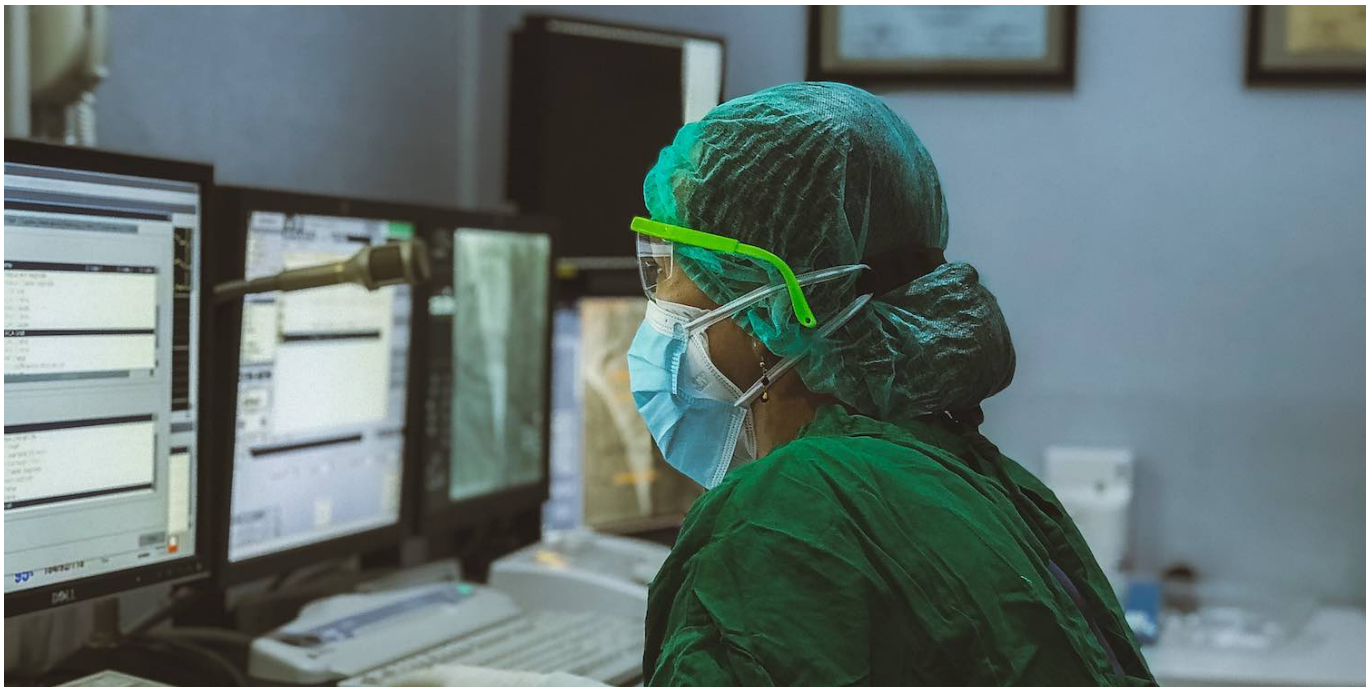
Cancerworld

Cancer & Covid: Prevention and Treatment including Monoclonal Antibodies (MoABs) 2022

Adriana Albini / 28 July 2022



Introduction

Among the most crucial problems caused by Covid-19 pandemics are the difficulty in the management of chronic diseases, the comorbidities, the impact on life expectancy, the search for therapy and prevention, the host interactions with the vaccines.

Cancer patients constitute a high risk patient group during the pandemic due to several causes. Screening, surgery, therapy and follow up all encountered hurdles and challenges, particularly during the first wave. A very recent report examining a total of 58 studies, involving 709,908 participants and 31,732 cancer patients evaluated comorbidity and risk factors for SARS-CoV-2 infected patients with cancer, with important warnings.

SPCC Cancer & Covid Task Force

SPCC has gathered a group of experts to prepare an educational programme with two webinars on the impact of Covid-19 on cancer patients.

The aim of this project is to spread awareness and knowledge among Health Care Professionals on what is currently available to protect at-risk patients, prevent more serious damage due to COVID-19 disease, administer therapy and improve patients' quality of life in a COVID-19 risk or infection setting.

The idea came from a request received from Walid Kandeil, Regional Medical Head, Europe & Canada – Vaccines and Infectious Diseases at AstraZeneca. The task force, comprised of oncology and onco-hematology experts, held a closed remote meeting on 22 June. The meeting was chaired by Matti Aapro, medical oncologist based in Genolier, Switzerland, and President of SPCC. Five speakers each gave a ten-minute presentation, followed by Q&A and a discussion on the project.

General overview of the impact of Covid-19 on cancer patients

The first presentation was by **Gianni di Perri**, infectious disease physician at the University Hospital Amedeo di Savoia, Turin, Italy. Dr di Perri has devoted his career to infectious disease care and clinical research. His subspecialty is clinical pharmacology of anti-infectious agents, and he runs an epidemic unit inside his clinic at the university.

SARS – CoV – 2 Infection Outcome in Cancer Patients

EPICOVIDEHA (Epidemiology of Covid-19 Infection in Patients with Hematologic Malignancies: A European Hematology Association) is an international open web-based registry for patients with hematologic malignancies (HM) infected with SARS-CoV-2. A project aiming to collect Covid-19 cases occurring in HM patients in 2020 was carried out on behalf of the Scientific Working Group Infection in Hematology of the European Hematology Association (EHA). The study sample included almost 4000 cases. The most numerous subgroups were those with non-Hodgkin lymphoma, followed by multiple myeloma, acute myeloid leukaemia, and chronic lymphoid leukaemia. The results showed that the mortality rate, especially in some subcategories, was significantly higher than in the overall population. Acute myeloid leukemia and myelodysplastic syndrome were counting for the lowest survival rate among the patient group, followed by non-Hodgkin lymphoma, multiple myeloma, and the other malignancies. Another finding suggested by this article is that in the second wave the same patients showed a better survival rate, probably due to improvement in their overall care.

An investigation published by Jama Oncology this year analysed the records of more than half a million patients who had Covid-19. 97.2% did not have cancer, while a subgroup of 14,287 patients had cancer. 70% did not receive recent treatment, while 30% did. Looking at the crude mortality rate in these subgroups, we see an expected 1.6% in the general population, while it was 5% in those who had cancer but did not receive recent treatment (here the definition was within three months before Covid infection). But for those who received recent treatment the mortality was almost 8%. Looking deeper in this case series we can see that those with recent treatment had a higher mortality rate, but there were also concomitant Covid related factors accounting for a higher risk of death. Factors in the subgroups associated to a worse outcome were metastatic solid tumour, hematologic malignant neoplasms, radiotherapy, chemotherapy or chemoimmunotherapy, and obesity (with a BMI over 40).

A meta-analysis and systematic review of articles published between December 2019 – January 2021, conducted by J. Wahyuhadi et al., confirmed what we had suspected, that patients with solid malignancies in general have a better prognosis upon Covid-19 as compared to those with hematologic malignancies.

What is the response to Covid-19 vaccination in cancer patients?

A small study published by Mayo Clinic in April this year, was carried out to evaluate the magnitude of humoral response to SARS-CoV-2 messenger RNA vaccines in patients with cancer receiving active therapies. Patients 18 years or older in whom SARS-CoV-2 spike antibody (anti-S Ab) levels were measured after 2 doses of SARS-CoV-2 mRNA vaccines, were included in the study, while patients with prior Covid-19 infection or receiving other immunosuppressive therapy were excluded.

Out of the 201 individuals who met the criteria, 61 were immunocompetent, 91 had a hematologic malignancy, and 49 had a solid malignancy while receiving treatments associated with cytopenia, including chemotherapy or cyclin-dependent kinase 4 and 6 inhibitors. The conclusion was that a substantial proportion of patients with hematologic and solid malignancies receiving chemotherapies and CDK4/6i had poor humoral responses to Covid-19 vaccination. We can also see from the data that HM recipients had the worst figures, while those with solid malignancy were more or less at an intermediate level compared to the immunocompetent.

Another study, by Moshe Mittelman et al., is an on-field analysis that shows the effectiveness of Covid-19 vaccine not just in terms of antibodies but also of protection from infection in patients with hematologic neoplasms as compared to the general population. The higher risk is statistically significant in the overall group of patients with hematologic neoplasms, and higher still for those on active treatment.

All of the studies mentioned above were made at the time of more virulent variants like Alpha. So far, with Omicron we have noted quite a significant decrease in overall mortality, and figures should be re-evaluated with the new variants.

Cancer & Covid – a Danish perspective

Carsten Utoft Niemann, MD, PhD, is Principal Investigator, Head of CLL Laboratory, and Chair of Nordic CLL Study Group. His presentation focussed mostly on patients with chronic lymphocytic leukemia (CLL), taking this as a model disease to demonstrate the significant immune dysfunction both in treatment-naïve patients and patients in active or previous treatment. Dr Niemann talked about a case he studied with his team almost two years ago. It was the first CLL patient they saw who suffered from Covid. He would have been treated with Fludarabine, Rituximab and Cyclophosphamide until half a year before he was infected. It was March 2020.

For the first week or so he was doing fine. Then he slowly deteriorated and went to hospital to receive supplemental oxygen and was close to going to the ICU. He was put on the first remdesivir trial and improved for the first ten days of treatment, both his temperature and his CRP measurements lowered while his lymphocyte and platelet count improved. He deteriorated again after stopping remdesivir and was then put on a second course of the drug. He had exactly the same response and was discharged from hospital during this course. But he deteriorated once more and was then treated with convalescent plasma. At that point in time there was no access to monoclonal antibodies. He eventually recovered a week later and was discharged. This example shows that patients with some but not all hematologic malignancies, and in specific situations, suffer from a significant higher risk of severe courses of Covid; those patients seem to benefit from antiviral therapy for prolonged periods of time.

The same is reflected in the serological response to Covid vaccination. A study published by Dr Nieman’s group shows that treatment-naïve patients have a rather low response to vaccination, patients on active treatment had the lowest response, but patients who had been treated for CLL disease and went into remission had a much better response. This result challenges the concerns

about whether or not to treat patients, because during treatment their response to vaccination and their immunity might be impaired, but afterwards it actually improves the immune function. Therefore, the recommendation would be to treat patients in need of treatment.

Looking at the GAIA/CLL 13 trial, whose primary outcome was presented at the EHA Congress in June 2022, seven patients contracted Covid at the beginning of the pandemic during or right after treatment with combination chemoimmunotherapy or venetoclax and anti-CD20 monoclonal antibodies with or without Ibrutinib. The neutrophil counts went down during the CLL treatment but went up after the treatment. Patients who contracted Covid months after stopping treatment had quite a short course of disease, while 2 patients contracting Covid during or just after stopping therapy with venetoxlax and anti-CD20 monoclonal antibodies plus Ibrutinib (for one case) had a fatal disease course. This again emphasises that, although we put patients on a transient risk during treatment for hematologic malignancies, they have improved immune function and a lower risk of severe courses of Covid afterwards.

We must also stress that the serological responses may not be the main measurement for immune function and immune response to vaccination and Covid infection. In the study by Ehmsen et al., on T-cell responses to Covid, we can see that a significant proportion of patients with CLL or small lymphocytic lymphoma (SLL) actually had a T-cell response even though they had no serological response. This again indicates that we need to have a more holistic or thorough assessment of vaccine responses and immune function in patients to judge whether they are at a higher or lower risk of a severe course of the disease.

Then we need to take into account that the Covid pandemic changes all the time. Again, taking CLL as a model and looking at the hospital charts from different times, in the first wave the probability of admission for CLL patients with Covid was 50%. In the second wave it was up to 75%. This was due to the introduction of convalescent plasma, remdesivir and other precautions. And almost all patients were admitted in order to receive prophylactic treatment during the third wave in December 2021.

Many of them could be treated as outpatients. In the Omicron period around 50% were admitted to hospital. As for the risk of ICU, wave three was a mixture of Delta and Omicron, while four was almost only Omicron, and almost no patient went to the ICU. For the mortality rate, data were initially based on Covid tests performed at test sites adjoint to the hospitals in half of Denmark, but they seemed too high for the third and fourth waves. When using a CLL registry with all the positive Covid-19 tests, the mortality rates appeared much lower, less than 2% for the whole CLL population during the Omicron era. This emphasises the need to scrutinise data before they get published and aim for close to real time data to best guide our patients. It emphasises also that we have now a small proportion of patients with CLL with close hospital contact due to Covid, who need specific precautions, whereas the majority of patients with CLL and probably also other hematologic malignancies, in treatment or not in treatment, who do not have a close contact to the hospital are not at high risk during the Omicron period. This obviously reflects a population which is more than 80% vaccinated.

We need to recognize the pattern of those in trouble

The take home message was that we need to consider which patients are at risk. And we need to smartly use the data to achieve this. Dr Nieman’s team used the electronic health record data, a little more than 3000 different variables for all patients testing positive for Covid, and they used this to model the individual risk for patients with Covid. We must identify patients who would need specific precautions or pre-emptive treatment with monoclonal antibodies or other prophylactic measures. We need to personalize this; we need to use the extensive health data that we have

available, and we need to join forces with engineers and data scientists who can perform such modelling.

MoABs: evidence in patients with solid tumours

Rafal Dziadziuszko is Deputy Head of the Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland.

There are no studies with neutralizing antibodies against Covid-19 which are exclusive to patients with solid tumours. There are studies that include patients with solid tumours, and some that are also focussed on hematologic malignancies. As already mentioned, the risk of Covid infection is higher in these malignancies. The PROVENT study, published two months ago, gives us some data about AZD7442, which is a mixture of two long-acting neutralizing antibodies against Covid-19, tixagevimab and cilgavimab. The inclusion criteria for the study were subjects with suspected inadequate response to Covid-19 vaccination, such as the elderly, obese, immunocompromised, and those with comorbidities such as chronic obstructive pulmonary disease (COPD), congestive heart failure, chronic kidney disease and chronic liver disease. The group also included patients with appreciable exposure risk, defined as those who are healthcare workers, military personnel and those who live in high density population, for example, students in dormitories. The efficacy analysis showed a significantly lower incidence of symptomatic Covid-19. The other study with the same drug is the TACKLE study. In contrast to the previous one, this is a therapeutic study looking at patients (90% of which with baseline co-morbidities) who got mild Covid-19 and were treated early on as outpatients.

Looking at the WHO scale of progression, the percentage of patients who progressed to severe Covid was about halved in those who were treated in the control group, which confirms that in adequate circumstances the use of neutralizing antibodies is effective.

The efficacy of all these drugs seems to vary. In the ACTIV-3 trial, patients who were hospitalised due to Covid-19 were given active neutralizing antibody versus placebo with no real difference. There was also another combination of two antibodies studied in the same trial and again with no real benefit.

Implications for patients with solid tumour

Patients with solid tumours may have different risk levels for getting Covid but also for a severe course of the disease. Probably those on chemotherapy have higher risk of severe Covid, while for those on targeted therapies or immunotherapy, which is not B-cell directed, the risk is only slightly higher. Neutralizing antibodies, when proven clinically, are a new option for prevention and or treatment of patients with solid tumours, especially those with other risk factors. And these risk factors may not just be well known ones, such as age, comorbidities, obesity, diabetes, gender, etc., but also those that are being identified from electronic health records. Immunosuppression may come from the treatment such as anti-inhibitors for example or steroids, but also from the tumour itself. Importantly, neutralizing antibodies may be considered in patients requiring uninterrupted therapy.
Last but not least, we need to provide the best possible measures of safety for the staff to ensure uninterrupted care.

Covid and cancer: a dynamic process

Carsten Bokemeyer is Head of the Department of Oncology and Hematology and director of the University Cancer Centre in Hamburg.

There have been rapid changes in virus variants from Alpha to Omicron, with different clinical pictures, morbidity, and mortality for those variants, and we also learned that re-infections can occur. From 2021-2022 we also saw an increase in the vaccinated population, particularly in cancer patients, as these may be more cautious than others and more willing to take vaccinations. We went from two vaccinations to booster and, for some, a second booster vaccination in 2022. We must remember this background, because when we look at trial results, we hardly ever look at the same population in any of the trials. Furthermore, on the vaccines used in different countries – depending on national availability – may have different efficacy. In addition, there is also an increase in overall immunity in populations with more infections now that Omicron has taken over. Probably 20% of the German population have had Omicron in the last months, so there may be a large population acquiring some level of immunity. And we now have certainly many more personal protective measures, coming from an initial lack of masks in early 2020 to the widespread use of FFP2s in recent months. Also, many treatment approaches have and are still being developed, including both antivirals as well as monoclonal antibodies. Their efficacy is also highly dependent on the virus variants. Thus several factors are influencing the Corona Virus situation in a highly dynamic manner.

The task to define the role of MoABs in Covid treatment and prophylaxis specifically in patients with solid tumours is thus very difficult. Frequently patients with solid tumours are not specifically characterised in trials in terms of their additional risk factors, such as obesity, COPD etc., or stratified for specific anticancer treatments used. And no antibody trial fully reflects the current virus variants. We see, for instance, that Omicron is less dangerous even for cancer patients compared to most of the previous variants. On the other hand a number of MoABs developed last year are not effective anymore in Omicron infected patients. So, there is no high-level evidence for recommendation of the use of MOABs in patients with solid tumours with respect to the most current situation.

What do we know?

Patients with solid tumours are less endangered by Corona compared to those with hematologic malignancies. They are less immunosuppressed by their type of cancer and the treatment is less immunosuppressive in most types of solid tumours (no allo-STC, no B-cell directed therapies, shorter duration of neutropenia). Initial studies indicated the highest risk for mortality in patients with lung cancer, but that was in the period of Alpha and even Delta variants when the virus was mostly infecting lung cells. We also know that despite vaccination, breakthrough infections do occur. According to a recent JCO publication, the odds ratio is 1.12 for solid cancer patients and 4.6 for hematologic malignancy patients compared to the non-cancer population.

Looking at MoABs used in Covid patients, some of the antibody constructs which were active with Alpha became less active in the following variants and have lost all activity with Omicron. Sotrovimab is still active in treatment but seem s to lose its activity in the Omicrom BA 4/5 variant, the Evusheld combination recommended for prophylaxis also has some activity left, but not as good as at the time point it was developed in the period of Gamma and Delta variants. The REGEN-COV antibody combination that led to reduced severity and hospitalisation with previous variants is not an effective agent with Omicron and is not used anymore.

We also know that there are additional risk factors that might impair the efficacy of antibodies: race, ethnicity, gender, cancer history and age.

What remains now in terms of antibody treatment is Sotrovimab for patients at increased risk of progressing to severe Covid-19. It is approved by FDA and EMA. Bebtelovimab is only approved in the US, it is not available in Europe, and has the same indication and may be the only antibody effective in the current newest Omicron variant (BA 4/5). We have the pre-exposure prophylaxis,

which also works with the Omicron variant to some degree, the Evusheld antibody combination, indicated in moderately to severely immunocompromised individuals, e.g., receiving active antitumour treatment. But what does this mean specifically for solid tumour patients? Looking at the original publication of Evusheld prophylaxis, we can see that the number of patients with solid tumours was 7.4%, a small minority of the overall patient population with various other risk factors. And there is no interaction of risk factors showing in most trials, so we don't know, if those cancer patients had additional risk factors or not.

What should we do?

Dr Bokemeyer concluded his presentation with some personal recommendations. Keep up the hygiene rules, masks and distance rules. Recommend vaccination for all solid tumour patients. Recommend testing prior to the start of (intensive) chemotherapy and delay start of chemotherapy in patients until recovery from Covid (as long as the Omicron variant is predominant) in a palliative tumour setting and discuss risk versus effects in a specific curative setting (e.g., germ cell cancers, adjuvant therapy, etc.) Individualise decisions for cancer treatment and MoABs based on further risk factors (type of therapy, antibody levels in vaccinated patients, and others). Evusheld should be used in non-responders to vaccination as prophylaxis and maybe as a rapid post-exposure therapy. The use of Sotromivab in infected solid tumour patients undergoing active medical oncology treatment is still a possibility, but we must anticipate that all of these recommendations are undergoing constant changes in their management overtime with new variants and new indications coming up.

EMA perspective

The final speaker was **Marco Cavaleri**, Head of the Office of Biological Health Threats and Vaccine Strategy at EMA and chair of the emergency task for EMA on COVID-19. Dr Cavaleri spent several years in research and development of antibacterial agents, antifungals, and anti TB agents, and then moved to EMA where he gained almost 20 years' experience in vaccines, how they are developed and how they are regulated.

Vaccines

So far, the EMA has approved five vaccines for Covid-19: two messenger RNA vaccines, Comirnaty from Pfizer BioNTech and Spikevax from Moderna; two adenovirus vector vaccines, Vaxzevria from AstraZeneca and the Jannsen vaccine, now called Jcovden. It has also approved a more traditional vaccine, Nuvaxovid from Novavax, which is a nanoparticle subunit vaccine. There is also another vaccine due to be approved, the Valneva, which is based on the whole virus technology, and is adjuvanted with aluminium and CpG. It is not the most immunogenic vaccine, and it will be approved only for primary series for the time being. The mRNA vaccines are the ones currently used in Europe. We were expecting to see a bit more uptake of the Novavax vaccine, but that has not been the case so far, also because it is approved only for primary series, even if there is potential approval as a booster. The mRNA vaccines are the most used including in immune-compromised patients, although we have seen proposals, for the use of some adenovirus vector vaccines for immuno-compromised patients. However, adenovirus vector vaccines are not essentially used in Europe and now, even in the United States, the use of the Jannsen vaccine is decreasing.

As we know, cancer patients experience lower levels of effectiveness after vaccination than the general population. Certain types of treatment, like anti-CD 20 for example, have a significant impact on the immune response achieved and on the protection. Although, even if patients do not have B-cell responses or humoral immunity, because of the T-cell component, they are able to be protected from most severe disease. We generally look at antibodies, but cell-mediated immunity plays an important role, particularly for protection from severe disease, and therefore we should not

undervalue its possible impact. The problem in this setting is that it is difficult to measure T-cells responses in a way that makes us understand which markers would allow to make a correlation with protection, and which patients might have high levels of protection coming from T-cell immunity.

In terms of a fourth dose of vaccine, we already have a general recommendation for severely immune-compromised patients, particularly transplant patients. But this type of recommendation should be expanded also to other groups that are at risk of severe Covid that might not respond well to vaccination. Therefore, some patients, such as hematologic malignancy patients, could or should be already considered for a fourth dose. Looking at the first data we have seen in transplant patients when it comes to a fourth dose, remarkably there are patients who did not respond even after a third dose, but achieve quite a decent response after a fourth dose. So, there is something to gain even in those cases in which we have not seen antibodies being generated after two or three doses or generated in a very low amount. This type of evidence really speaks in favour of still going in the direction of giving additional boosters to this population.

Other vaccines that are being looked at are the traditional subunit vaccines such as the one from Sanofi Pasteur, which could play a role later on this year. Hipra, a Spanish company, also has an interesting vaccine, which essentially is limited to the receptor binding domain of the spike protein, but in a chimeric combination with Alpha and Beta variants portions linked together and is adjuvanted with MF59. This is a well know adjuvant. It is used for influenza vaccines for example. All of these additional vaccines may come later and be helpful in order to expand the portfolio of vaccination options. But to start with at the beginning of the autumn, it looks like we will rely on the messenger RNA vaccine primarily.

Therapeutics

Dr Cavaleri then gave an overview of therapeutics. In terms of approval for prophylaxis, there are two approved products. One is the cocktail from Regeneron, Ronapreve or REGEN-COV, which is based on casirivimab/indevimab. It is a potent cocktail and it performed very well in clinical trials. Unfortunately, with the arrival of Omicron it completely lost activity. The other one, which has already been mentioned, is the cocktail from AstraZeneca, Evusheld, a combination of two monoclonal antibodies, tixagevimab and cilgavimab. The PROVENT study showed that the cocktail can provide protection for at least 3 months based on how it is engineered, providing a longer life and possibly can protect for a period up to six months. However, it failed to meet the primary endpoint in the study in post-exposure prophylaxis essentially because of lower efficacy in people who were already infected. Therefore, the focus has been more on its use for pre-exposure prophylaxis. The EMA is now in the middle of assessing a potential approval for treatment which will be based on a dose that is double the one used for prophylaxis. But this approval for treatment is in the context of mild Covid-19, not hospitalised or severe Covid. Antivirals can be extremely effective if used very early on when viral replication is still at the beginning and when the patient is not yet very sick. If you wait too long, the effect of the antiviral will diminish progressively until it likely disappears, or it will remain effective only in patients who have continuous viral replication for different reasons. However, in the majority of patients, you will not easily see a remarkable efficacy of antivirals in the overall patient population if you wait too long or if the patient is too sick, so it is important to keep this in mind. This aspect needs to be considered for high-risk patients such as cancer patients so that they can receive timely antiviral treatment once infected. In the context of hospitalised patients with severe Covid-19 or requiring supplemental oxygen, we have not seen fantastic results with antivirals so far. The only good results that were coming out were the ones from the Regeneron cocktail, but in patients who were seronegative at baseline. A study conducted in the UK by the RECOVERY team showed that in patients who are hospitalised with severe Covid and are seropositive to Sars-Cov2, there is not a significant effect of the antiviral treatment. But if

the patient was seronegative, so not yet exposed to the virus, or not vaccinated, then there was a significant effect, which is something that is being now evaluated in order to decide whether these products can be approved in this context. However, the question that arises here is that in the future, most of the patients who will be hospitalised will be seropositive, either because of vaccination or because of natural exposure, so we do not really know how much the effect we have seen in this study will translate to the population we will see in the future.

There are three monoclonal antibodies and two antivirals approved for treatment of patients with mild Covid-19 symptoms who do not require supplemental oxygen but are at higher risk of progression to severe disease. The treatment can start within three to five days from the onset of symptoms. Remdesivir initially was approved for more severe Covid in hospitalised patients, but now has also received approval for use in mild Covid, based on convincing clinical trial results that showed that it is effective as an antiviral in this setting. Paxlovid, which is nirmatrelvir combined with ritonavir, is the first oral antiviral that has been approved and is going to be used for treating mild Covid-19 immediately after onset of symptoms in subjects that are more at risk of progression to severe disease. Sotrovimab and casirivimab/indevimab are also approved for this use. Another monoclonal, called regdanvimab, was approved last year but it turned out that even with Delta there was a significant problem in terms of neutralization and therefore its use never quite materialised.

A real-world evidence study has just come out of Israel, “Oral Nirmatrelvir and Severe Covid-19 Outcomes During the Omicron Surge”. A two-month study of over 100,000 participants, it showed that this drug is particularly effective in patients that are over 65 years old. Lack of prior immunity was most significantly associated with higher rates of hospitalisation due to Covid-19 and it represents the subgroup in which antiviral treatment was more clinically impactful. However, it was noted that in subjects older than 65 years, the antiviral was effective even in those already vaccinated. This data can be very important to select the patient population that might be deriving benefit from the use of these antivirals. It is important to conduct these type of real-world evidence studies beside the pivotal clinical trial(s) that lead to an approval, which of course cannot cover all the different settings and different populations. Also, they were done at a certain point in time. So, with different variants in circulation, we always have to conduct additional research to understand how best to use all these antivirals.

Of course, we cannot avoid talking about variants because this is a crucial variable. For all the antivirals that are approved now, most of the pivotal clinical trials were conducted when Alpha and Delta were around, not Omicron. We saw that in these patients at risk, when they had mild Covid in the placebo arm, the progression to hospitalisation and severe Covid was pretty high, around 6% or more. This is not the case now with Omicron and the higher rates of vaccination. The landscape has changed from this perspective. So, to really understand the clinical benefit of all these interventions we need to conduct additional studies post approval. The other important aspect is cross-neutralization. To what extent all these monoclonal antibodies remain effective when the virus accumulates new mutations in the spike protein? Sotrovimab looked like one of the best options when BA.1 was around, because even Evusheld was not doing well with BA.1. But when Omicron evolved first to BA.2 and then to BA.4/5, Sotrovimab had a reducedin neutralising activity. Looking at the results of an in-vitro study carried out by Yunlong Cao et al., we see that the IC50 dropped with BA.2 and with BA.4/5. , Such drop has raised concerns that the efficacy would be affected and led to adjust dose by US FDA and now to limit its use. Unfortunately, we do not really understand how such drops in neutralisation would translate in reduced clinical efficacy, and if for example we see a reduction of neutralisation in vitro of 10-20%, whether this could result in a reduced efficacy or not. This is why it is so difficult to make clear recommendations based only on these in vitro tests when new variants emerge. Bebtelovimab is a new monoclonal antibody from Lilly. It is not yet available in Europe, but it is used in the US,that could secure supply of the product. Bebtelovimab

binds to a conserved region of the spike protein and therefore retains neutralization activity against all the different Omicron subvariants that have emerged so far. With respect to Evusheld different laboratories have reported data with a variety of small or larger neutralization drops against omicron subvariants. The use of very different assays, some using pseudoviruses, others the whole virus, make it complicated to get a clear picture on the actual in vitro activity. In any case, the drop in neutralization detected with Evusheld is not so profound based on current data that efficacy against BA.5 might still be retained. We are calling the scientific community to generate additional data from cohorts or other studies, as it would be extremely important to establish the correlation between in-vitro activity and the actual clinical efficacy, so that we can understand how to promptly interpret laboratory data once new VOCs emerge.

So, **what's next?** The treatment indication for Evusheld is under review. The study from RECOVERY for the treatment of hospitalised patients is also under review. The EMA is looking at a new generation of monoclonals which are active against Omicron or binding to more conserved epitopes and will endeavour to approve them rapidly. There are other antivirals in development. One is called Ensovibep from Novartis, it is a DARPin biological product, an interesting new concept. And then there are new protease inhibitors, such as a product from Shionogi. The last important point are the variant vaccines, because now is the time to decide what vaccines to use in the autumn vaccination campaign. Moderna and Pfizer-BioNtech have advanced products. They are looking into bivalent vaccines that comprise Omicron strains in their composition, and we will see if the data will be sufficient to lead to an approval at the beginning of September, that could allow this vaccine to be used for boosters in the autumn. The EMA is also looking at other products like the Sanofi Pasteur vaccine, a beta variant subunit vaccine with interesting neutralization of Omicron subvariants, and will see if we can advance this product as well. More in the longer term, we would be looking into second-generation vaccines, i.e. vaccines that would be variant-proof, not susceptible as the current ones to the sudden changes in the composition of the virus and in need of continuous updates, or, even more ambitiously, we are looking into pan-serbocovirus vaccines that will cover not only Sars-Cov2 but also Sars-Cov1, MERS, and maybe other bat coronaviruses that might cause spill over in the future. Last but not least, all the vaccines that we have now are excellent, but are not very good in terms of protection from infection. They are systemic vaccines, and for a respiratory virus like SARS-COV2, if you do not get very good mucosal immunity, it would be extremely challenging to prevent infection. So, we are looking into this kind of options as well.

Final discussion

To start a programme of education for the public around some oncological theme, the SPCC's first step is to call in a task force of experts to explain the current situation, the perspective for the future, the hurdles, and the accomplishments. On that basis it is decided whether to go public and organise some informative webinars. The task force participants all agreed to go ahead with the Cancer & Covid project, and brought out various points. It is a fast-moving sector, and there are organisational aspects to be improved. Most experts in oncology and hematology are not fully aware of the preventive and therapeutic weapons now available to improve the outcome of Covid infections in cancer patients. It is important to better define the population for risk factors, as populations are not well defined in clinical trials, and to have a review on the changing landscape for treatment possibilities, trying to identify which patient should be treated and with what. Then, there are the challenges of emerging variants, where we need to assess which agents are still active. It is a complex and fast-moving scenario, so even if we plan it now, it may be different when we deliver. Many factors present themselves, like changes in the virus, vaccination status, and the level of general immunity. It is important to understand when antivirals are beneficial, in which patient they should be used and when. It is necessary to go beyond the clinical trials that led to the approval and try to generate more evidence, and communication between experts is essential. Another more

general point to keep in mind is that while perception of COVID as a risk and a threat will be decreasing in the near future in the general population, in the setting of cancer patients it will remain very delicate.