European Society for Medical Oncology

Risk/benefit ratio of new immunotherapy strategies

A panel expert discussion

The increase in knowledge about the way the immune system functions is leading to exciting new therapeutic possibilities for cancer patients. A panel of experts met during the **ESMO Symposium on Immuno-Oncology** (15-16 November 2013, Geneva, Switzerland) to discuss about risk/benefit of:

- Vaccines
- Checkpoint inhibitors
- Adoptive T cell transfer.

Moderator:

Solange Peters

Panel experts:

- Scott Antonia
- George Coukos
- Pierre-Yves Dietrich
- Winald Gerritsen
- Carl June
- Ignacio Melero
- Olivier Michielin

Introduction:

Solange Peters opened the panel giving a summary of the risk and toxicities from novel immunotherapy strategies. The introduction was followed by panel discussion on expected treatment benefits with an aim to provide conclusion on risk/benefit ratio for each option.

Solange Peters: It's a great honour for me to have such a panel here for discussion. The idea of this session is to review together some of the main strategies in immunotherapy today and I will probably divide - but of course the panel has no obligation to follow this rule - this discussion into three chapters: The vaccine, the checkpoint inhibitors and the adoptive T cell transfer, because, the various risks and benefits have some differences to be stressed out.

I will give you some introductory slides for each chapter, mainly focusing on a very brief summary of the risk and toxicity and then I will let the panel discuss the expected benefit, as well as, the ratio that could be concluded and the risk/benefit of every strategy.

First of all the vaccines – I am completely biased because I am a lung cancer specialist, but very interesting in lung, it is very interesting at every big lung meeting, we have a new vaccine trial and what these trials have in common, is to be negative, first of all the first endpoint is never met. I'll just lead you through the two last trials, one which was presented by Dr Giaccone, which was a vaccine belagenpumatucel-L

with four allogenic cell lines injected to the patients. These were metastatic patients and the strategy was a maintenance strategy. As I told you, it was a negative trial but what I wanted to say, what was in common, was this trial had a very low toxicity, apart from injection site reaction and some gastrointestinal toxicity of grade 1 and 2, this was not toxic.

The other one, presented by Professor Vansteenkiste a L-BLP25 vaccine, which was also a negative trial, you can see the potential of immune-related adverse event. Again, not toxic – grade 1 to 2 mainly digestive ones and some fatigue, but of course again, what they have in common is the fact that the toxicity is almost inexistent using this strategy.

Last but not least, and Johann Vansteenkiste has left and I hope this trial will not be negative at the end, I will know it next year – the MAGE A3 trial is a phase II version that had only very, very minor toxicity as you can see here in orange, some general injection site toxicity, some muscular skeletal pain and some difficult to explain general pain of grades 1 and 2 but no toxicity. So if I go to risk benefit ratio, I would, from a clinical point of view, just think that the risk is very low and the question to my panel is: Do you believe that the benefit, clinical benefit of such strategy, could be high enough to result in a good ratio? So, who would like to start to discuss vaccine strategy, maybe leaving the lung and going along to another disease?

Scott Antonia: In lung it is not at all impressive, of course, obviously the ratio is low because the toxicities are low but given by themselves – vaccines, I'm unenthusiastic.

George Coukos: Can I make a comment, clearly vaccines have developed a reputation, and they have been very controversial. Steve Rosenberg had a very nice review a few years ago demonstrating that molecularly defined vaccines at best have a response rate of 45%, and what is very interesting is that this sort of meta-analysis and other meta-analyses have shown that vaccines that are polyvalent are typically performing better, particularly when they are in an autologous setting. And now, we know why; we know that the majority of tumours actually do have private mutations which may result in mutated neoepitotpes which maybe drive the immune response. Now this has been demonstrated very nicely in melanoma. I think it is only a question of time until we demonstrate it in lung cancer, which has an equal number of mutations, and also in other tumours. There is no evidence that having 40 or 50 mutations is less good that having 200 private mutations; I mean you could still probably have immunodominant epitopes in that repertoire which could drive an immune response. Clearly, as Carl pointed out, vaccines are not an effective therapy because we just cannot drive enough T cells with high avidity and high frequency to the tumour or that can make an impact; the tumour environment is very well organised to counter this response.

Scott Antonia: My reticence in providing any sort of positive answer to that question was as a single agent; but I am extremely enthusiastic about combining these strategies and then I think you're going to see efficacy. I can't help but believe, that you know, that vaccines or adoptive T cell therapy on top of these inhibitors of the immunosuppressed tumour microenvironment won't be synergistic or at least endive.

George Coukos: And the ovarian cancer vaccine that I showed, we think that there are some interesting data there. We do not see objective response in the majority of the patients, but we actually see very clear clinical benefit in terms of very prolonged and very unusual progression-free survival and overall survival, and I think this is the case overall in many other tumours, that people increasingly report this kind of data with polyvalent, autologous T cell vaccines. Clearly now, the opportunity is going to be with oncologically viable checkpoint inhibitors and other immunomodulatory drugs. I think this now becomes a very important opportunity where you can expand tumour reactive cells with vaccine and then push them with an immunomodulatory drug.

Solange Peters: What about the prostate cancer where probably we have some data, encouraging data.

Winald Gerritsen: I think the most important question is what kind of patients do you want to treat. We heard today results in difference patient populations and only the T cell really had a dramatic response, in say, patients with high tumour burden. But that is the only example. If I am correct, also for prostate cancer, it looks like it is only working in patients with a low disease burden, so low PSA, no metastases, and also, if I am correct, in the lung cancer field, the studies are negative but if you do a subgroup analysis of the patients who were stage 3 then it looks as if these studies would have been positive if there would have been enough patients in this group of patients, correct?

Solange Peters: It is an interesting signal, yes.

Scott Antonia: So I would disagree that only adoptive T cell therapy can produce significant responses in bulky disease - anti PD1 clearly you can have very bulky disease that can go to a CR (complete response).

Winald Gerritsen: But still, it's not as regular as what was presented today by the T cell and I still think that we have to consider...

Scott Antonia: What do you mean by 'not as regular'?

Winald Gerritsen: Almost all of your patients

Scott Antonia: Oh, yes.

Winald Gerritsen: And I still think the results with the checkpoint inhibitors are very promising but what I don't think is that now we should start treating patients only with bulky disease and end stage disease; we should really go more in an early state of metastatic disease or at least that is my view.

Scott Antonia: I guess I still would disagree with that: I've had some of my best responders who have had borderline performance status and who came back to normal who had bulky disease. I don't think, at least with checkpoints, that the bulk of disease predicts for responsiveness.

Solange Peters: Comments from the room, don't hesitate, you can also raise your hand, yes.

Audience (Michael Kalos): I don't know if I being controversial in 2013, but I think we have to come to realise that targeting using self antigens as vaccines is really never going to work robustly. I mean Carl pointed out the three points from Bill Paul's paper that, you know, central tolerance is insured with the high potency T cells to self-antigens, and CT antigens are self-antigens, are really fundamentally deleted. So al the responses and I know I'm being extreme here, but time and time again we've seen this, there's polyvalent vaccines that are stimulating robust responses but we don't know what the antigens are. PD1 and other checkpoint inhibitors are unleashing potent T cell responses but we don't know what these responses are and when we've looked at the nature of the infiltrating TILs (tumour infiltrating lymphocytes) at tumour sites and take all of the antigens that we know and say what frequency of those TILs is represented by the known universe of antigens its typically pretty small. So there's a potent, a very potent T cell response to tumours, that's why tumours develop these immunosuppressive mechanisms and down regulate class 1, that is really true and we are unleashing that at the checkpoints but to continue to go after self-antigens, we're going to keep hitting our head against the wall, just to be...

Carl Jung: I think that's a really good point and I agree but I guess the data that we have that goes against that, is that, in lots of vaccine trials, even though they are clinically inefficacious, you can demonstrate an expansion of T cells that are specific for these self antigens, right? So you are breaking tolerance. I mean the dendritic cell vaccine for P53 - P53 should be very well tolerised and we get responses in 40% of the patients.

Audience (Michael Kalos): When you have an opportunity to look at the quality of those T cells, and I've done some of that work and my work has been published, the affinity of those T cells is typically one to two logs lower than the affinity of virus specific T cells, so they come out, and we saw some of these data today, and you see these by tetramer but they are not the potent T cells that we need to mediate the kind of responses that we need.

Ignacio Melero: There is a paper from Jeff Weber, and I don't know if it is worth commenting on, but it is already accessible in your Annals of Oncology, but they ran a blockade PD1 clinical trial by vaccines mounted to many of the self antigens and it was very curious because there was no correlation with response and expansion of those self antigens because of the vaccination. And there is a tendency there that those patients with anti ESO-1, for example, were not doing very well per treatment, I strongly suspect that the individual mutatome is going to have a clear role and particularly these patients when they go to surgery and the tumour is available for sequencing by whatever means and identify mutated epitopes, this is probably the best possible scenario to formulate private vaccines and try to see whether these could really impact survival.

Scott Antonia: That's a good point. The point I'd like to make and just one quick comment, is be careful about interpreting the Weber data because he actually didn't see an induced immune response in the patients either, so the fact that didn't add any clinical benefit, it could just have been that it was a bad vaccine.

Carl Jung: So I'd like to get back a little bit to the prostate. And the best case is if you take primary tumour cells from most of the solid tumours, and they can't grow prostate really but we've done this with pancreatic, lung and ovarian, and then you get around the allo effect by having a high affinity CAR (chimeric antigen receptor) and what you find is the CAR T cells can kill just about any epithelial tumour cell you have in vitro so they are non cross resistant and if the CAR gets there, I should think be capable to kill, because it does in vitro. Now, in prostate cancer, the natural history of that is the more TGFß the tumour makes and the micro environment, then that's adversely associated with survival. Ton Schumacher and his lab published a paper either this year or last year in tran (transgenic) model in mice and the T CAR in the tran model cure mice with prostate cancer if you also knocked out TGFß. So, I think prostate cancer now maybe with a standard approach, it does work on low burden patients but I think it will work on high burden patients as Scott's saying but we need to take into account these other things in the tumour microenvironment, in particular in prostate I think we need to get rid of the effects of TGFß if we're going to have a chance at bulky disease.

Solange Peters: So lets' move on to, ... sorry can I just take one more question before we move on to the next chapter.

Question from the audience: Well, to be a bit provocative. I think we are too early in trying to vaccinate in a curative way; we have been doing that for years and we have no idea how to do it. What we are doing using the same with the self peptides, now the disease is too tolerised, we don't understand how to do it. We don't know which adjuvant to use, the antigen, we know it but to date the problem is not the antigen: we don't know how to vaccinate in the sense which adjuvant which route - we know how to get the cells to the place they have to be but they are dead two minutes after we inject them. They do not know how to migrate to the lymph node where we have to prime, they don't survive. That's the first main reason. And the second main reason is: We cannot vaccinate against cancer because we don't have autoimmunity and so the new system has done all the effort to stop reaction against self that we are not able, as the previous speaker said, we are not able, the reaction will overcome it. And the block, the checkpoint inhibitors are part of what we are understanding today but we are very far from being able to vaccinate in a prophylactic... in a curative way, I'm sorry,

Solange Peters: So on this pessimistic point of view, you helped me to switch to the checkpoint inhibitors, maybe.

Question from the audience: No it's not pessimistic.

Scott Antonia: Let me just say, clearly vaccines have produced clinical response so I think you're probably exaggerating to make a point because clearly you can shrink tumours; there's a 5% response rate - in those 5% of people it tells you biologically it is possible to immunise and get efficacy. It's just low frequency.

Solange Peters: Thanks, let's move to the checkpoint inhibitors (Slide: Checkpoint inhibitors). I'm sure we will speak about combination at the end or, or at the next chapter, so the check point inhibitors. CTLA-4 inhibitors have been described to be related to a huge panel of autoimmune phenomenon that we have discovered; we know the kinetics of this phenomenon and are now more or less used to observe them across patient cases and in the clinical practice.

Now we have guidelines that have helped the entire community to manage specific toxicities, I am quite convinced about it. You, as a clinician, you now have these very user friendly guidelines that help you to very actively and very efficiently go to the problem of your patients with every kind of organ and this is divided like it was discussed this morning, into specific organ or specific immune regulated class of effects and these guidelines are more than easy to follow so I think this has rendered the field of managing toxicity a bit more available for any medical oncologist in the field.

I would say it was discussed this morning by professor Michielin that the toxicity profile of CTLA-4 and anti-PD-1 is very different in terms of intensity, the frequency of severe toxicities encountered but I think these guidelines have helped us to deal with both kinds of toxicities.

In the lung cancer field what we have feared more than everything more than anything is this rare but often fatal effect of pneumonitis and I think still remains open having anti- PDL-1 and anti-PD-1 and drugs we still do not know if one or both will be more toxic at the lung level but we have to pay lots of attention to this rare but sometimes very severe, adverse event.

So if I open the discussion of risk/benefit ratio I think that these guidelines and all the material we have are available to allow us encounter with calm this toxicity and have made the risk manageable and we discussed this morning the benefit of these strategies. I would guess the ratio has become favourable or very favourable in the field of most of the cancer types today so what is the opinion of the panel about it and what is your opinion about the management of toxicity in this checkpoint inhibitors field.

Olivier Michielin: I think clearly those guidelines are extremely efficient, we have proved this with a recent phase III trial where the number of severe toxicities was remarkably reduced. I think one very important point in applying these guidelines is to be able to react extremely quickly, the sooner you act the more efficient you're going to be and the less immunosuppression you're going to need and probably the less you are going to hamper the clinical response. This actually is stressing the medical system as a whole; as long as the patient are followed in really well-trained centres, you get these fast responses of the team and sometimes it is more difficult when clinicians are less experienced so that is something that we see when we treat patients together with colleagues that are less experienced - that the whole infrastructure has to be aware of the fact the patient with metastatic cancer having diarrhoea is not necessarily needing, I mean you can give them steroids actually and so that is sometimes a limitation, that is an indication for us oncologists internists to have an efficient team around those guidelines.

Winald Gerritsen: In the Netherlands we had a whole discussion about the treatment with checkpoint inhibitors, especially about ipi (ipilimumab) and where to treat it, and in the end we decided we use the drug in at least in ten patients per year, so to ensure that your team has enough experience we concentrated the treatment of melanoma now to 12 centres in the Netherlands.

Solange Peters: Next, Caroline?

Audience (Caroline Roberts): I think we need to consider the checkpoint inhibitors and toxicity is really not the same kind of severity and also we have to consider them as drugs although these drugs will be evaluated in the adjuvant setting, so it is a very different context. So I think of course, treatment with these agents needs to be done in centres that are used to it and even then we need to keep our eyes open because I am sure we haven't discovered yet the whole spectrum of side effects; I think it is very underestimated, a lot of patients complain of cephalalgia, we have a lot of meningitis because we know to look for it; if you don't do a long term control you think it is almost normal for a metastatic patients to get a polyocular neuritis in the adjuvant setting with a patients who almost dies, I mean it is very rare but you can have very strange things - we also had an acquired haemophilia, so we really need, even though we think we are very experienced and very trained we really need to examine patients, very very, deeply. Even so I am much less stressed to give anti-PD-1 antibody than ipilimumab because the side effects are less severe and less frequent. The thing that I am very concerned about having treated more than 100 patients with MK3475 is the fatigue, because they are doing well on one level, almost normal but they are tired and I would like to have some help to under why they are tired; I would like to understand why they are tired, It seems like they are tired like how you are tired when you get old. Things seem to function very well but patients don't seem to be working out very well. So we need to understand something here.

Solange Peters: Is the toxicity observed in the adjuvant setting different from that in metastatic disease?

Caroline Roberts: Well we'll see, my feeling is yes but also the dose was high so we'll see.

Solange Peters: The panel, feel free to start.

George Coukos: I think an important measure to reduce toxicity will be to develop better biomarkers for the selection of patients, something that will not only help in increasing the efficacy but clearly to spare unnecessary toxicity in some of these patients. The field is moving towards that direction in the case of PD-1; for example in PDL-1, I think pre-existing T cells in the tumour or the gene signature of pre-existing immunity in the tumour bed may also be an important biomarker to be tested. So I think these will be important tools that will be coming into the clinic in the next few years to start identifying high patients.

Solange Peters: Yes, please.

Audience (Laszlo Radvanyi): I think this is a very important topic because you know, for example, when high dose chemotherapy came in to treat childhood leukaemia, we're now seeing the effects of that, because we now have long terms survivors from the 70's and they're coming down with all types of problems, premature aging phenomenon and things like that and I think this is one of the issues from unleashing the brakes on a T cell response; for example, will we see premature senescence of the immune system as these patients survive longer and longer. I think we need to follow-up on this, so I second the thing with biomarkers but not only short term biomarker analysis but long term biomarker analysis where we follow changes in T cell clones, oligoclonal expansion, in patients long-term that have been treated with these checkpoint blockades. I think it's going to be very important. And also this addresses why the GP 100 ipi (ipilimumab) trial of ipi plus gp100 peptide vaccine versus ipi alone didn't really show the difference one would have expected and it could be that, and this is an argument that people didn't really want to listen to, is that you could actually be pushing the over expansion of certain clones and perhaps exhausting those clones to senescence, which is what we see with TIL? That is a major problem - that's going to be something we're going to have to deal with.

Audience (Michael Kalos):. It is not clear to me why we should expect to have no toxicity when we are inducing a potent T cell response against heavy disease burden. I mean, I'd love to see what happens in the adjuvant setting, but you know we're going to get toxicity, the mindset that we should expect no toxicity, I think, leads us a little bit down the wrong track, I mean our patients at Penn they come to expect and actually want to get the fevers because that means that they are responding and not everybody manifests severe toxicities but it comes with the therapy, right?

Carl Jung: Yes, I want to comment on what Caroline just said about because I hadn't heard this, that people on checkpoint blockade who are on these long-term survival curves actually continue to feel tired. If you do a Pub Med search, there is a paper that just came out I think may speak to this; it's by Bill Murphy and a group of immunologists entitled ' Aging predisposes to acute inflamatory-induced pathology after tumour immunotherapy" and so they showed, and this is in mouse models, it's a very important paper, that we're going to have to just as Lazlo was saying, judge acute versus delayed toxicity and so I'm wondering, do these patients have elevated TNF which can lead to a lot of these effects and has that been looked at in these PD.1 PDL-1 blockade therapies. If it does, then there is immunosenescence and all these things they're talking about in this paper then what it means is, we've going to have to have a way to shut that down, we have to find out as a field are we getting sterilising cures and then can we turn the immune system back off? And we don't know the answers to those questions.

Ignacio Melero: I find that experimental medicine paper fascinating and in that regard I have a suspicion and it is very difficult to confirm, and can only be addressed really in mice, that the microbiota is playing a huge role in the most frequent reactions which are in the skin and in the gut. I don't know about the endocrinopathies, probably that's more related to the soil, I mean the genetic background of the patients, but regarding the intestinal complications and the skin, most likely we are not facing real autoimmunity reactions but an appropriate response to flora. Looking at the monoscope of the T cell receptors there, it doesn't look like oligoclonality, and on the other hand there are several aspects such as reversibility. When you are

dealing with inflamatory bowel disease or ulcerative colitis that's really really difficult, and in these cases, I mean, it is just taking the patient off the drug and giving a reasonable amount of steroids in most instances it slowly goes away and that's it. That's not autoimmunity, autoimmunity is another thing.

Solange Peters: The last comment from our radiotherapy colleague and then we'll move on to the last chapter.

Audience (Dirk De Ruysscher): A lot of times a patient has received radiation or concurrent chemoradiation before they develop recurrent disease or metastatic disease. Does this influence the side effects because you have influenced inflamatory response and the T cell response a lot, I think.

Scott Antonia: It's been looked at for the development of pneumonitis for instance, and it turned out not to be the case, so there was no tracking of pneumonitis with prior radiation to the chest. I do want to make one comment, not leave the audience with the feeling that this fatigue happens in all patients. I have no experience with the Merck antibodies, so maybe its antibody specific, but I have the experience that patients paradoxically actually feel better whereas their disease burden goes down. I have lots of patients who really, -- so, yes, it can occur but it kind of seemed like we were sort of being left with the idea that fatigue occurs in everybody.

Solange Peters: Let me move to the last chapter which may be more complex the adoptive cell transfer because we should address all the subchapters, TILs, engineered T cell receptors CARS, and of course we will group them and try to make the discussion more interesting.

Some of our colleagues tried to cite and quote every clinical trial and to describe every single toxicity which is basically related to the antigen which is targeted and as you can see here I just put up three recent publications on toxicities, cardiovascular toxicity, melan A in the skin eye and ear toxicity and CEA (carcinogenic embryonic antigen) gastrointestinal toxicity using this strategy of T cell receptor modification and of course there are several reviews about those challenges but also the achievements of CARS. As you can see here I have made a chart that just summarises the fact that CAR response is highly specific and can target both the on target and off target antigens and this is especially the case with second and third generation CARs containing protein combination of signalling and co-stimulatory molecules that have the potential to respond to all levels of targets physiologically expressed resulting in a generation powerful activation signal leading to a 'cytokine storm' that we have discussed previously and that may be one of the risks. So this may be the most interesting chapter because we have the risk benefit, as we probably have discussed this afternoon, a high risk procedure but also a potentially a highly beneficial procedure where some of the experts will aim for or speak about cure so this is probably a risk/benefit of interest for the medical oncologist/advanced disease community. Who would like to start in the panel?

Carl Jung: All right, one thing I want to highlight I would like to disagree with what was shown on that slide, what they said was cytokine storm – cytokine storm is an off target issue that occurs, for instance, when the whole immune system gets activated and it's not treating the tumour, so that can happen and did happen with a T genero anti-cd 28 agonist that was immediately after infusion of an agonistic antibody. What

we are seeing with CARS and the rest of the field is not cytokine storm, it's cytokine release syndrome and it's on target and it occurs when the T cells proliferate. So ok, distinguishing between on and off target toxicity is going to be very important; chemotherapy oncologists for decades have caused much off target toxicity, alopecia, gastroenteritis, etc. and it is not helping against the tumour. Our patients who are having on target toxicity which is cytokine release syndrome, with fevers and those kinds of things, they accept that because at the same time they know it correlates with benefit. So we need to be careful as a community to distinguish between on and off target toxicity and actually that the patient will accept on target toxicity if it's associated with benefit, so in fact I think it's an obligation, I mean, we need to educate the public and general physicians about the difference. The only association most medical oncologists know anything to do with immunotherapy is really an allogeneic bone marrow transplant and unless they are specialists like in this room they've never seen anything like this.

I think we can reinterpret the TIL data; for many years it failed and the reason it really failed was because it was never taken beyond boutique trials and done in a randomised fashion because they were doing TIL cultures that required two or three months and cost $100,000 to do. NCI, and now in the Netherlands and in Copenhagen, they are doing TIL cultures that last 10 to 14 days it's much cheaper and the efficacy is holding up where there's a 50% response rate with TILs and metastatic melanoma and George Coukos brought up today, it was brought up in both ovarian and lung cancer I think, that TIL therapy could be done. Now you can reinterpret that now we know about the mutanome and the high affinity in self reactive T cells against these new mutations and it might be that the best place to get those cells is maybe in the tumour microenvironment. So the TIL therapy now I think needs to be revisited and, with checkpoint therapy, may be much more efficacious now than it was in the past and with more modern cell cultures, so I'll leave it at that.

George Coukos: So Carl, Clearly as we treat more patients, we know how to manage them more and given that a lot of the on target toxicity with cytokine release is related to Il-6, at lease in your hands, do you envision that at some point in time one could develop a prophylactic regimen with some low dose steroids and Il-6 antibody given immediately after CAR infusion or within 24 hours to prevent the peak, the explosive peak of immune activation?

Carl Jung: Yes, I think some cytokines are different somewhat in mouse than in human and Il-6 was tested, as far as I know, as a therapeutic for cancer in only one trial. It was done by, at the National Cancer Institute, it might have been Roche but I can't remember the company that made it and it was done in a dose escalation trial and they ended up stopping the trial for hepatotoxicity. It was not looked at in a way..., I think we should revisit, first of all whether Il-6 can be used as a therapeutic now that we're seeing it as a biomarker and so the other thing is that right now when we're blocking Il-6 we're using an antibody that has about a three week half life. It would be nice to have a signal transduction blockage inhibitor and those exist with the JAK kinase inhibitors to block Il-6 signalling dialate, we don't know if it could be done prophylactically as you're saying and then increase the therapeutic index and then be able to treat high burden tumours without life threatening metabolic syndromes that we're seeing or we're going to have to go to lower burdens when we're talking about T cell receptors and CARS. Finding a way to manage this immunotoxicity with cytokine blockade and/or steroids is now a very big issue and

you can look back in history on bone marrow transplantation; when I first started we were treating graft versus host disease with horse anti-thrombocyte globulin and basically depleting T cells that way and now we have much better ways of managing graft versus host disease so the field and basically clinical oncologists have figured out how to manage GvHD; I think they'll figure out have to manage cytokine release syndrome.

Ignacio Melero: I would like to add on the comment that Il-6 is a very powerful modulator of STAT3 which is one of the more conspicuous immunosupressor mediators in signalling and I think that it makes full sense, I know that Frances Balkwill in London is starting a trial with IL-6 in ovarian cancer, which is extremely powerful at producing IL-6, and I think that it won't be against mechanism of action to preblock Il-6 it can even be even synergistic so I think there is a good reason to go for cixutumumab in this setting.

Carl Jung: I would agree. Either there it's a partial agonist, partial antagonist and maintaining helping macrophages that can be turned on to help macrophages are very effective in killing tumour cells. And then there are trials that will start and may be already have started using Il-1 blockage so the balance in that is going to have a lot of renaissance.

Ignacio Melero: With Il-6 the only risk is the regeneration; you should not block it, that is one of the major drivers, so it is resection or liver toxic drive then it is you should be careful about that but other than that I think for tumours eventually it will be a good target.

Solange Peters: Are there questions or comments?

Question from the audience: Do you think at the opposite of the cytokine release storm in the checkpoint blockage we could have a kind of chronic cytokine release that could for example explain some of the symptoms that these patients could have at the opposite side of the cytokine storm. Do we have some evidence of the level of cytokines that are produced in these patients of what could have evidence there is a continuous immune response in this kind of patient, but not a storm-like stimulation?
Solange Peters: Any answer from the panel?

Ignacio Melero: To tell the truth, chronic fatigue in cancer metastatic patient was not our problem for awhile, maybe it will be in the future, so far we were worried about other things.

Solange Peters: Yes I think we have a last question there on the right on the back and then I will have to close.

Question from the audience: I'd like to go back to the construction of the T cells for adoptive transfer. The current dogma is that the higher the affinity of the transfer of the CAR or the chimeric antigen receptor the better, according to the results that you can achieve in vivo. This is an aspect that is not considered sufficiently: the aspect of activation of new cell death that can be induced when you have an antigen overload. So what I would like to hear from Carl June or from the panel or from other people in the audience who have experience with this kind of transfer, is whether they are really sure that this is the only way, because I'm thinking that for example if you want

to find a big marker tumour and you have extremely high affinity or avidity, these cells or chimeric antigen receptors, what you can get is an overload cytokine storm and the kind of immuo-chemicals which are not only detrimental for the patient but also for the same T cells, which have very good chances to be destroyed in the interaction with the tumour. Why could the lower affinity, for example of these chimeric antigen receptors, afford to recognise the tumour while sparing the normal uses which have a lower expression of the same shared antigen? What is your opinion?

Carl Jung: So it's a complex thing, there is both the biophysical measurement of avidity and the affinity of the actual T cell receptor and there is the downstream wiring which the cell actually adjusts to, and so it's not the maximum affinity, for instance these T cell receptors; what has been found, and it is sort of the consensus of the field now, is what you want to get is a T cell receptor similar that with viral affinities over evolution the T cell receptor has been optimised to what we see with viral affinities of T cell receptors . There are data mostly from Den Jacobsen, and in adaptive immunity where they have looked at a lot of T cell receptors from either self antigens or viral antigens there is about a thirty-fold difference in affinity of those T cell receptors when you make them monoclonal and look at them, so basically improving by that amount, and that puts them into the viral range and then you can show that tumours, particularly where the tumour - is not like a flu infection where they have a lot of MHC peptide on them - it's a lot lower density on the tumour and so affinity enhancement can help, but that doesn't mean maximal. And the same thing for CARS; we don't know yet the optimal affinity of the single chain variable fragment and we think it is, I didn't show it but Michal Kalos has data on this: , Those CAR cells in the patients, they survive with very high affinity and yet, the ones that survive, obviously didn't have AICD (activation-induced cell death) some of them probably do and the ones that don't have AICD are the ones we see that propagate and form the memory pool of CAR memory cells, then they don't have a normal phenotype though; they don't look like resting central memory cells that are CCR7 positive and has all the other things you see after a viral vaccination when the antigen goes away. So they look like they are protecting themselves - they are PD1 positive, for instance, and yet they are fully functional, these CAR cells so I think that's why they're not having AICD, so there's a lot left to learn, there's probably plasticity in the rewiring and the signal is different between CD4 and CD8 cells and the optimal receptors in those cells may differ, so we're still at a very early stage; the amazing thing is that it works at all, from what I think.

Solange Peters: Thanks a lot...

Carl Jung: One other point I'd like to make that we haven't brought out for oncology, what we are going to need to do for adoptive therapy That's not done now, generally, what bone marrow transplantors do is they harvest stem cells and immunotherapists are going to have to harvest T cells, so before someone undergoes very lymphodepleting therapy, its best to harvest and cryopreserve T cells so you have cell to later use for growing them and bioengineering them.

Solange Peters: I want to thank the members of the panel and all of you for remarks and comments.