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New frontiers in NSCLC immunotherapy

Transcript from a touchEXPERT OPINIONS

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THE EXPERTS:

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INTRODUCTION

In this activity, international lung cancer experts discuss the current role of immunotherapy in the management of non-small cell lung cancer and outline the most promising emerging immunotherapeutic strategies targeting inflammatory mediators, with a focus on the interleukin-1 pathway. Dr Marina Garassino also provides insight into the impact of the COVID-19 pandemic on the care of patients with lung cancer.

LEARNING OBJECTIVES

After watching this touchEXPERT OPINIONS, you should be able to:

- Recognize the remaining challenges in terms of long-term survival for patients with NSCLC despite the availability of checkpoint inhibitors
- Describe the tumour immune cycle and the therapeutic opportunities it may provide
- Discuss the potential for reduction in cancer morbidity and mortality with IL-1-targeted agents and its implication for early treatment of NSCLC

TOPICS DISCUSSED:

- The current role of immunotherapy in NSCLC and its limitations
- Key features of the tumour microenvironment in relation to anti-tumour immune responses and possible therapeutic targets
- The relevance of the IL-1 family of proteins in cancer immunity and emerging IL-1-targeting treatments for solid tumours
- The rationale for targeting the IL-1β pathway in NSCLC and the clinical development of IL-1β-targeted agents
- The impact of COVID-19 on lung cancer patients, including global epidemiological data and its effect on provision of care

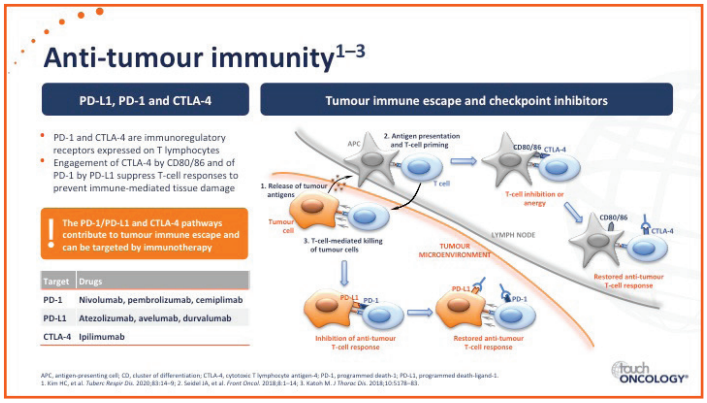
ASSESSING THE FUTURE OF IMMUNOTHERAPY IN LUNG CANCER

Dr Marina Garassino:

My name is Marina Chiara Garassino, I am the Chief of Thoracic Oncology at the National Cancer Institute of Milan, Italy.

Which therapeutic targets are currently exploited in immunotherapy for NSCLC?

We can exploit in 2020 mainly two immune checkpoint inhibitors. These two checkpoint inhibitors are the ones against the PD-1/PD-L1 axis, and we are starting now also to use anti-CTLA-4. PD-1 and CTLA-4 are expressed on T lymphocytes, while PD-L1 is expressed on the tumour, on the macrophages and on some other cells. So when you inhibit the PD-1 and PD-L1 axis, you reactivate the T-cell response.



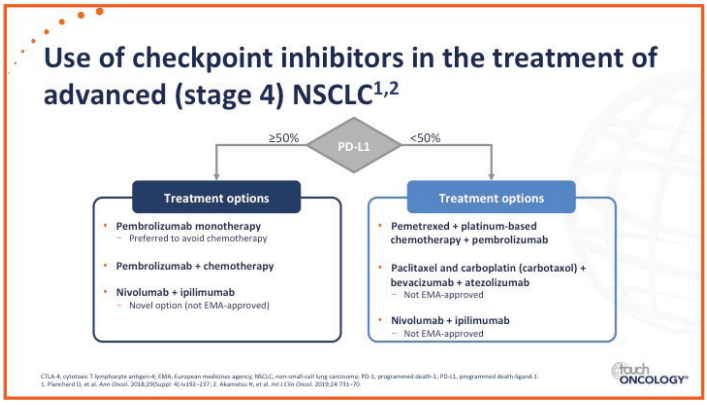
So we know that this kind of pathway is very important for immune escape and by targeting these pathways, we are able to reverse the immune escape. The most relevant drugs that we have to target immune checkpoints are nivolumab, pembrolizumab and also cemiplimab and targeting PD-L1 we have also atezolizumab, avelumab and durvalumab. Moving to the anti-CTLA-4, we have the possibility now just to use ipilimumab.

When are checkpoint inhibitors currently used in the NSCLC treatment pathway and what are the associated outcomes?

Now we have several possibilities to use the immune checkpoint inhibitors in the treatment of metastatic non-small cell lung cancer. The first is for patients with a tumour expressing PD-L1 more than 50%. We have two possibilities: one is to use single agent PD-1 blockade, which is pembrolizumab, or for this population, potentially we can also use the combination of chemotherapy and immunotherapy, and based on recent data, also the combination of anti-PD-1 and anti-CTLA-4.

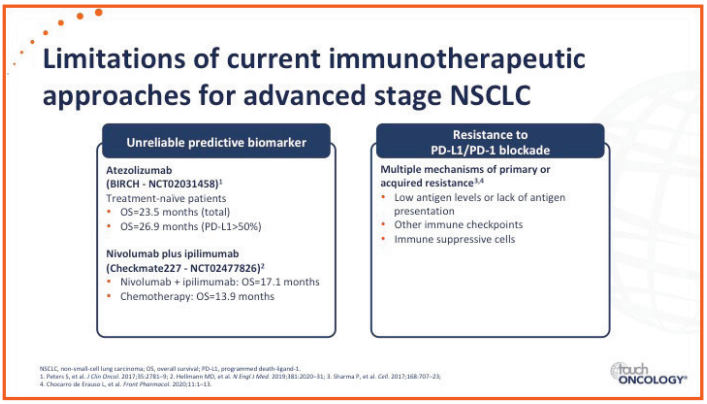
So how can we decide? We don't know, because we do not have direct comparisons among clinical trials. So we try to use a chemo-sparing regimen as much as possible. For the majority of patients, maybe pembrolizumab alone can be enough, but there are some categories of patients, for example those with a bigger tumour burden or the never smokers, in whom it may be potentially very important to use it in combination with chemotherapy.

Then we have a large portion of patients whose tumour has less than 50% PD-L1 positive cells and for whom nowadays we have approved combinations with chemotherapy that in non-small cell lung cancer can be platinum/pemetrexed and pembrolizumab or the combination of carbotaxol, bevacizumab and atezolizumab. Recently, data suggested also that for these patients we can use the combination of anti-PD-1, anti-CTLA-4 and two cycles of chemotherapy. Again, also in this setting it is still debatable when to use one combination or the other. What we know is that, both for the grey area between 1 and 49% and for patients who are PD-L1 negative, combination therapies play a very important role because they increase the survival of these patients. Further research will be needed to address whether to use one approach or the other.



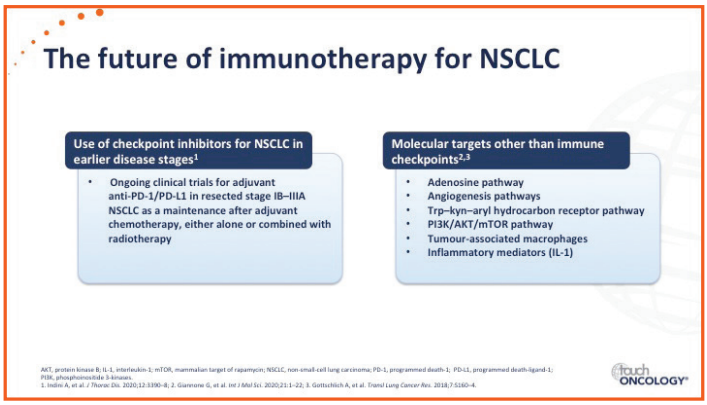
What are the limitations of current immunotherapies in the treatment of NSCLC?

There are some problems that are for example, the lack of biomarkers for these patients. We have nowadays only PD-L1 as a biomarker. So in the beginning, we are unable to understand who are the patients who will benefit from single agent, combination therapies and who will benefit from immunotherapy in general. The second big point is that we need to work on the primary and on the secondary resistance; we don't really know very well what the mechanisms of resistance are. Potentially they can be multiple and overlapping and they can rely on low antigen expression, they can rely on a microenvironment with a very immunosuppressive component from the beginning. So it is possible that it is not just a single mechanism of resistance, like for the targeted therapies, but we have a combination of multiple mechanisms of resistance. The next step will be very important to select the population that will better respond to immunotherapy and to increase the outcomes in the primary and the secondary resistance.



How do you envision immunotherapy for NSCLC will evolve in the future?

The future of immunotherapy is very challenging because we are now in a sort of a plateau. I think that in the future, we have to promote as much as possible the neoadjuvant setting, where it seems that with immunotherapy we are able to have also major pathological responses that were unseen with chemotherapy. We will have to wait for the adjuvant trials, after the surgical resection and clearly the next wave of immune checkpoint inhibitors will be very important. So all the pathways targeting the microenvironment and also all the pathways overcoming the mechanisms of primary resistance. There are some pathways that are more interesting than others but it will be crucial to understand what are the biomarkers behind, to foster proper research for the future of non-small cell lung cancer.



UNTAPPED POTENTIAL IN THE TUMOUR MICROENVIRONMENT

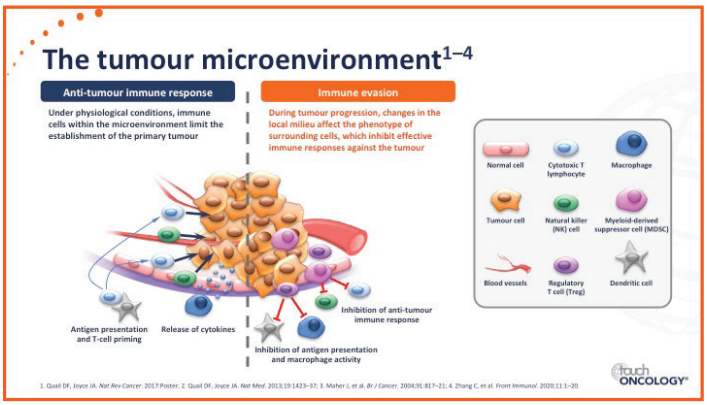
Prof. Sebastian Kobold:

My name is Sebastian Kobold, I am Professor of Medicine and Experimental Immunooncology and Vice-Chair of the Department of Clinical Pharmacology here at the University Hospital of the Ludwig-Maximilian-University in Munich.

What is the tumour microenvironment?

So, the tumour environment or microenvironment is an overarching term that in the end describes the environment of a tumour. It is a conglomerate of cellular structures and non-cellular structures that encompasses and surrounds the tumour. I think that one of the essential aspects for today that are present within the tumour microenvironment are really immune cells, and cells that will then communicate both with each other and with the tumour cells.

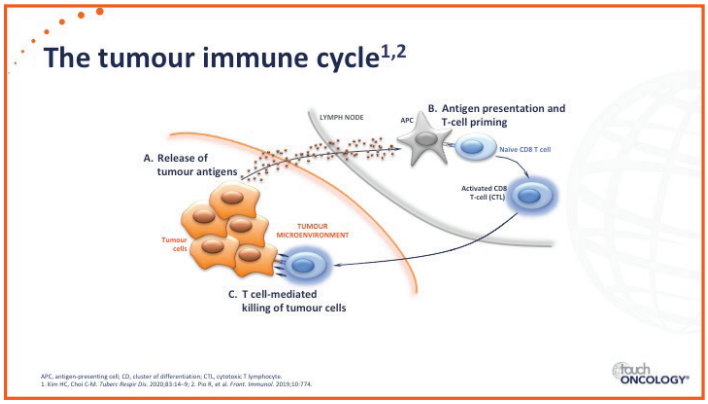
I just think what is important to bear in mind is that this tumour environment is typically constituted of cells that are both in favour of an anti-tumour immune response, that can contribute to an anti-tumour immune response, such as cytotoxic cells, NK cells, particular types of myeloid cells that are pro-inflammatory, but at the same time, and I think this is also the essence of why you have a cancer disease, there are also a lot of immunosuppressive cells or cells that actually contribute or support the tumour in its effort to escape the immune system.



There are a variety of these cells, and I just want to name some examples here such as regulatory T cells, myeloid-derived suppressor cells, immune suppressive macrophages, also called M2 macrophages, and many others. The interplay of these different types of cells, together with the tumour cells, in the end determines whether, in the first place, you will ever go to an active disease, because we know that many of those cells are also already able to control the disease, or progress to a clinically apparent disease, which is what we see in the clinic. I think what is also important to bear in mind for the next topics is simply that the balance of these cells can make the difference between an active, ongoing immune surveillance and immune response, or just a progressive disease.

How does the tumour microenvironment influence the tumour immune cycle?

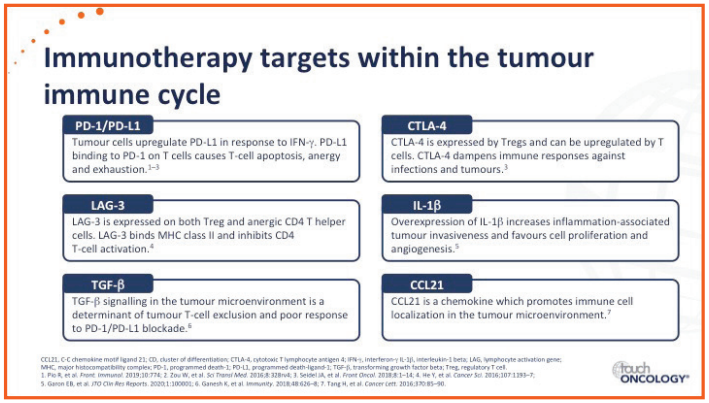
I will start out to answer this question by maybe briefly introducing the tumour immune cycle, which in the end, describes the interaction of the tumour and how it gives rise to an immune response and how this immune response can, in the end, fight cancer. So this starts out, as many times when it comes to specific immunity, with the release of tumour antigens that are then being taken up either locally or to more distant sites, like in lymph nodes by so-called antigen-presenting cells that take up the antigen and then present it or cross present it to surrounding T cells, specifically also CD8 T cells. Whenever a specific CD8 T cell hits its antigen on an APC, it becomes activated, starts recirculating out of the lymphatic structure and can go to the tumour to eliminate it.



So this is, I would say, the ideal world or the ideal situation. But in the real world, this cycle is shaped massively by the tumour environment and everything that comes from the tumour environment. You need to differentiate between cellular structures, cell-bound structures and soluble structures. I think the essence of a tumour or the essence of a cancer disease is that it has developed a variety of cell structures, cell-bound structures and soluble structures to actually suppress different aspects of this immune cycle, the immune reaction and also the activity of an ongoing immune reaction.

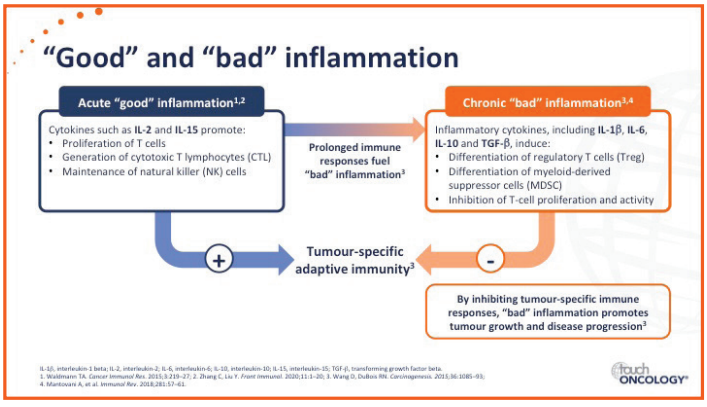
There are a number of examples. I think the most prominent examples that hit this immune cycle are of course the programmed death receptor 1, programmed death receptor 1 ligand axis that plays a role both at the site of the recognition of a tumour cell by a T cell, but it can also play a role within the priming phase. And whenever this interaction is active, the priming phase or the recognition of the tumour by a T cell is suppressed. Other examples include cytotoxic T lymphocyte antigen 4, which is upregulated, especially in lymphatic structures, and then prevents productive immune response and the mounting of specific immunity.

Then you have, of course, the soluble factors. So those we have just discussed are the cell-bound factors,then you have the soluble factors, one of the oldest ones is TGF-β. So transforming growth factor-β can be released by the tumour cells, by its surroundings and suppresses T-cell activation, T-cell proliferation and can also lead to some level of cell death. Then another very prominent factor that will also be important for later in this talk is interleukin-1β, which is frequently produced at relatively high amounts in the tumour microenvironment and has manifold actions; it can polarize and recruit myeloid cells, it also boosts the polarization of specific T cell subtypes towards something that is not desired. All of this has in the end, a very immunosuppressive action and can also blunt the effect of the tumour immune cycle.



What is the dual role of inflammation in the tumour immune cycle?

In a nutshell, we like to consider inflammation as a good and a bad thing and this really depends on the context. In principle, inflammation, from a therapeutic perspective, is something we would like to have because, as we've learned in the past using blockade and other approaches, inflammation can be very beneficial. At the same time, we also know that that inflammation can actually promote cancer development, progression and also immune suppression. I think the difference between an acute, or good inflammation, and bad inflammation starts already with the duration of it. So typically something that is very acute is rather good because it helps you to clear pathogens. It can also help you to clear a tumour. However, if the inflammation is sustained and is being entertained without actually being cleared, because you want to clear inflammation at some point, if it's not cleared, it turns out to be chronic and typically a chronic inflammation, at least in tumour immunology or in oncology, is a bad thing. So what makes this response acute as opposed to a chronic response? Typically, examples of acute cytokines or structures that are associated with actually a good inflammation are, for example, interleukin-2 or interleukin-15, that would promote very productive immune response with T cells, with NK cells, and boost those cells and help them to sustain the tumour environment and eliminate the tumour cell.



Eventually, if this phase, meaning that the cells that are being activated fail to clear the disease, and this obviously in oncology is a frequent situation, other factors might either be concomitantly or at later phases released by this ongoing inflammation, such as some of the mentioned factors like interleukin-1β, also TGF-β, which are as such not per se bad guys, but when their release is being sustained and the levels go up, they actually

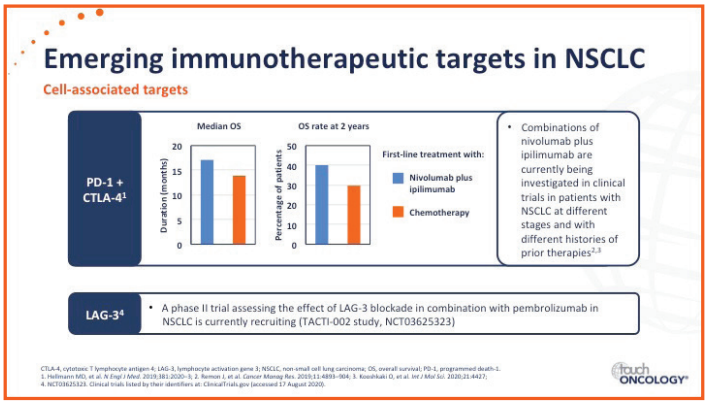
start drifting away from the natural physiological function, which is desired to maintain immunity and control immunity. Sustained inflammation leads to the production and differentiation of cells like regulatory T cells, myeloid-derived suppressor cells that, as we've already mentioned, can actually help the tumour to grow or protect it from this previously mentioned good inflammation. So I think in a nutshell, it's important really to just have the differentiation that inflammation can be good or bad, depending on the context and also the duration. It's much easier, so to speak, to go from a good inflammation to a bad inflammation than to move it backwards.

And this also describes the difficulty of treatment options to actually use the immune system or use inflammation to treat cancer, because while it's easy for inflammation to become chronic, it's not so easy to clear chronic inflammation.

Which mechanisms of the tumour immune cycle are potential future targets for immunotherapy in NSCLC?

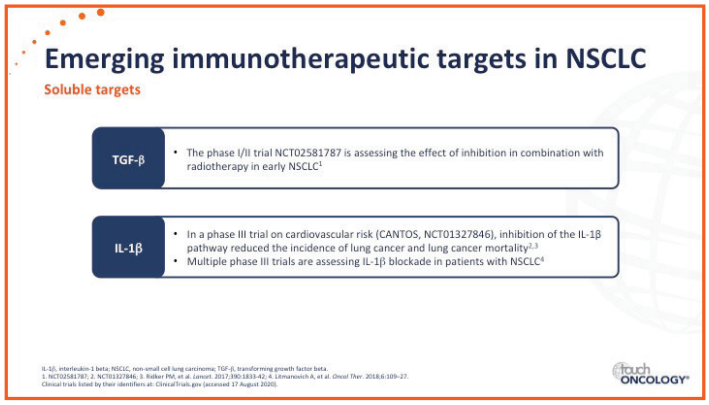
I've already mentioned quite a number of structures in the previous questions that have relevance in the tumour microenvironment, like cells that are either suppressive or activating, like cell-bound structures that can be suppressing or activating too, and also soluble factors. I think that's how I would like to guide my answer to this question. A very desirable thing typically would be to deplete cells that you don't like, but the problem is of course, that it's difficult to do this selectively because you will deplete them anywhere. So that's why that's not a viable option.

So coming to the certainly very successful so far cell-bound structures, I mentioned PD-1 blockade earlier that is clearly successful in non-small cell lung cancer, but a very comparable molecule that has been of use very recently is CTLA-4. There are monoclonal antibodies targeting it that have been approved for melanoma and are currently being investigated in other diseases. So there is, I think, a combination of PD-1 blockade with CTLA-4 blockade already approved for NSCLC as a first-line treatment. Early data reported very promising results, so I think that's something to be very excited about, and it's also very advanced. I think LAG-3 is also the checkpoint molecule that is already in advanced development for NSCLC, I believe also as a combination partner, but the data are less mature, because I think we are only talking about phase II trials here.



Among the soluble factors, TGF-β is a very old molecule in immunooncology that has been tested many times before with small molecules, but right now is still being reinvestigated in clinical studies, with very promising results as combination treatment in NSCLC. Also very important is the cytokine I've already mentioned, interleukin-1β, which is also, I think, one of the oldest mediators of immunity that has been described. I believe formerly called in the old days lymphodrag because it was released by lymphocytes and no one really knew what its function was, but now we know. A lot of exciting data from preclinical studies have shown the importance of IL-1β in promoting inflammation in cancer and promoting cancer growths and metastasis, and very recently, I think less than two years ago actually, there was a big phase III trial with interleukin-1β blockade called the CANTOS trial. It actually was investigating cardiovascular outcomes in patients with high risk for cardiovascular events.

That was the main reason why the study was powered for, and it included thousands of patients. I think it was the biggest trial ever done with cytokine blockade to reduce cardiovascular mortality. There's a very interesting side note actually, although it was not the primary endpoint of the study, but it was one of the outcomes that was intended to be measured. They could actually see that they reduced dramatically both the incidence of and the mortality from non-small cell lung cancer and those patients at high risk for non-small cell lung cancer. So all these preclinical data for IL-1β have indicated that it might really have a role in cancer treatment. I believe that now this agent that neutralizes IL-1β is in different clinical trials, even phase III clinical trials, investigating the impact of IL-1β blockade in different aspects or different clinical situations for non-small cell lung cancer.



In your opinion, which emerging immunotherapeutic agents are showing the most promise for NSCLC?

Personally, the two agents or the two combinations of agents I am most excited about are the combination of PD-1 and CTLA-4 blockade because I think it's a mode of action that immunologically makes a lot of sense and has been shown to be effective in other diseases like melanoma and I believe also in kidney cancer. As I mentioned, there is also data showing promise in non-small cell lung cancer. So that's something where I think there is a lot of promise for non-small cell lung cancer. The other thing I'm very excited about, certainly also because that's one of my areas of primary research and interest, is the blockade of IL-1 or specifically of IL-1β, because I think that's a strategy that has been around for a very long time, that has seen ups and downs and also the difficulties of neutralizing cytokines for cancer treatment. This CANTOS trial I've mentioned in the previous question, that as a side effect, so to speak, showed that this might actually reduce both lung cancer incidence and mortality, indicating that IL-1β blockade with this agent might actually be a viable therapeutic option for non-small cell lung cancer, is something I'm really very enthusiastic about, simply because it's something that biologically makes a lot of sense that has been so far, at least clinically, under explored. I believe that these ongoing phase III trials, both I believe as a single agent and as a combination partner, will hopefully reveal a lot of very exciting data. Hopefully, of course, to the benefit of all those patients that suffer from this very hard disease.

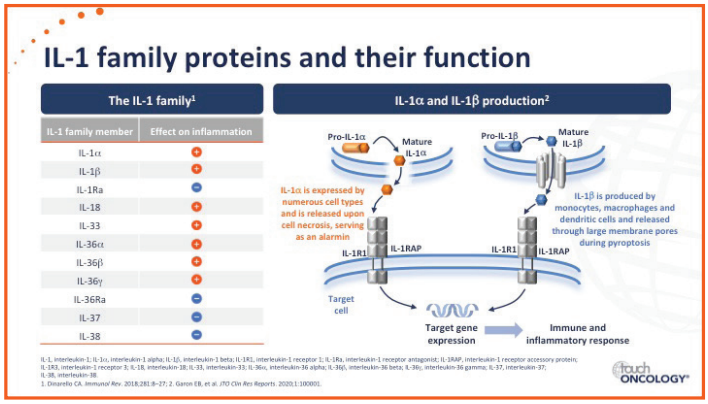
IS IL-1 THE KEY TO PROGRESS IN SOLID TUMOURS?

Prof. Fabrice Barlesi:

I'm Fabrice Barlesi. I'm Professor of Medicine and an expert in thoracic oncology. I'm currently the Medical Head and the Head of Clinical Research at the Gustave Roussy Institute in Villejuif in France.

What are the key elements of the IL-1 family and what are their roles in a physiological immune response?

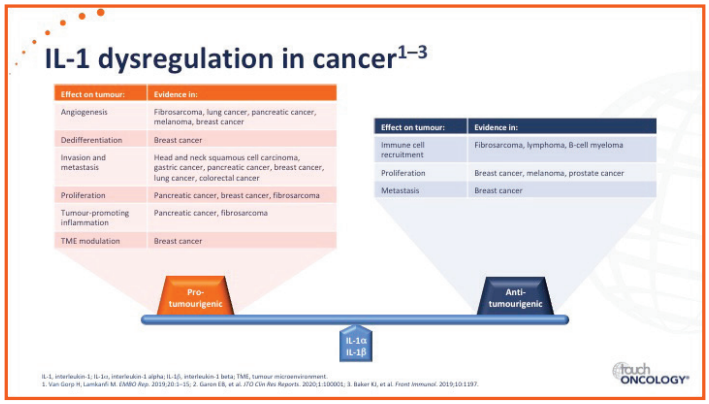
The key elements of the IL-1 family and their roles in physiological immune response and the complexity is first exemplified by the number of members of the IL-1 family. We have 11 members for the IL-1 family of cytokines and we have 10 different members regarding the IL-1 family of receptors. IL-1 is involved in a broad spectrum of immunological and inflammatory responses. IL-1α and IL-1β are the most studied members of this family. You can see the 10 members of this family on the panel on the left, and you can see that the activity and the effects on inflammation may vary across these different family members.



What we should have in mind is that IL-1α is largely constitutively expressed in a large number of cells. Conversely, IL-1β is produced by a limited number of cells, especially monocytes, macrophages and dendritic cells. IL-1α is released by the cells in case of necrosis especially and serves as an alarmin. Conversely, IL-1β is released by the mechanism called pyroptosis, which is a different form of regulated cell death and this process allows the release of IL-1β by large pores of the cells and also activates the system. This is what is illustrated on the graph, on the figure on the right.

How do solid tumours affect the production and function of proteins of the IL-1 family?

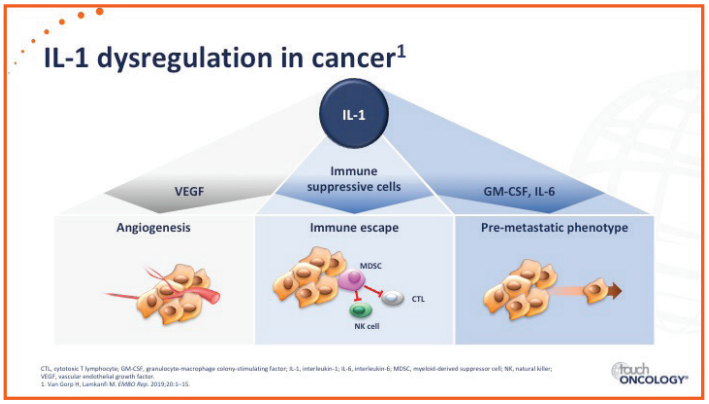
Solid tumours affect the production and the function of the IL-1 family proteins in different ways. In fact, we have to imagine a balance that is influenced by the role of IL-1 as we said before, given that some of the IL-1 family proteins are pro-inflammatory or contrarily against the inflammation. In fact, when we look at this balance, we can see how these pro-inflammatory characteristics may promote the tumour in different ways. We will see in the next slide.



As it is illustrated in these figures, we can see that in some tumours there is evidence that the IL-1 superfamily has an anti-tumourigenic effect. It has been demonstrated in different types of haematological disease or solid tumours, and the effect could be via the influence on the immune system, the proliferation and the metastasis on one side. On the other side, some of the components of this IL-1 family have an influence in some of the same tumour types but also some others. Pro-tumourigenic effects, as illustrated, and you can see that especially we're getting angiogenesis, invasion and metastasis, but also the promotion of inflammation of course is influenced by the IL-1 superfamily.

How do functional alterations of the IL-1 pathway contribute to disease progression in solid tumours?

Then the functional alterations of the IL-1 pathway contribute to the disease progression of tumours in different ways. We can isolate three, I would say, main mechanisms by which the IL-1 family is promoting the tumours. The first one is through the activation of the VEGF pathway - we have a promotion of the pro-angiogenic effects on the tumour and we know how neo-angiogenesis promotes both the development of the tumour, but also its capacity to involve other organs. The second way, which is probably one of the most important today, is by the influence on immune suppressive cells, by decreasing the effects of the control and increasing immune suppressive cells. We can see as it is illustrated here how the IL-1 superfamily may decrease the activity of the NK cells and the activated lymphocytes. So the third way is to modify the specific phenotype and promoting the metastatic involvement by the tumour, especially by the means of GM-CSF and IL-6.

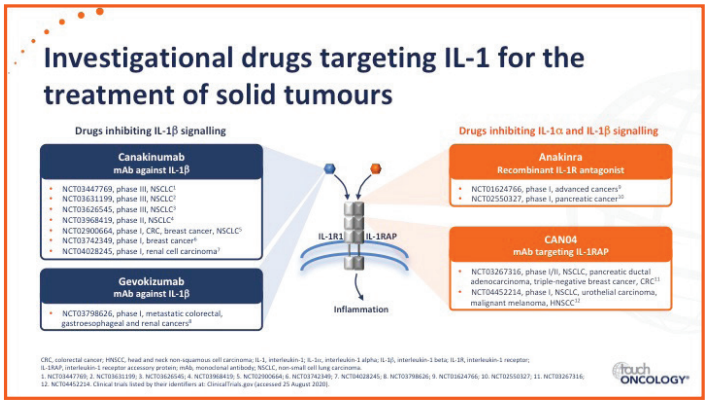


One of the additional points when we look at how IL-1 dysregulation is impacting the cancer development is also to better understand how IL-1 will be influenced by the other mechanisms used by the tumour for its development, and especially all the other immune mechanisms and all the different checkpoints that the tumour may use will also be influenced by the IL-1 pathway. In order to think how we'll be able to combine the different treatments that we will have in our hand, and probably in the majority of the tumours, the best activity will be based on the combination of different mechanisms of modifying the microenvironment.

Which emerging agents targeting IL-1 are being investigated in solid tumours?

Various types of drugs are currently being developed and are currently investigated in order, therefore, to control this IL-1 family and in order to act against the pro-tumourigenic effects of the component of the IL-1 family. We have globally four different agents, probably canakinumab is the agent that is most advanced regarding its development with different phase III trials already active, especially in the field of non-small cell lung cancer, the advanced setting, but also some active trials in the early stages.

There is also development of canakinumab in colorectal, breast and renal cell carcinoma. Canakinumab is a monoclonal antibody against IL-1β. The second drug is anakinra, which is a recombinant IL-1 receptor antagonist, which is currently in phase I development. The third drug is gevokizumab, which is a monoclonal antibody against IL-1β like canakinumab, and this monoclonal antibody is currently being explored in phase I trials in various types of solid tumours. And lastly, CAN04 is a monoclonal antibody targeting the IL-1RAP and this agent is currently being explored in two different phase I trials, mainly in solid tumours. Then we have various types of agents in development that will probably, in the future, help us to better control the tumour and to better act on the different pathways activated by IL-1. Of course, we still have to understand how to use these different drugs and how to predict their activity.



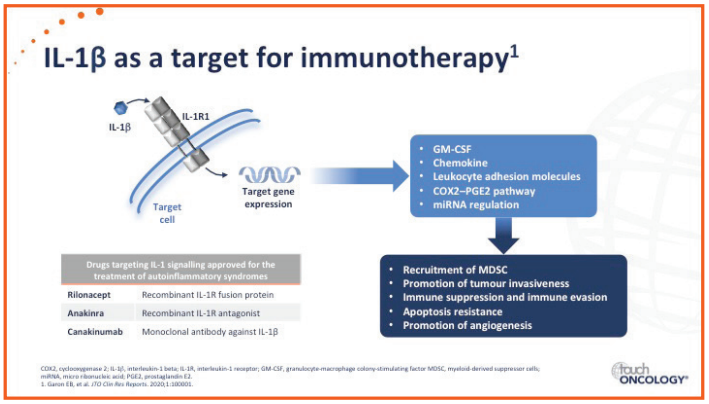
IL-1β AS A FUTURE OPTION FOR NSCLC IMMUNOTHERAPY

Dr Edward Garon:

I am Edward Garon. I am Professor of Medicine at the David Geffen School of Medicine at UCLA in Los Angeles, California.

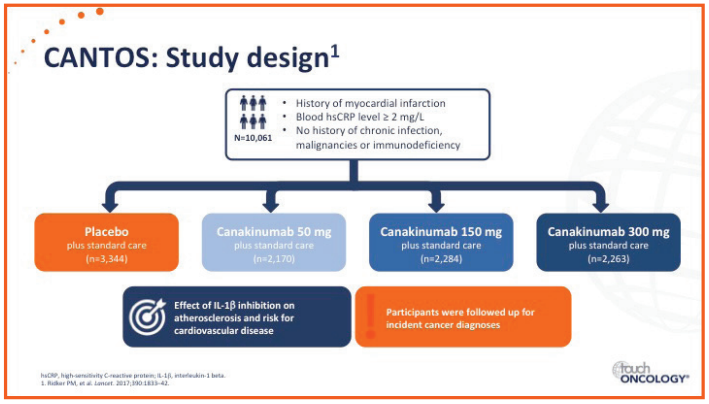
What makes IL-1β a potential candidate target for cancer immunotherapy?

So IL-1β and its interaction with the IL-1 receptor has been fairly well studied in terms of a role in inflammation. In fact, there are multiple agents that are approved for inflammatory conditions. The effect of IL-1β binding to the IL-1 receptor is to set a transcriptional approach in motion that leads to a variety of different functions. Many of these functions end up being functions that are sort of promoting the development or spread of cancer.

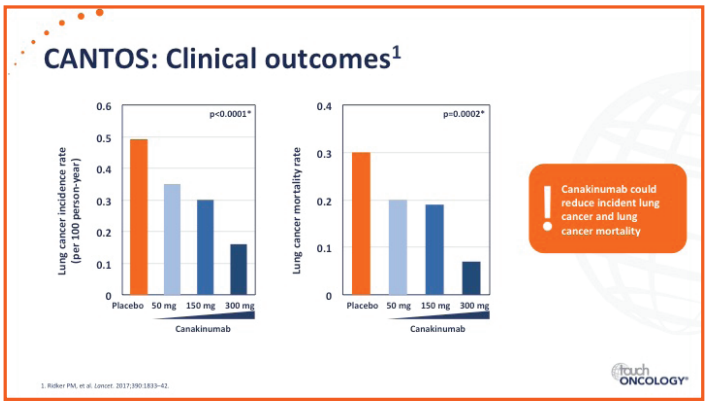


What is the clinical evidence supporting the therapeutic potential for IL-1β inhibition in lung cancer?

The development of IL-1β inhibitors in lung cancer I would say took a somewhat nontraditional route in its development. In fact, the clinical data are largely based on an analysis of a large study that was conducted for a disease other than cancer. So the CANTOS study randomized over 10,000 patients who had elevated CRP and coronary artery disease, and patients were randomized into a placebo group or groups that received canakinumab, an IL-1β inhibitor, and that was at three separate doses.



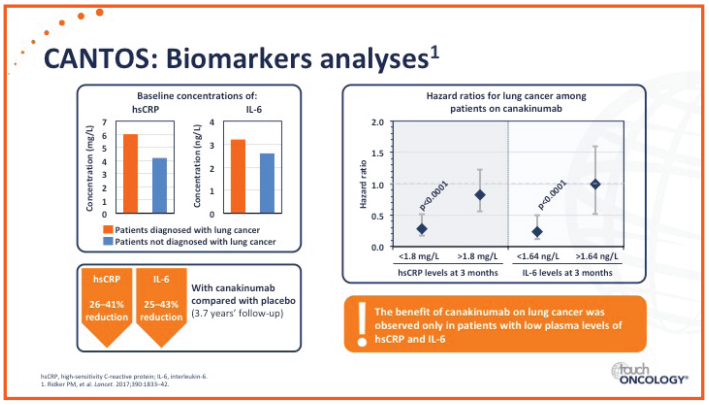
What was seen as part of that study was an effect on rates of cancer and most specifically lung cancer. So in order to enroll in the CANTOS study, patients had to have no active malignancies. As part of this study, the development of and death from cancer was prospectively evaluated. What was seen as part of this very large cardiovascular study was that among patients who received canakinumab, they were less likely to both develop lung cancer and to die from lung cancer. What was particularly interesting was that the effect was not only seen in patients who received canakinumab versus those who received placebo, but the effects for both incidence and mortality appeared really to be dose dependent, meaning that the group of patients who were randomized to receive the highest dose of canakinumab actually ended up having the least risk. Whereas there was intermediate risk for those who were in the groups that received lesser doses of canakinumab and the greatest risk in those who were randomized to placebo.



What clinical evidence suggests that the beneficial effect of IL-1β inhibition in lung cancer is due to a reduction of inflammatory responses?

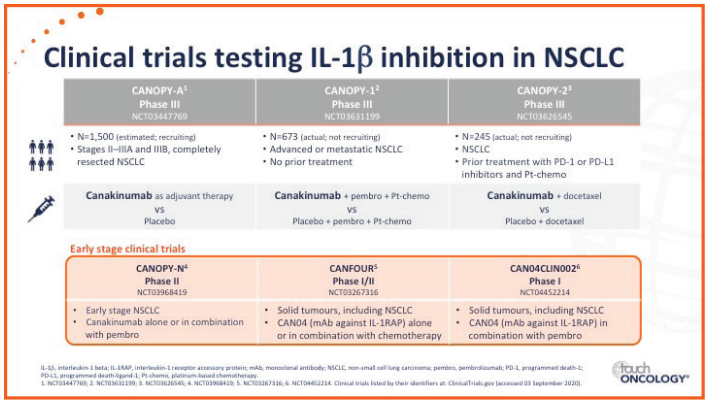
So there have been extensive studies, at least on a preclinical and correlative level, with respect to inflammation and its role in lung cancer. Of course, in many cases, lung cancer is the result of cigarette smoking, repetitive injury to the lung, and this is something that people have looked at in a great deal of detail.

What was seen as part of the CANTOS study was that patients who had a higher level of CRP as well as IL-6, that is a group of patients who were at greater risk to develop lung cancer. In fact, it was very clear from the study that the levels of CRP and IL-6 did go down substantially among the patients who received canakinumab. The other thing that was of interest is that really the benefits in terms of relative reduction in lung cancer were really seen amongst the patients who had lower levels of CRP and IL-6. This really sort of at least argues that the potential anticancer effect of canakinumab is from reducing inflammation, which of course is what the anticipated mechanism of this agent is.



What is the current status of clinical testing of IL-1β inhibition for the treatment of lung cancer?

So based on this very intriguing data from the CANTOS study, as well as data that has been generated over many years related to both the role of inflammation in lung cancer and specifically the role of IL-1β, there are multiple studies that are ongoing. This includes early phase studies looking at canakinumab as well as other agents that are targeting the IL-1/IL-1 receptor pathway. In terms of the large phase III studies, there are actually three large phase III studies that are ongoing. The largest is CANOPY-A. This is projected to be a 1,500-patient study that is focusing on adjuvant therapy, and in many respects adjuvant therapy appears to be a particularly attractive target for canakinumab based on the data from CANTOS. The idea is, that since the development of cancer was reduced, to look at this early phase of disease and that you would potentially be able to reduce the risk of recurrence. That study is looking at canakinumab versus placebo after patients have completed the appropriate post-surgical therapy. There are two other trials that are ongoing. One is along with chemoimmunotherapy in treatment-naïve advanced non-small cell lung cancer patients and the other is in patients who were previously treated along with chemotherapy, in this case docetaxel. So in addition to some of these smaller studies, there's also a neoadjuvant study looking at canakinumab and, as I say, other studies looking at other agents directed against this pathway. There are already three ongoing large phase III studies that will help us to evaluate what the role of IL-1β inhibition is in non-small cell lung cancer.



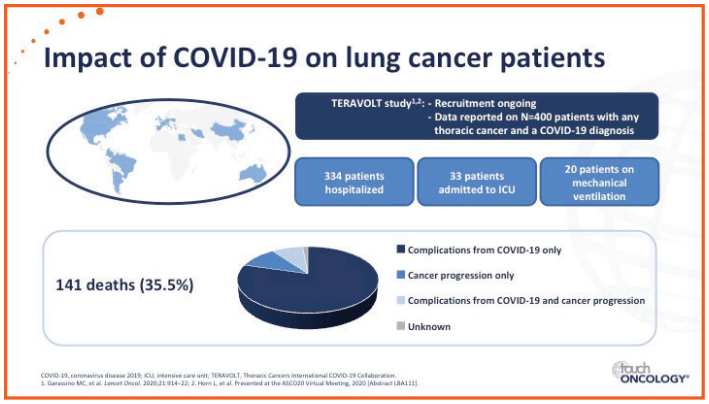
COVID-19 AND LUNG CANCER MANAGEMENT

Dr Marina Garassino

My name is Marina Chiara Garassino. I am the Chief of Thoracic Oncology at the National Cancer Institute of Milan, Italy.

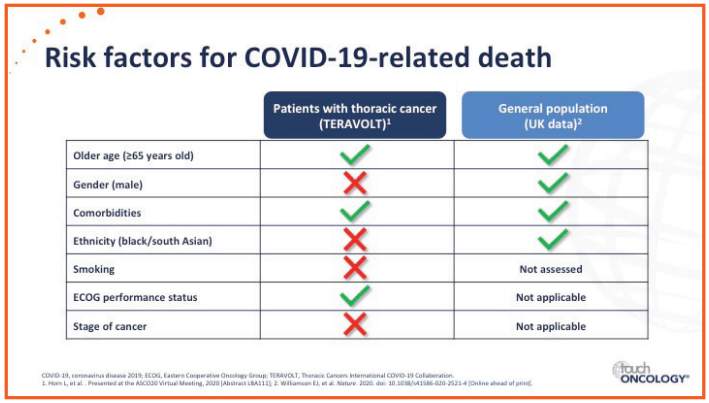
What are the clinical consequences of the COVID-19 pandemic for patients with lung cancer?

What we know is that lung cancer patients are at higher risk of mortality compared to the general population and it seems that they are at higher risk of mortality compared to other types of tumour. The TERAVOLT trial is enrolling patients with COVID-19 and thoracic cancer. We are now at more than 1,000 patients included in the trial and we show that there is a risk of death of 35%, which is huge. If we compare these results without the registries, without other types of tumour, the mortality rate was about 15, 16%. So it seems that lung cancer patients are a frailer population compared to other patients and the majority of them died from COVID-19 and not from cancer.



Which are the risk factors associated with mortality in patients with lung cancer infected with COVID-19?

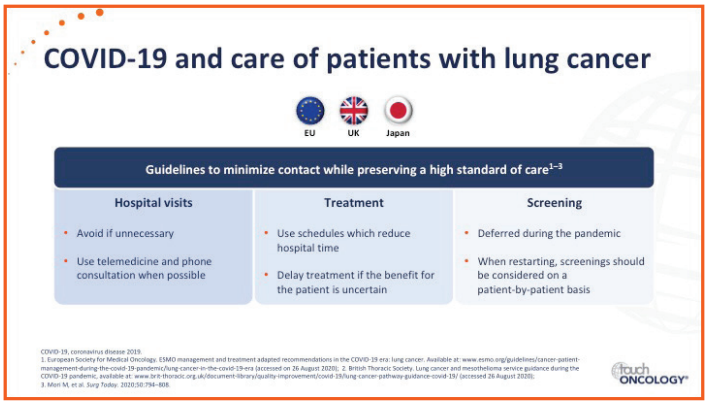
There are some risk factors, and they are mainly older age. In TERAVOLT we demonstrated that patients with an age older than 65 are at higher risk. It is still debatable if gender can play a role for increasing the risks, but it is sure that comorbidities can play a role. Comorbidities can be diabetes, can be COPD, can be cardiovascular disease but, in general, the presence of comorbidities is very important. We also know that about 30% of patients with lung cancer have more than three comorbidities, and this could be the reason why these patients have so much mortality due to COVID-19.



How has COVID-19 affected the provision of care to newly diagnosed and existing patients with lung cancer?

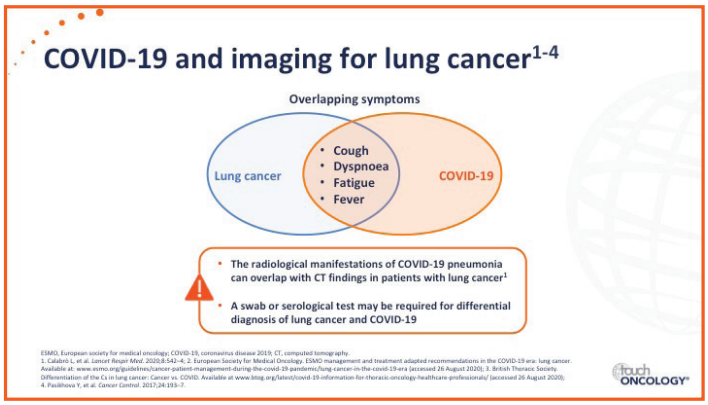
When the pandemic started, I think that the majority of the scientific society created some guidelines in order to avoid useless visits to the hospital in order to reduce the possibility of contagion of these patients. So we tried to implement, as much as possible, telemedicine and also phone calls whenever it was possible. That clearly was not possible for very symptomatic patients. When the benefit of some treatments was debatable, for example, the third or the advanced lines, we decided to wait for the flattening of the COVID-19 curve. So we can't say that we didn't treat these patients but I think that the majority of them were treated in a different way with more telemedicine and with, for example, schedules with immunotherapy which delayed the treatment. What I think was very affected were the screenings, not just for lung cancer but for all types of tumours.

For example, in Italy, we are now starting to do these screenings, but when you have to balance the risk of death for COVID-19 and the benefit of screening, you have to discuss patient by patient what the best possibilities are.



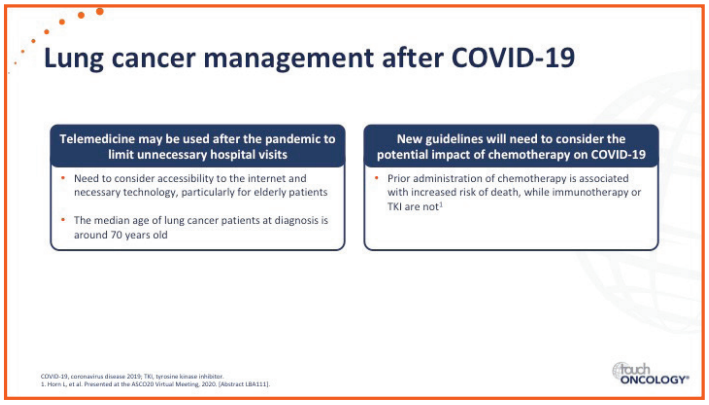
What challenges does COVID-19 pose to imaging in patients with lung cancer?

This is a very challenging problem because the symptoms of COVID-19 and the symptoms of lung cancer sometimes are really superimposable. So you may have a patient with a fever and with fatigue and with dyspnoea and a CT scan that can be suggestive of COVID-19. So the differential diagnosis for these patients is very important because you sometimes have very overlapping features, very overlapping radiological features and, in many cases, you have to do the swab or the serological test to do the differential diagnosis.



How do you envision the care of patients with lung cancer will be affected in the near future and in the post-COVID-19 era?

I think that we understood that telemedicine is fundamental for treating our patients, and to stay also connected with the patients when they are at home. This can be also without COVID-19,to reduce useless access if we can do it online. There is a huge problem with disparities because telemedicine is not available for everyone and the internet, even in 2020, is not available for everyone,so this is a problem. Then in lung cancer, we have an older population, so the majority of these patients are not able to use a smartphone, are not too able to use Skype, Zoom or whatever. So I think that we need a learning curve also for that. The second point is that we have demonstrated with TERAVOLT that patients receiving immunotherapy and patients receiving targeted agents potentially are at lower risk of dying from COVID-19 compared to patients who are on chemotherapy and on combinations with chemotherapy. So in the future, I hope that we will be able to shape the guidelines according to the different risks that we see for these patients.



Abbreviations

APC, antigen-presenting cell; CD8, cluster of differentiation 8; COVID, coronavirus disease; CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte antigen 4; GM-CSF, granulocyte-macrophage colony-stimulating factor ; IL-1, interleukin-1; IL-1RAP, interleukin-1 receptor accessory protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; LAG-3, lymphocyte activation gene 3; NK, natural killer; NSCLC, non-small cell lung carcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand-1; TGFβ, transforming growth factor beta; VEGF, vascular endothelial growth factor.