ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

SUMMARY

ImmunoScience Academy National Meeting

16 December 2020

organized and supported by

Bristol Myers Squibb™

ImmunoScience Academy
National Meeting
16 December 2020

The third national meeting of the ImmunoScience Academy (ISA) planned ‘in person’ on 16 December 2020 was turned on his head due to the COVID-19 pandemic. The meeting took place in a fully virtual setting. As COVID-19 turned ISA 2020 inside out, the experts did the same with COVID-19. The meeting provided a mix of immunology, immunotherapies, and cancer in a COVID-19 cup served on a unique multidisciplinary table.
Belgian and Luxembourg speakers from different therapeutic domains brought highly educational presentations, thoroughly engaging and focused on current medical challenges.
Prof. Dr. Pierre Coulie (Immunology, De Duve Institute, UCL, Brussels) welcomed the delegates on behalf of the scientific committee. Dr. Paul Lacante, EU Cluster Medical Head / Medical Lead Benelux, welcomed the audience on behalf of BMS.
With more than 250 healthcare professionals involved in cancer care attending this webinar, the virtual edition of ISA 2020 was a big success.

Table of content

Short-term and long-term consequences of COVID-19 on cancer management

Prof. Dr. Ahmad Awada (Head of the Medical Oncology Clinic, Jules Bordet Institute, Brussels) presented his view on the pathway of COVID-19 and cancer management in 2020 (Figure 1).

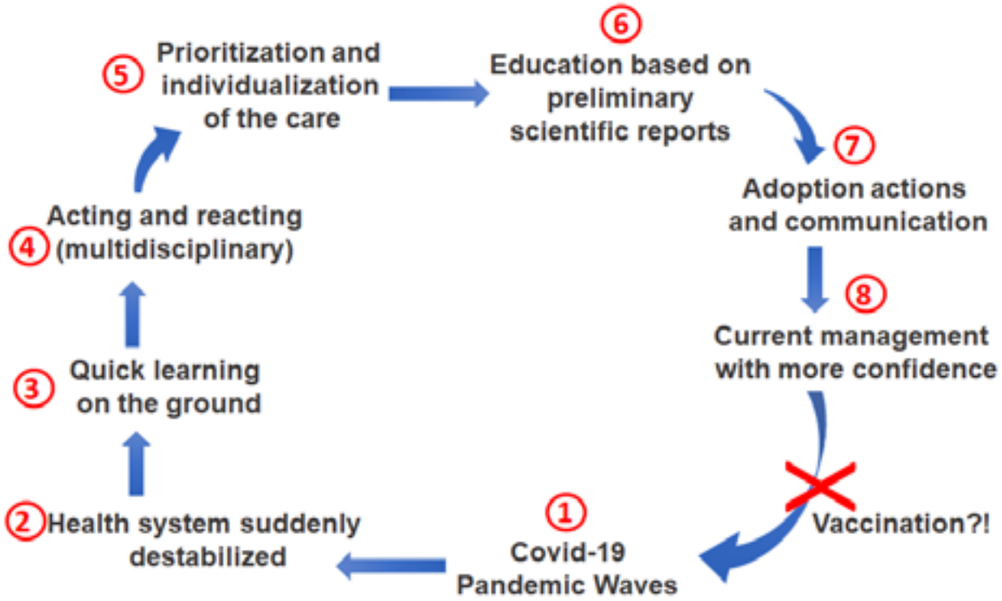


FIGURE 1 *The pathway of Covid-19 and cancer management during 2020*

The COVID-19 pandemic outbreak had a serious and unpredictable impact on cancer patients, caregivers, and hospitals. The health system suddenly destabilised, and there was quick learning on the ground with acting and reacting within the multidisciplinary team. Later on, doctors started to prioritise and individualise cancer care. After 2-3 months, the first scientific reports and recommendations appeared, which improved communication with patients and colleagues, and disease management could be done with more confidence. Prof. Awada emphasised that vaccines are needed to break this cycle.

In the short-term, cancer management was disturbed at diagnosis, treatment, and follow-up. Analyses by the Belgian Cancer Registry showed a decline in the number of new cancer diagnoses between March and September 2020 compared to the same period in 2019 (Figure 2).

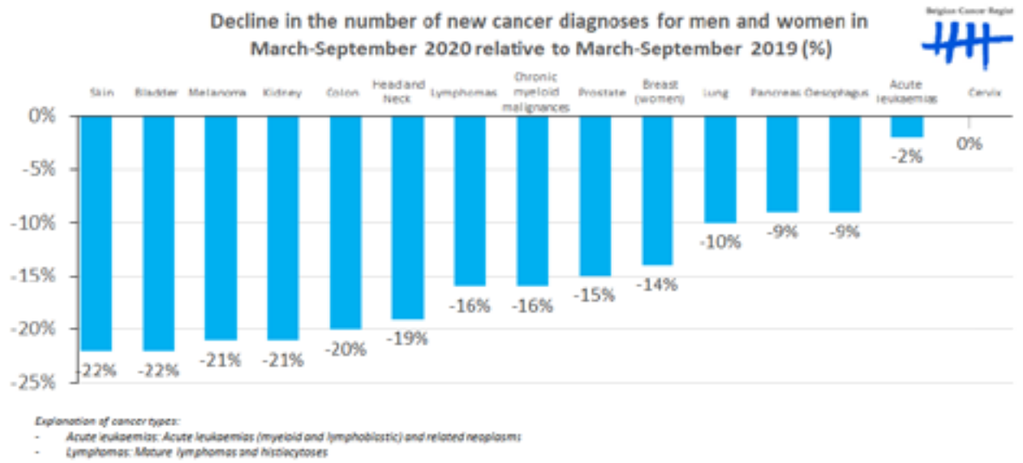


FIGURE 2 *Decline in the number of new cancer diagnoses in Belgium in 2020 relative to 2019 I ADAPTED*
https://kankerregister.org/media/docs/publications/Kanker-Impact-Coronacrisis_ENG_finaal_Nov2020.pdf

Prof. Awada presented results from an international survey done by his colleague Prof. Jerusalem among 109 representatives from oncology centers in 18 countries (62.4% academic hospitals) (Jerusalem G. ESMO 2020. Abs. LBA76_PR). Treatment modalities mostly affected by the pandemic (cancellation/ delay) were surgery (44.1%) and chemotherapy (25.7%). Earlier cessation of palliative treatment was observed in 32.1% of centers, and 64.2 % of participants agreed that undertreatment was a major concern. Teleconsultations were performed for follow-up (94.5%), for oral therapy (92.7%), but also for patients receiving immunotherapy (57.8%) or chemotherapy (55%). Approximately 82% of participants estimated that they would continue to use telemedicine. Most participants reported more frequent use of virtual meetings, but 45% disagree that virtual meetings are an acceptable alternative to live international conferences. The pandemic also profoundly impacted caregivers at various levels (work, health, education, and wellbeing).

The clinical research activities changed, with fewer patients being accrued and adaptation of guidance for clinical trials. There was a need to take quick decisions at the institutional level that impacted the entire hospital (daily work, capacity, research, education). There was a necessity to prioritise the type of patients that could be managed. Luckily there was a strong collaboration between the available teams. Thanks to digitalisation, part of the cancer care could be transferred to the home of the patients. Communication at all levels was optimised.

The long-term consequences of the altered cancer management due to COVID-19 are difficult to estimate at this stage. The delayed cancer diagnosis by stopping screening programs and due to the lockdown will undoubtedly have an impact, according to Prof. Awada. The role of ‘salvage’ cancer management between the various COVID-19 waves is not yet thoroughly evaluated.

Short-term and long-term consequences of COVID-19 on cancer management

Prof. Dr. Pierre Coulie shared immunological insights on COVID-19. The SARS CoV-2 virus belongs to the Coronaviridae family, in the Nidovirales order. It is a ß-coronavirus that can infect mammals, including man. Coronaviruses are encapsulated viruses with a crown-like appearance due to the presence of spike glycoproteins on the envelope (Figure 3).

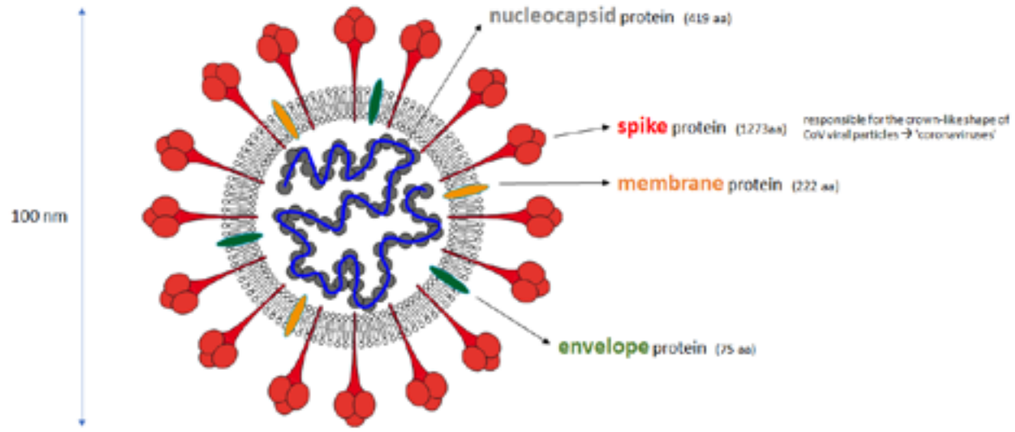


FIGURE 3 *SARS-CoV-2 structural proteins*

They have large, single-stranded, positive-sense RNA genomes. The genome is split into 14 open reading frames, which code for 16 nonstructural proteins and four structural proteins: the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S protein is cleaved into two subunits, S1 and S2.
S1 contains the receptor binding domain and is involved in viral entry into host cells via the cell surface receptor angiotensin converting enzyme 2 (ACE2) glycoprotein. The ACE2 expression profile, present in multiple organs, is key to COVID-19 symptoms. Following receptor binding, the virus must gain access to the host cell cytosol, which entails two proteolytic cleavages between domains S1 and S2, followed by fusion to allow insertion into the plasma membrane. The membrane protease TMPRSS2 is a host factor for binding. Cell surface co-expression of ACE2 and TMPRSS2 is needed to get infected with SARS-CoV-2. A unique feature of SARS-CoV-2 is a specific furin-like protease recognition site present in the S protein, making the virus more infectious via neuropilin-1 binding.

INNATE AND ADAPTIVE IMMUNE RESPONSES

For the immunologist, SARS-CoV-2 is a perfectly normal virus. It induces innate and adaptive immunity with classical effector mechanisms to which it partially resists. Today, the peculiarity of SARS-CoV-2 appears to be a proportionally low interferon type I response. This low IFN response is responsible for more viruses during a longer time, and these viruses continue to trigger the inflammatory response (chemokines and inflammatory cytokines). Together, these mediators continue to recruit innate immune cells (of myeloid origin) at sites of virus production, notably the lungs. This explains the switch from a simple virus reaction to inflammatory reactions and sepsis. Cellular and animal models of SARS-CoV-2 infection, in addition to transcriptional and serum profiling of COVID-19 patients, consistently revealed a unique and inappropriate inflammatory response. Reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving features of COVID-19. Among the effectors of an adaptive immune response, B cells and antibodies are produced, as well as CD4 T and CD8 T cells. We do not yet know for how long these responses maintain their protective effects, stated Prof. Coulie. At late stages of the disease,
T lymphodepletion can occur.

VACCINES

The main aim of vaccines is to stimulate the production of neutralizing anti-SARS-CoV-2 antibodies, and all vaccines in development aim to induce anti-spike protein antibodies. The antigens have to be inoculated in such a way that they stimulate an in vivo adaptive immune response. The vaccination modality is a key factor for immunogenicity: either co-inject the antigen and immunological adjuvants or inject DNA or RNA encoding the antigen, which is then produced by the vaccinee's own cells. DNA or RNA has to be 'packed' (lipid nanoparticles, recombinant viruses), and the role of packaging is to protect against DNAse/RNAse and promote entry into cells.

To date, Belgium has signed contracts with BioNtech-Pfizer (mRNA vaccine), Moderna (mRNA vaccine), AstraZeneca/Oxford (non-replicating viral vector vaccine ChAdOx1), Johnson & Johnson (non-replicating viral vector, Ad26), and Curevac (mRNA vaccine) (Figure 4).

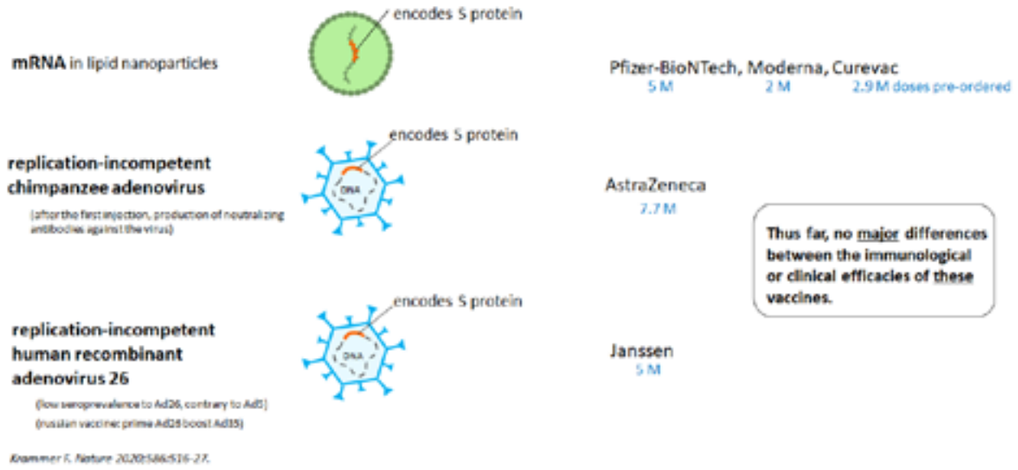


FIGURE 4 *Overview of SARS-CoV-2 vaccines for Belgium (December 2020)* I ADAPTED

Thus far, there are no major differences between the immunological or clinical efficacies of these vaccines. During the discussion, a comment was made about the fast development of the vaccines. Prof. Coulie emphasized that the current vaccines are based on existing platforms, making them easier to produce. All the vaccines induce the production of antibodies, a fraction of which are neutralizing.

Management of patients with hematologic malignancies and solid tumours in the COVID-19 era

Prof. Dr. Tessa Kerre, head of Clinic Haematology, Ghent University Hospital, and Dr. Stefan Rauh, medical oncologist at Centre Hospitalier Emile Mayrisch, Esch-sur-Alzette, Luxembourg, discussed the management of patients with respectively **hematologic malignancies** and **solid tumours** during the COVID-19 pandemic.

The experts started with an overview of the ESMO consensus recommendations defining cancer patients truly at risk during the COVID-19 pandemic, i.e. patients receiving chemotherapy or who received chemotherapy in the last three months, patients receiving extensive radiotherapy, people who had bone marrow or stem cell transplants in the previous six months or who are still taking immunosuppressive drugs and patients with some types of blood or lymphatic system cancer which damage the immune system, even if they don't need treatment (for example, chronic leukemia, lymphoma or myeloma). Specific risk groups are cancer patients with an impaired immune system such as leukocytopenia, low immunoglobulin levels, and long-lasting immunosuppression (steroids, antibodies). For patients on active treatment, the ESMO also gives recommendations, and a safe hospital environment should be guaranteed for real-life consultations.

Both specialists wondered if routine repeat polymerase chain reaction (PCR) patient screening is useful. He referred to a recent study in a tertiary care hospital where cancer patients were routinely tested for SARS-CoV-2 RNA by nasal swab and real-time PCR and only 0.3% of the 1,016 patients tested positive. The data indicate that the continuation of active anticancer therapy and follow-up visits is feasible and safe after implementing strict population-wide and institutional safety measures during the current COVID-19 pandemic (Berghoff A et al. J Clin Oncol 2020).

ARE CANCER PATIENTS AT HIGHER RISK OF BEING INFECTED WITH SARS-COV-2?

It is not clear if non-hematological patients are more prone to get a COVID 19 infection. Screening of a nation-wide database of patient electronic health records of 73 million patients in the US for COVID-19 and eight major types of **hematologic malignancies** revealed that patients with hematologic malignancies had increased odds of COVID-19 infection compared to patients without hematologic malignancies for both all-time diagnosis (malignancy diagnosed in the past year or prior) and recent diagnosis (malignancy diagnosed in the past year), with the strongest effect for recently diagnosed acute lymphoid leukemia, essential thrombocythemia, acute myeloid leukemia and multiple myeloma (Wang Q. Blood Rev 2020).

ARE CANCER PATIENTS AT HIGHER RISK FOR A POOR OUTCOME AFTER COVID-19?

A matched cohort study observed that patients with COVID-19 and cancer had similar outcomes than matched patients without cancer. This finding suggests that a diagnosis of active cancer alone and recent anticancer therapy do not predict worsen COVID-19 outcomes. Therefore, recommendations to limit cancer-directed therapy must be considered carefully in relation to cancer-specific outcomes and death (Brar G. J Clin Oncol 2020). Subgroup analysis revealed age and two or more co-morbidities as major risk factors. A more extensive Chinese survey showed that the highest risk factors for mortality after a diagnosis of COVID-19 were cardiovascular disease, followed by diabetes, chronic respiratory disease, hypertension, and then cancer. In a logistic regression analysis, the presence of cancer was an independent risk factor (HR= 2) for COVID-19 disease severity and mortality. Still, the highest risk factors (HR >2) were age, performance status ≥ 2, and ≥ 2 co-morbidities. Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to cancer patients. Longer follow-up is needed to understand better the effect of COVID-19 on outcomes in patients with cancer, including the ability to continue specific cancer treatments (Kuderer N, Lancet 2020).

In a prospective observational study with 800 patients, mortality from COVID-19 in cancer patients appears to be principally driven by age, gender, and co-morbidities. The study did not found evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatments are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment. Patients with cancer with different tumour types had varying susceptibility to SARS-CoV-2 infection. Individualised risk tables for patients with cancer, considering age, sex, and tumour subtype, were created that could be useful to assist physicians in informed risk-benefit discussions to explain COVID-19 risk and enable an evidence-based approach to national social isolation policies. (Lee L. et al. Lancet 2020; 395: 1919–26)

Patients with a hematological malignancy have a higher hospitalization rate and a higher mortality rate compared to patients without hematologic malignancies (Sanchez-Pina JM, Eur J Haematol 2020). Patients with chronic lymphocytic leukemia (CLL) and acute leukemia seem to do worst. A systematic review and meta-analysis of 3,377 patients demonstrated that adult patients with a hematologic malignancy and COVID-19 had a 34% risk of death. Patients on systemic anticancer therapy had a similar risk of death compared to patients not on treatment (RR 1.17; 95% CI, 0.83-1.64) (Vijenthira A et al., Blood, 2020). Age was strongly associated with mortality: among those > 60 years, mortality was estimated at 47% (95% CI, 41% to 54%). Recent systemic anticancer therapy did not impact mortality. Most patients with a hematologic malignancy and COVID-19 survive. A report from Sciensano from June 2020 also confirmed that a hematologic malignancy is a risk factor in dying in the hospital. Still, gender, age, and chronic liver disease have a higher risk (Figure 5).

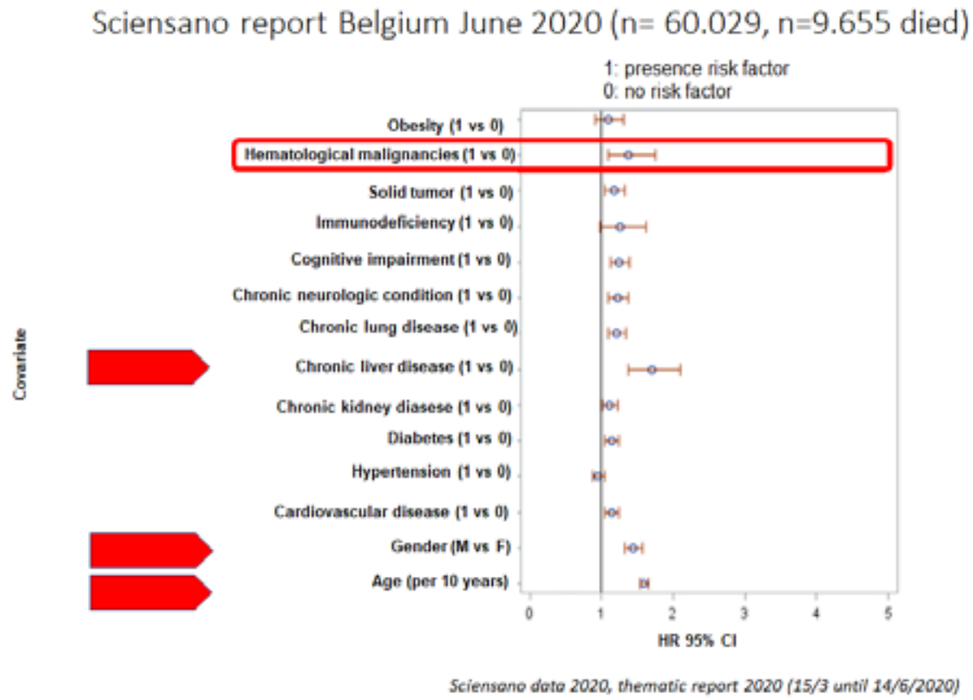


FIGURE 5 *Risk factors to die of a COVID-19 infection in the hospital* I ADAPTED

In patients with a haematologic malignancy, the same Identified predictive factors present at diagnosis are predictive for poor outcome and death at diagnosis, as could be identified in the general population: high age, comorbidities, high ECOG PS, high C-reactive protein (CRP), leucocytosis, neutrophilia and lymphopenia. Moreover, for haematological patients, additional specific risk factors could be identified, such as an active malignancy, disease progression, intensity of therapy and the underlying disease. At the moment of admission, the following factors predictive for poor outcome and death, could be identified for patients with hematologic malignancies: age above 70 years, ECOG ≥2, CRP >11, platelet count < 40.000, LDH > UNL, and absolute lymphocyte count < 600/mL.

SHOULD WE ADAPT THE TREATMENT OF CANCER PATIENTS DURING THE COVID PANDEMIC?

A retrospective study demonstrated that recent cytotoxic chemotherapy treatment was not associated with adverse COVID-19 outcomes. Patients with active hematologic or lung malignancies, peri-COVID-19 lymphopenia, or baseline neutropenia had worse COVID-19 outcomes. In univariable analysis, no association was observed between treatment with cytotoxic chemotherapy, immunotherapy, or targeted therapy within 35 days of COVID-19 diagnosis and severe or critical COVID-19 infection. However, the interactions among anti-neoplastic therapy, cancer type, and COVID-19 are complex and warrant further investigation (Jee J. J Clin Oncol 2020). Nevertheless, both experts agreed that the underlying disease should be continued when possible because of the expected long duration before normalisation of hospital care.

Some treatments should be adapted or postponed in cancer patients during the COVID pandemic (Van Doesum J. Leukemia 2020). Corticosteroids as anti-emetics should not be prescribed if avoidable and should be limited in patients treated with immune-checkpoint blockade (ICI) to reduce vulnerability to COVID-19. Oral or subcutaneous treatments are preferred over infusion-based treatments to reduce time spent in the hospital. Supportive treatments (e.g. bisphosphonate infusion) should be omitted, except in the case of hypercalcemia. When possible, the administration of intravenous maintenance treatments should be organised at home. If this is feasible, these treatments' frequency should be reduced in patients with less aggressive metastatic cancers. There has been some controversy about immunotherapy and COVID-19 in cancer patients, but this seems as safe as other treatments. There is no clear evidence of higher toxicity or risk of a cytokine storm. The guidelines for immunotherapy are similar to those of other anti-neoplastic therapies. The treatment benefit and risks should be evaluated on an individual basis. For patients with high-risk hematological diseases (e.g. acute leukemia), treatment should be started as soon as possible. Still, for lower-risk diseases (e. g. CLL, low-grade lymphomas), a delay can be considered.

SPECIFIC POINTS OF ATTENTION IN TREATING COVID-19 FOR CANCER PATIENTS

Recipients of stem cell transplantation (SCT) or CAR-T therapy who are positive for SARS-CoV-2, should not be treated in rooms with laminar airflow or other rooms (HEPA) with positive pressure unless the ventilation can be turned off. There are no clear recommendations on specific therapies in SCT recipients due to limited data and unknown risk versus benefit. Even less data are available for pediatric SCT patients. Treatment should be given in close collaboration with infectious disease specialists.

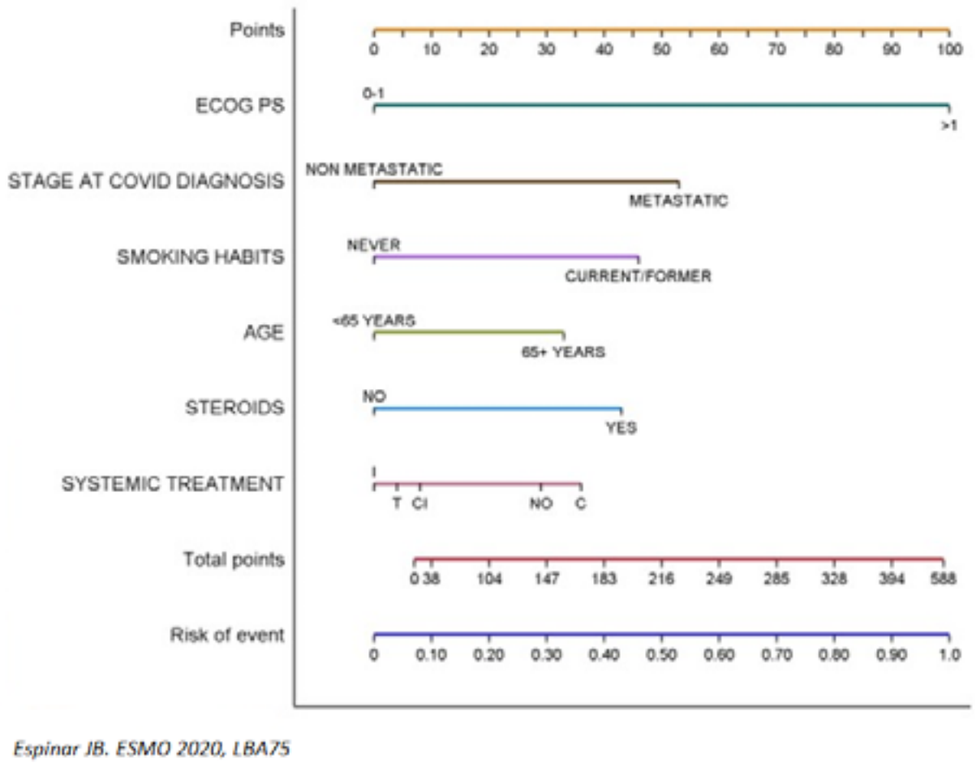
Antiviral drugs could not show a significant impact on death rate. The EBMT recommendations of November 2020 (11th version) mentioned that five days of remdesivir might provide benefit, especially in SCT patients with moderate to severe COVID-19. However, this recommendation was weakened in the 12th version (December 2020) of the EBMT recommendations. Anti-inflammatory therapy with corticosteroids might have value in non-transplant patients with a haematological malignancy. Short-term corticosteroid therapy (7-10 days) in immunocompromised patients with severe/critical COVID-19 resulted in a lower mortality, but other anti-inflammatory therapies (including tocilizumab) show conflicting data. Supportive care is crucial including non-invasive ventilation and anti-coagulants to prevent thromboembolic complications. Regarding convalescent plasma, randomized trials showed no effect on mortality. In contrast, observational trials found reduced mortality in subgroups of patients that received plasma with higher antibody levels or when the plasma was given within three days of a COVID-19 diagnosis. Treatment of viral, bacterial, and fungal co-pathogens should be optimized. It is currently recommended that immunosuppressive prophylaxis/treatment is continued.

Managing lung cancer patients in the era of COVID-19

Prof. Johan Vansteenkiste gave his view on what lung cancer means for COVID-19 and what COVID-19 means for lung cancer patients. Patients with lung cancer are thought to be particularly susceptible to COVID-19 given their older age and immunosenescense, smoking habits, related co-morbidities, and lung cancer therapy. The international, registry-based cohort study TERAVOLT evaluated the effect of a SARS-CoV-2 infection on patients with thoracic malignancies. A preliminary analysis of the first 200 cases demonstrated that thoracic cancer patients have a high risk of COVID-19-related mortality (33%) (Garassino M. Lancet Oncol 2020). The type of systemic therapy, including tyrosine kinase inhibitors (TKIs), chemotherapy, and immunotherapy, did not affect survival in patients with COVID-19. At ESMO 2020, an update on 1,012 patients was presented (Espinar JB. ESMO 2020, LBA75).

The results were in line with the initial analysis, with 72% of patients being hospitalized, 12% being admitted to ICU, and around one-third (32%) died while infected with COVID-19. Multivariate analysis revealed that age, smoking habit, cancer stage, ECOG performance status, prior steroids, and anticancer treatment class seem to be variables related to COVID-19 mortality, with a poor performance status as the most important risk factor.

The TERAVOLT nomogram could be a useful tool to predict mortality in thoracic cancer patients who develop COVID-19 and could aid physicians in discussions related to cancer or COVID-19 treatment (Figure 6). Chemotherapy and TKI use was not associated with increased mortality, and interestingly, patients on immunotherapy appeared to be at a decreased risk for mortality.



Espinar JB. ESMO 2020, LBA75

FIGURE 6 *TERAVOLT risk nomogram to predict risk of mortality in lung cancer patients with COVID-19*

WHAT DOES COVID-19 MEAN FOR LUNG CANCER PATIENTS?

Prof. Vansteenkiste presented the current approach in the COVID-19 era for patients with various lung cancer stages (Passaro A. ESMO Open 2020). ESMO has established guidance for clinicians, defining three levels of priorities regarding therapeutic interventions (Figure 7).

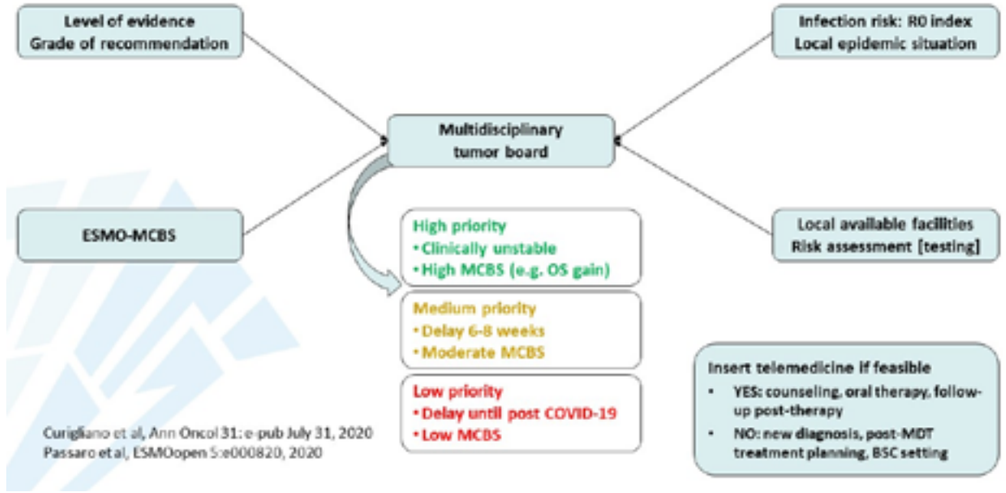


FIGURE 7 *ESMO guidance for clinicians to prioritise treatment of patients with thoracic malignancies*

Multidisciplinary teams should make patient decisions, taking into account the magnitude of the country's epidemic and the local healthcare structure resources such as testing facilities and availability of intensive care units. Prioritisation of patients is guided by the magnitude of benefit of the treatment. Patients that are clinically unstable and/or where the magnitude of benefit qualifies the intervention as high priority (e. g. significant overall survival gain and/or substantial improvement of the quality of life (QoL)) are considered high priority. A medium priority is given to patients in a non-critical situation, but a delay beyond 6 to 8 weeks could potentially impact the overall outcome. Low priority patients have a stable condition to delay services for the duration of the COVID-19 pandemic or are patients in which the treatment would not provide benefit.

Outpatient visits should be reorganized. Established patients with symptoms or patients with high suspicion of new lung cancer must be handled within standard pathways, ensuring protective measures are in place. The capacity of thoracic surgery has been significantly reduced, and access to the intensive care unit after elective surgery might have been restricted. Due to these restrictions, setting up a priority framework for lung cancer surgery is essential. The multidisciplinary team plays an essential role in prioritizing different lung cancer surgical procedures while preserving the highest possible standards. Once again, the risk/benefit ratio, including not only patients and disease aspects but also alternative treatment modalities such as (chemo)radiation therapy for high volume disease or stereotactic ablative radiotherapy for T1-T2 N0 tumors, should be carefully explored.

The role of adjuvant chemotherapy should be reconsidered, based on a priority scale that includes mainly the relative survival benefit and functional co-morbidities. It should be proposed in fit and young patients (≤ 65 years) with resected T3/T4 tumors or in case of pN2 disease, but should be withheld in frail, elderly patients with significant co-morbidities.

Given the significant curative potential, the treatment for a patient with stage III NSCLC should receive high priority. These include neoadjuvant treatment in potentially resectable stage IIIA tumors and concomitant or sequential chemoradiation (CT/RT) in stage IIIA/IIIB/IIIC tumors, both supported by the use of granulocyte colony-stimulating factor (G-CSF) as previously proposed. For patients with disease control after CT/RT treatment, the subsequent use of durvalumab as consolidation therapy should be guaranteed within 42 days after CT/RT completion, without any planned delay.

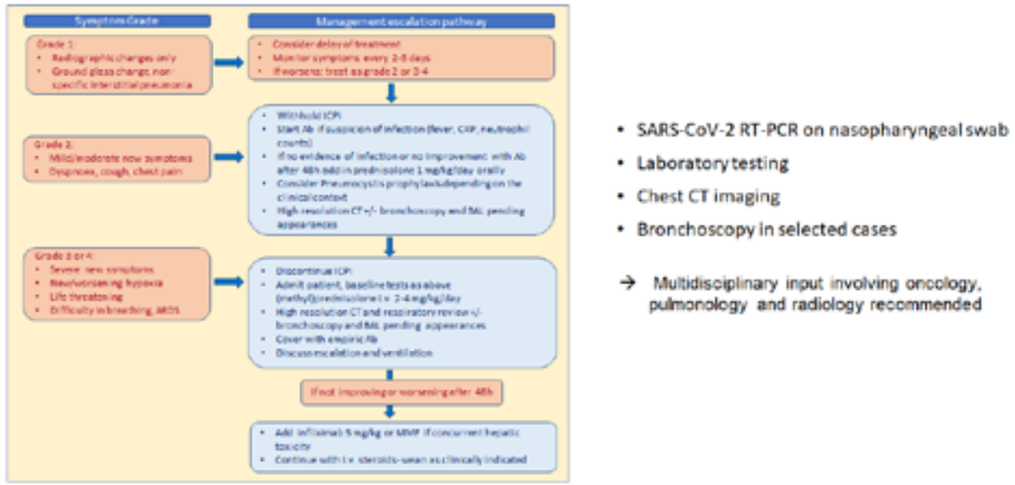
To limit cancer-related mortality in patients with a new diagnosis of metastatic NSCLC, all standard options for first-line systemic therapy should be considered, including chemotherapy, immunotherapy, TKIs, and different combinations. This approach aims to improve prognosis, cancer-related symptoms, and QoL and should be prioritized whenever possible. The same holds for second-line treatments in patients with symptomatic, progressive disease, where delaying the treatment could compromise the patient's survival (high priority). For patients on immunotherapy for more than 12 - 18 months, delaying the subsequent cycle, omitting some cycles, or generally expanding intervals should be considered. Antiresorptive bone-protective therapy (zoledronic acid, denosumab), not deemed urgent for malignant hypercalcemia, should be withheld unless deliverable in the community or at the patient's home (low priority).

Managing pneumonitis in ICI-treated patients in times of COVID-19

Prof. Dr. Els Wauters (Respiratory Oncology Unit, Department of Pulmonology, UZ Leuven) illustrated that a severe COVID-19 infection and immune-related pneumonitis have an 'excessive' immune response in common that induce a hyperinflammatory state in the lung. Severe COVID-19 pneumonia and severe ICI-induced pneumonitis have comparable clinical and radiological presentations, so it is challenging in clinical practice to make a differential diagnosis. Discriminating ICI-induced pneumonitis from COVID-19 pneumonia is essential, as a delayed or incorrect treatment increases the risk of a severe disease course.

REVIEW OF THE WORKUP OF POSSIBLE ICI-INDUCED PNEUMONITIS

A review of the workup of possible ICI-induced pneumonitis is a challenging diagnosis of exclusion (Figure 8).



Adapted from Haanen et al, Annals of Oncology 28 (Supplement 4): iv119-iv142, 2017

FIGURE 8 *Immune-related pneumonitis is a diagnosis of exclusion* / ADAPTED

The workup is based on a combination of laboratory testing and chest CT imaging. A bronchoscopy is recommended in symptomatic patients (grade 2 or higher) before starting high-dose corticosteroids to exclude a respiratory infection or disease progression. Multidisciplinary input involving oncology, pulmonology, and radiology is recommended.

A SARS-CoV-2 PCR test on a nasopharyngeal swab is necessary to exclude or detect COVID-19. Unfortunately, the sensitivity of this test in clinical practice is moderate. This means that a negative PCR test does not exclude an infection in a patient with suggestive COVID-19 symptoms coming from an area with a high COVID-19 prevalence. In symptomatic patients with a negative COVID-19 test, we perform a CT scan, explained Prof. Wauters. The CT findings can be truly suggestive of COVID-19, e. g. ground glass regions and crazy paving. But not all COVID-19 patients present with typical CT findings, resulting in an indeterminate CT classification. In ICI-treated patients, this complicates the interpretation of the CT findings.

ROLE FOR BRONCHOSCOPY

Bronchoscopy can help to make a decision if the clinical suspicion of COVID-19 is high and the nasopharyngeal swab negative. However, it should be performed safely, i.e., in clinically stable patients and with full safety measures for caregivers in place. If so, it provides SARS-CoV-2 PCR BAL fluid with a high sensitivity (93%) in COVID-19 patients. It also allows making alternative diagnoses. Neutrophils are markedly higher in COVID-19 (35%) than in non-COVID pneumonia (10%) or in ICI-induced pneumonitis. Lymphocytes are higher in ICI-induced pneumonitis (37%) than in healthy BAL fluid and COVID-19 (11%) (Wauters E. Cell Res 2020). The diagnostic value of these findings needs further evaluation.

Immune-related diarrhea and COVID-19 gastro-intestinal symptoms

Prof. Dr. Eric Van Cutsem (Digestive Oncology, University Hospitals Leuven) started with an overview on potential mechanisms of increased immune system activity that may lead to immune-related (ir) diarrhea, such as increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of pre-existing autoantibodies (e.g., in the thyroid gland) and increasing levels of inflammatory cytokines (e.g., in the gastro-intestinal tract).

Diarrhea frequently occurs in patients treated with ICI. Patients should be informed that diarrhea/colitis usually begins approximately six weeks after treatment initiation. The reported incidence of diarrhea (all grades) ranges from 8 to 33%, and grade 3-4 diarrhea from 1-10% (Samaan MA. Nat Rev Gastroenterol Hepatol 2018). Treatment recommendations are based on the severity of diarrhea (Figure 9).

Gastrointestinal (Diarrhea & Colitis)

Grade		Grade	
1	• Continue ICI • Symptomatic treatment (fluids, loperamide, low fiber/lactose) • If G1 and persists > 14 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea	3 - 4	• Withhold ICI • If G2 and persists for > 3 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea • Do not wait for sigmoido/colonoscopy to start If no improvement in 72 hours or absorption concern, treat as G3/4. Steroid wean duration: o Moderate: wean over 2–4 weeks o Severe: taper over 4–8 weeks
2	• Withhold ICI • If G2 and persists for > 3 days or worsens give prednisolone 0.5–1 mg/kg or consider oral budesonide 9 mg daily if no bloody diarrhea • Do not wait for sigmoido/colonoscopy to start If no improvement in 72 hours or absorption concern, treat as G3/4. Steroid wean duration: o Moderate: wean over 2–4 weeks o Severe: taper over 4–8 weeks		

ESMO, European Society for Medical Oncology; G, grade; ICI, immune checkpoints; irAE, immune-related adverse event

White	**Continue ICI**
Orange	**Hold/Temporarily Hold ICI**

Adapted from Haanen JBAG, et al. Ann Oncol 2017;28(suppl 4):iv119– iv142.

FIGURE 9 *ESMO management recommendations for immune-related (ir) diarrhoea I ADAPTED*

CHARACTERISTICS OF COVID-19 – GASTRO-INTESTINAL SYMPTOMS

COVID-19 is primarily a respiratory disease. However, increasing reports describe subgroups of patients with concurrent gastro-intestinal (GI) symptoms, notably diarrhea, anorexia, vomiting, and nausea. The onset of GI signs can occur before the respiratory symptoms but can also be present in the absence of respiratory symptoms. SARS-CoV-2 infections in the GI tract can cause bleeding and inflammation, which impacts the intestinal immune system and impair the whole body's immune system, worsening the disease process of COVID-19 in the lungs and other organs. Additionally, the viral balance in the GI tract is disordered during a SARS-CoV-2 infection, which could further impact the homeostasis of the microbiota.

The WHO defines diarrhea as three or more loose/liquid stools per day or an increase in the number of evacuations compared with the usual. Given the subjective nature, there is marked heterogeneity in patients' estimates with COVID-19 – associated diarrhea symptoms. Clinical studies show that diarrhea in COVID-19 patients with GI symptoms was one of the most common symptoms, ranging from 2% to 55% of cases. Several studies report cases of 3-8 evacuations per day and median symptom duration of 4 days. Gastro-intestinal symptoms seem to be associated with more severe COVID-19 and worse outcomes, and diarrhea could be associated with increased disease severity and worse prognosis (Ghimire S. ACG 2020). However, additional studies are needed to clarify this correlation.

PATHOGENESIS OF SARS-COV-2-ASSOCIATED DIARRHEA

D'Amico F. recently published a possible explanation for SARS-CoV-2-associated diarrhea (Clinical Gastroenterology and Hepatology 2020). SARS-CoV-2 uses ACE2 and the serine protease TMPRSS2 for entry in the lung epithelium cells. ACE2 and TMPRSS2 are not only expressed in the lung but also in the small intestinal epithelia. ACE2 is necessary for the surface expression of amino acid transporters of the small intestine. ACE2 is also expressed in the upper esophagus, liver, and colon. Like tryptophan, amino acids regulate the secretion of antimicrobial peptides by Paneth cells via the mTOR pathway activation. Antimicrobial peptides impact the composition and diversity of the microbiota. Disturbance of this pathway could drive inflammation (enteritis) and, ultimately, diarrhea.

MANAGEMENT OF COVID-19 – ASSOCIATED DIARRHEA

The recommendations for healthcare professionals in managing patients with COVID-19 and diarrhea are helpful, indicated Prof. Van Cutsem. There is no available evidence yet on antidiarrheal drugs' efficacy, but adequate rehydration and potassium monitoring should be performed as in all patients with diarrhea. Antibiotics and antivirals are often used for COVID-19 treatment, involving a likely alteration of the gut microbiota, causing diarrhea. Therefore, it is plausible that the gut microbiota could be a new therapeutic target, and probiotics could have a role in the management. A rapid improvement in diarrhea was also found after starting antiviral therapy.

Based on diarrhea pathogenesis and the key role of ACE2, ACE blockers' use is being investigated. ACE inhibitors have been associated with a significantly reduced risk of COVID-19 disease requiring hospital admission but not significantly associated with ICU care risk (Hippisley-Cox J. Heart 2020).

Adoption of new approaches beyond the pandemic

Prof. Dr. Ahmad Awada closed the meeting with a sign of hope with the vaccines in development. He also believes there's room for adopting "COVID" approaches of cancer patients and organizations beyond the period of the pandemic. Keeping the dynamic organization of cancer care and management seems to be a must. The extension of the continuity of cancer care beyond hospital walls should be evaluated. Telemedicine and homework seem to be more accepted today by all partners. Finally, there's hope for reducing the burden and bureaucracy of cancer care (clinical and research) following the pandemic. The ESMO is working on recommendations in this respect that can hopefully be integrated into clinical practice soon.

ImmunoScience Academy

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SUMMARY

ImmunoScience Academy National Meeting

16 December 2020

organized and supported by

Bristol Myers Squibb™

ONCBE2011301-11 – 02/21