? Is this to do with the microenvironment? Actually the secondary question with respect to the toxicity, what's CMV doing to the skin immunology, increasing the rate of skin toxicity? We know CMV affects the expression of ZNF683 or Hobit, which is a marker of resident memory. So we want to look in tissue specific effects of CMV potentially both prior to and after checkpoint immunotherapy. Then the bigger questions are - can we look in other chronic viral infections or work with other groups? Because you do require large data sets and it requires a sort of slightly open-minded approach and there are a lot of confounders here because we're looking in patients who develop the cancer. And so if they're protective effects, you might see different effects in the metastatic setting, for example. So there's lots to explore. But to summarise, focusing more on trying to dissect the mechanisms with you, but also looking at the potentially tissue-specific effects of CMV in our patient cohort.

Paul

Brilliant thanks ever so much. The paper’s gonna be available on the link, and we'll hopefully hear more from Ben in future.

Ben

Yeah. Thank you so much for asking me along. Thanks Paul.