9th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

▶ IN-PERSON CONFERENCE
From September
15th to 17th 2022

Revised Guidelines
slide set
September 2022

COVID-19 vaccination subgroup

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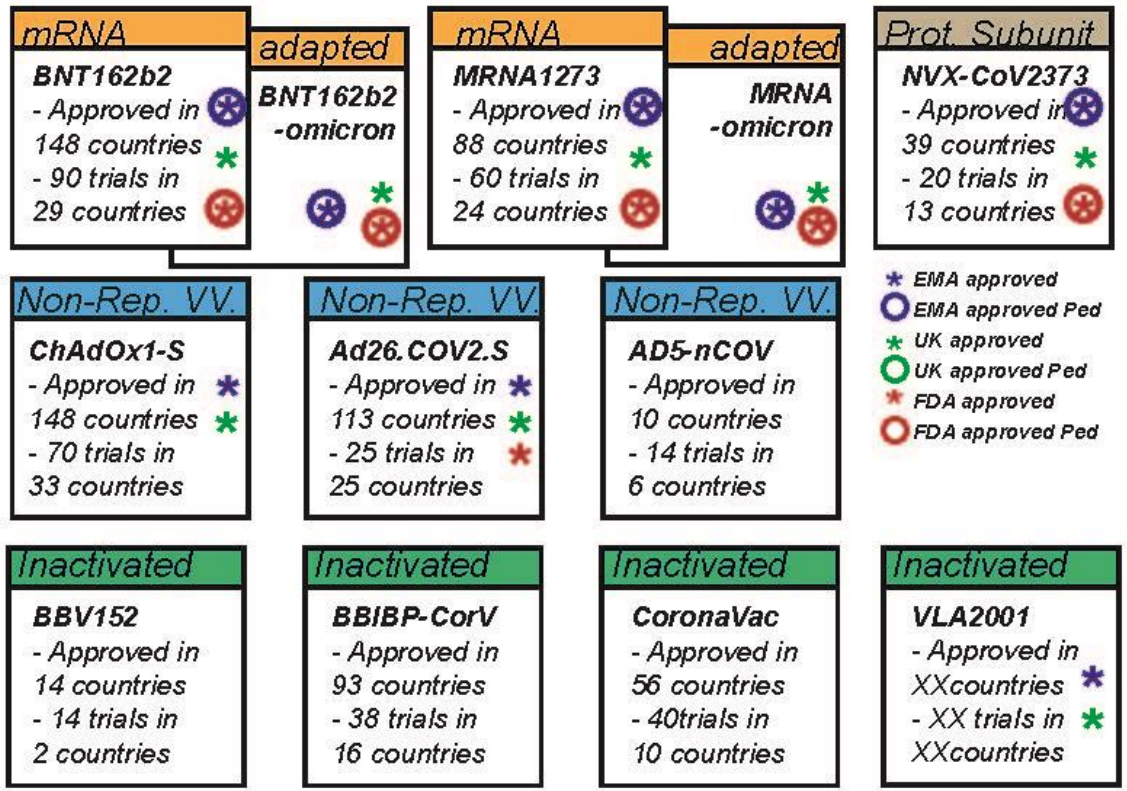
Clinically available vaccines (update 2022-09-13)



Omicron adapted:
BNT 162b2 “adapted”:
Bivalent vaccine “original + BA.1” approved by the EMA for boosters from 12 years.
Bivalent vaccine “original + BA4/5” approved by the FDA/EMA for boosters from 12 years.
mRNA 1273 “adapted”
Bivalent vaccine “original + BA1” approved by the EMA for boosters from 12 years.
Bivalent vaccine “original + BA4/5” approved by the FDA for for booster from 18 years.

Summary of the literature

- There are a large numbers of serological studies performed in different types of HM/HCT patients.
- They generally show that more doses (3 > 2; 4 > 3) improve seroconversion rate and increase antibody levels in previously seropositive patients
- There are no efficacy studies
- Breakthroughs are usually quite mild although severe infections in fully vaccinated patients have been reported
- With one exception, no specific toxicities have been reported

Recommendations

Common guidelines for all HM patients including HCT or CAR-T cell recipients

HM patients should receive a three-dose program of mRNA vaccines or a two-dose program with protein subunit vaccine according to recommendations by international and national authorities and authorized age range **AIIt/u**

The interval between the first two doses should be at least 3 weeks and the interval between the 2nd and 3rd dose mRNA vaccine (1)-3 months. **BIIt/u**

Additional (booster) dose(s) of mRNA vaccine should be considered after at least 3 months from the 3rd dose **BIIt/u**

For patients having COVID-19 infection, booster dose(s) should be delayed to at least 3 and preferably 4 months after the COVID-19 episode.

Common guidelines for all HM patients including HCT or CAR-T cell recipients

Whichever the vaccine response, HM pts should be informed of the ongoing risk of Covid-19 despite vaccination and keep the hygiene and social distancing recommendations of their community or country **BIIt**

HM patients with previous COVID-19 infection should be vaccinated with a primary schedule according to recommendations by international and national authorities and the authorized age range **AIIt/u**

The vaccination of the house-hold contacts of hematology patients including children, according to the EMA approval for specific age groups, is strongly recommended **AIIt/h**

Treatment with monoclonal antibodies should not prevent vaccination against COVID-19 in situations where such are indicated **BIII**

Guidelines for non-transplanted patients with hematologic malignancies

There is until now no specific safety issue of Covid vaccination with mRNA vaccines in non-transplanted HM pts.

Except in specific conditions where the expected response rate is very low, patients with HM should receive a full vaccination program with 3 doses starting preferably before treatment of the underlying disease or HSCT, or during maintenance or off-therapy phases **All h/t**

Covid vaccination should not delay the treatment of the underlying disease

Guidelines for non-transplanted patients with hematologic malignancies

Uncontrolled data and one metaanalysis indicate better responses with the mRNA1273 over the BNT162b2 vaccine *(Greenberger, Cancer Cell 2021; Stampfer, Leukemia; Thompson J Patient Cent Res Rev 2022; Wu Lab Med 2022; Nooka JCO 2022; Noori Int Immunopharm 2022)*. However, no evidence-based recommendation can be given on choice of vaccine in the absence of prospective comparative trials. The choice of the vaccine should be in accordance with official EMA recommendations and country recommendations.

Patients, who have been vaccinated before or during treatment, should be assessed 3-6 months after the end of treatment and revaccinated if they have low Ab titers **BIII**

Considering the low rate and heterogeneity of the response in the different HM and therapies, vaccinated patients should be assessed for their Ab response 3-5 weeks after the last dose to identify individuals who could benefit from pre-exposure MoAbs **BIIu**

Specific guidelines for patients with LPD or AL

In patient cohorts where the expected response rate to vaccine are low or very low, (eg. patients receiving anti-CD20 Abs, or within the 6-12 months following the last dose, profound hypogammaglobulinemia (≤ 4g/L), deep lymphopenia (<500/µL), BCMA targeted-bispecific therapy (Belantamab-mafodotin), pts starting an induction chemotherapy for AL), these patients may still benefit from vaccination ~~CIIu~~/**BIIu**.

However, these patients should be assessed for vaccine response one month after each vaccine dose (from dose 2) in order to assess their response, and discuss the use of pre-exposure MoAbs or other preventative measures

Recommendations in HSCT recipients

- HSCT recipients should receive COVID-19 vaccine with a three-dose primary schedule of mRNA vaccine **AIIu/t**.

- Vaccination should preferably be initiated at least 6 months after HSCT if transmission of SARS-CoV-2 in the community is low **BIIu**.

- Earlier vaccination should be considered if there is high prevalence of SARS-CoV-2 in the community. However, early vaccination is associated with a lower likelihood for an immune response **BIIu**

- There is a risk for worsening/eliciting GVHD in allogeneic HSCT recipients. This risk needs to be considered when deciding about time for vaccination **AIIu**

- It is possible that the risk for GVHD using the protein-subunit vaccine might be lower and could be considered in individual patients after careful risk assessment.

Recommendations in HSCT recipients

- Additional doses are able to improve the immune response both by allowing an increased proportion of patients to seroconvert and to increase the antibody levels. It is therefore recommended that patients should receive booster doses **(AIIt)** preferably with the new updated bivalent vaccines (according to authorizations for age) **BIIt**

- Based on data from other vaccines, it is likely that immunity obtained from either pre-transplant SARS-CoV-2 infection or vaccination will be wiped out by the transplant procedure. However, no data currently exists regarding this issue. A new primary schedule is therefore recommended **BIII**

- However, this will over time result in a large number of vaccine doses and the safety profile of such an approach is currently unknown

Vaccination of HSCT donors

- There is no specific recommendation for vaccinating stem cell donors for any other purpose than protecting the donor. However, previous vaccination of the donor might reduce the risk to jeopardize the donation

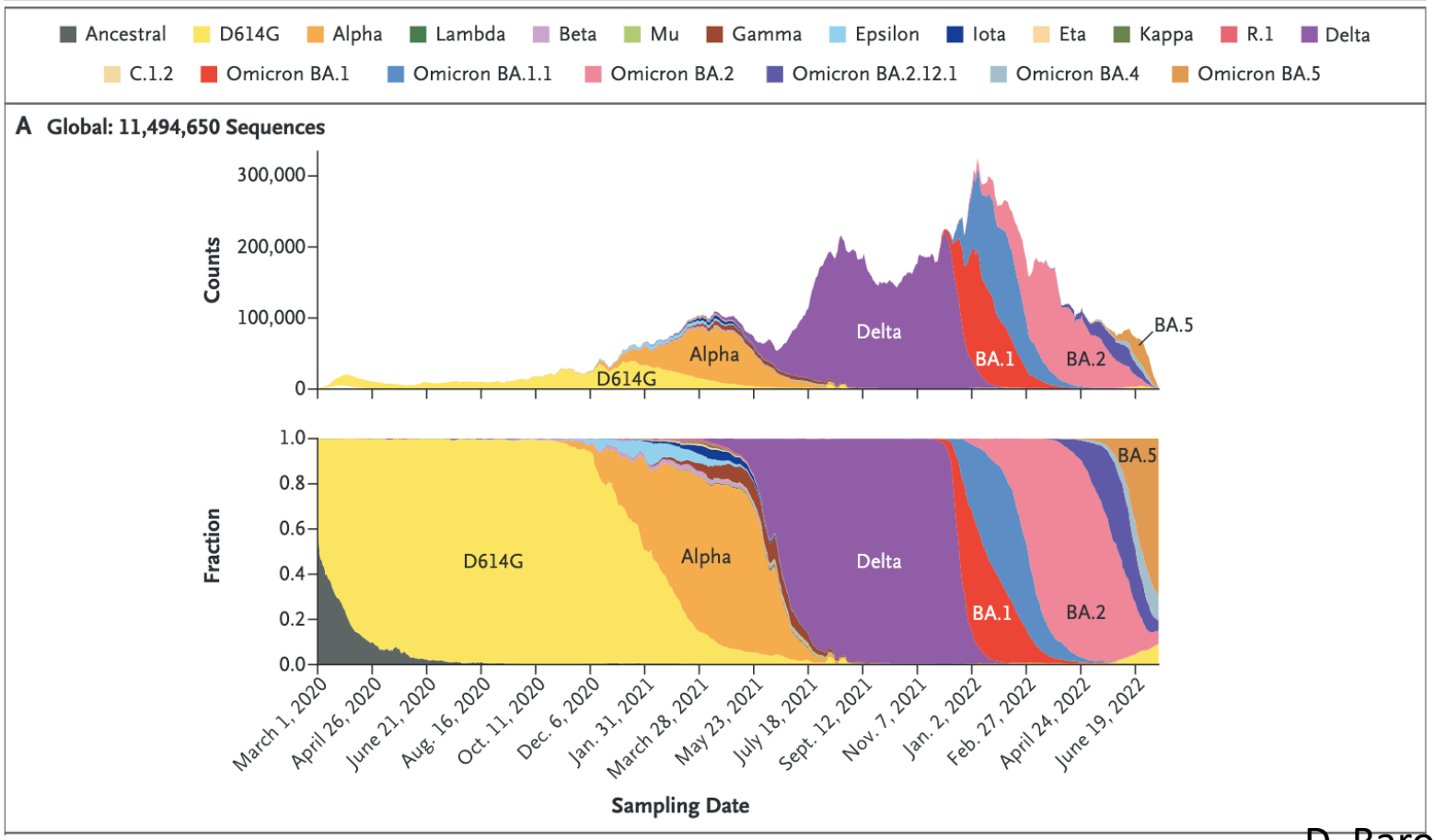
- There have been reports of transfer of donor immunity to allo-HCT recipients (Leclerc et al. Lancet Haematol 2022). However, whether this can result in protection against COVID-19 infection or disease in the recipient is unknown.

Patients treated with CAR-T cells

- Patients with B-cell aplasia after treatment with CD19+ CAR T cells are very unlikely to mount antibody responses.
- Repeated doses might show some benefit.
- T cell responses can be elicited in a majority of patients. Importance for protection in patients currently unknown
- These patients should receive pre-exposure monoclonal antibody prophylaxis **AIIt**
- Timing of vaccination should be based on individual consideration taking into consideration the immune status of the patient **BIII**

Background information

A moving landscape influencing vaccine responses



D. Barouch, NEJM

Safety and Adverse Events

- Overall incidence of AEs of SARS-CoV-2 viral vector vaccines, mRNA vaccines and inactivated vaccines of observational studies, surveillance studies and RCTs were at medium to high level (20.05–94.48%).
- Incidence of SAEs was low (3.56/100,000–1.25%).
- Allergic symptoms and cardiovascular and cerebrovascular symptoms were with low incidence rates (0.32/100,000 doses–28.3%).
- Compared with unvaccinated group or the placebo group, vaccination of viral vector vaccine may increase the risk of thrombosis, but decrease the risk of death.
- The incidence of vascular diseases decreased after receiving the mRNA vaccine.
- These results revealed the relationship between thrombosis events and viral vector vaccines.
  - The incidence of AEs after inoculation by inactivated vaccines was lower than control groups that showed good safety of inactivated vaccines.

Vaccine-induced immune thrombotic thrombocytopenia (VITT)

- Vaccine-related thrombotic events caused by VITT
  - rare but life-threatening AE.
  - VITT was mainly reported 5–24 days after viral vector vaccine inoculation [72].
  - VITT in particular associated with CVST and visceral vein thrombosis.
  - Mechanism of VITT unclear.
  - Postulated Effect of
    - anti-PF4 antibodies [73]
    - (adenovirus vector [74])
    - S protein of SARS-CoV-2 [75]
  - For patients with VITT, intravenous immunoglobulin should be started immediately to lower the risk of thrombotic events

LinYi Chen Vaccines 2022

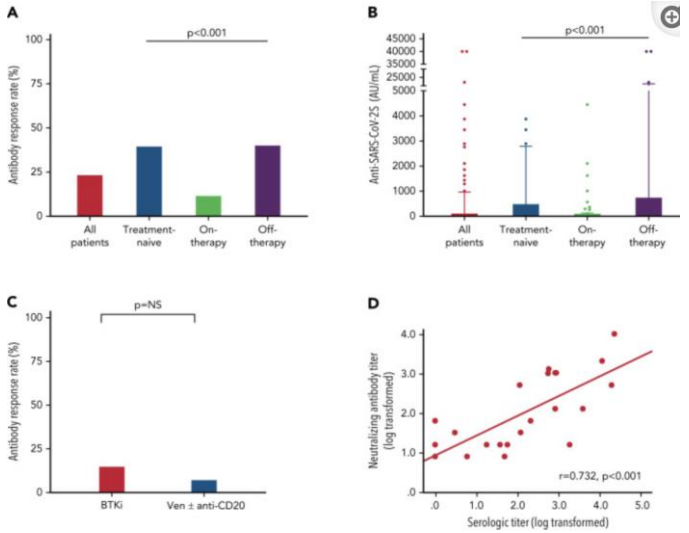
Myocarditis and Pericarditis

- Increased risk of myocarditis or pericarditis observed after COVID-19 mRNA vaccination
- highest in men aged 18–25 years after 2nd dose.
  - incidence BNT162b2 1.71/10^5 person-days; MRNA 2.17 1.71/10^5 person-days
- No statistically significant risk difference between mRNA-1273 and BNT162b2, but it should not be ruled out that a difference might exist.
  - Head:head IRR comparison BNT162b2:MRNA1273 1·43 (95% CI 0·88 to 2·34)
- benefit–risk profile, continue to support vaccination using either of the two mRNA vaccines.

Wong Lancet 2022

Update CLL 3rd Dose

- Herishanu Blood 2022 : patients with CLL/SLL who failed to respond to 2 BNT162b2 doses, close to a quarter responded to the third dose of vaccine.
    - 172 patients with CLL, the antibody response rate was 23.8% (extrapolated 55% response rate).
    - The median time from second to the third vaccine was 179 days (IQR, 175-187)
    - independent variables that were associated with response included:
        - lack of active therapy (OR = 5.6, 95% CI 2.3-13.8; *P* < .001)
        - serum immunoglobulin A levels ≥80 mg/dL (OR = 5.8, 95% CI 2.1-15.9; *P* < .001).
        - In patients with CLL/SLL who failed to achieve a humoral response after standard 2-dose BNT162b2 mRNA vaccination regimen, close to a quarter responded to the third dose of vaccine.
        - The antibody response rates were lower during active treatment and in patients with a recent exposure (<12 months prior to vaccination) to anti-CD20 therapy.
    - Antibody-mediated responses were lower during active treatment and after exposure to anti-CD20 therapy.



Update CLL 3rd Dose

- Galitza (Vaccines 20292 in 42 CLL patients assessment of antibody response after the 2nd and the 3rd dose.
  - 3 doses BNT162b2
  - Immunogenicity of the BNT1162b2 mRNA vaccines
  - After the second dose of vaccine, 13 patients (30%) showed an antibody response.
    - The presence of hypogammaglobulinemia, steroids or IVIG were factors associated with poor response.
    - Factors associated with a poor response after the third dose were the presence of anemia (p = 0.031), a history of infection before the vaccine (p = 0.014), and the last administration of anti-CD20 MoAb less than 12 months before the vaccination (p = 0.044).
  - After the third dose, 5/27 (18%) non-responders to the second dose showed an antibody response whuke,
  - only 1 patient (4%) showed an elicitation of the immune response by the third dose, with no significant difference
- Re Nat Comm 2022: HM patients
  - CLL 13 patients (9 of 9) and 8 of 8 NHL of non-responders to 2 doses did not respond to a third dose
  - D3 increases INF-g in whole cohort and in fraction of seroneg.
    - 5/13 patients (38.5%) without anti-S Abs had a positive Quantiferon assay before dose 3.
    - 8/13 (61.5%) patients with a positive Quantiferon assay after the booster dose leaving
    - double-negative population of five out of 22 patients (22.7%) without neither a T-cell response nor measurable anti-S Abs.

Myeloma and other plasma cell dyscrasias

Update summary of the data about Covid vaccination in MM and other plasma cell dyscrasia

- Several studies confirmed a response rate to the initial vaccine regimen (2 doses of mRNA vaccine (more frequent regimen) or 1 dose of ChAdOx1) between 73-95% for anti-S Abs (with lower titers than healthy individuals), but only 46-71% for neutralizing (n)Abs *(Enssle Blood 2022; Nooka JCO 2022; Terpos Blood Cancer 2021)* and 34-61% for T-cell response *(Ramasamy BJH 2022; Enssle Blood 2022).* There was no correlation between Ab and T-cell response *(Enssle Blood 2022; Marasco BJH 2021)*

- Several studies confirmed the negative impact of older age, lymphopenia, hypogammaglobulinemia, active disease, active treatment, number of lines of treatment, antiCD38 and mainly anti-BCMA drugs on the humoral and cellular response to Covid vaccination *(Ghandili. J Clin Med 2021; Lockmer Am J Hematol 2021; Avivi BJH 2021; Schiller-Salton, Am J Hematol 2021; Shah Clin Lymph Myel Leuk 2022; Ramasamy BJH 2022; Nooka JCO 2022; Marchesi BJH 2022; Ramasamy BJH 2022; Terao BJH 2022)*

- One study suggested that despite the negative effect of antiCD38 drugs on the initial vaccine response, these drugs could favor a late Ab response *(Terao BJH 2022)*

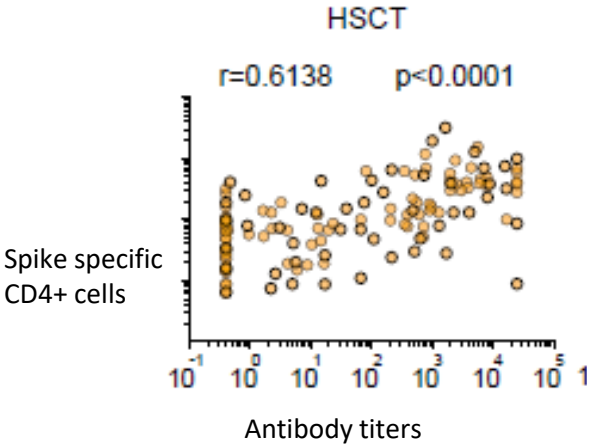
Update summary of the data about Covid vaccination in MM and other plasma cell dyscrasia

- Lenalidomide maintenance does not affect the Ab response *(Enssle Blood 2022)*
- Several studies *(Thompson J Patient Cent Res Rev 2022; Wu Lab Med 2022; Nooka JCO 2022)* and one metaanalysis *(Noori Int Immunopharm 2022)* showed a better response to the mRNA-1273 than to the BNT162b2 vaccine, possibly due to the higher dose of antigen in the mRNA-1273 vaccine
- Vaccine humoral response of patients with MGUS and smoldering MM is close to the one of healthy individuals of the same age range *(Abella Life Sci Alliance; Avivi BJH 2021; Wu Lab Med 2022)*

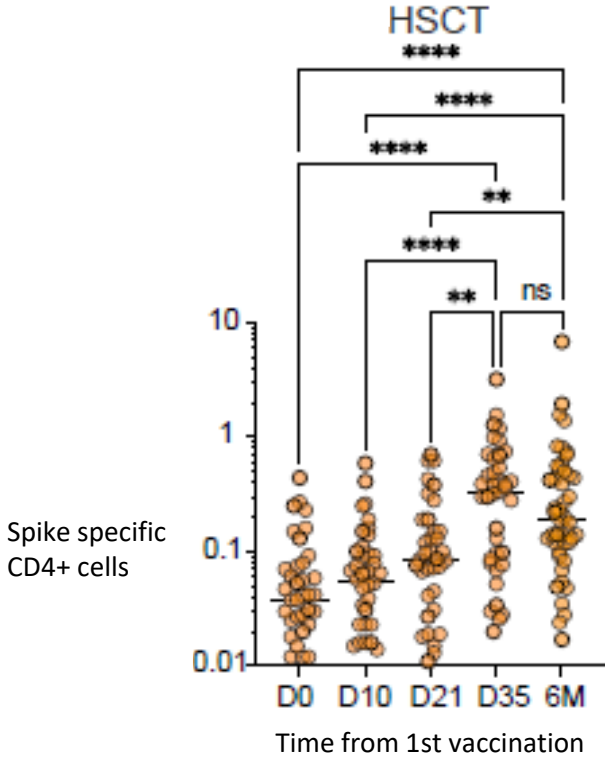
Efficacy and safety data of Covid-19 vaccines in HSCT recipients

T cell responses after allo HCT

- Although the protective properties of T cell responses against COVID-19 remain to be proven in immunocompromised patients, several studies have shown that repeated vaccine doses are able to induce such at least in subgroups of allo HCT patients. (Harrington et al; Cancer Cell 2021; Lindemann et al, Vaccines 2021, Clémenceau et al, Vaccines 2022, Einarsdottir et al Blood Advances 2021, Buggert et al, Immunity 2022)
- However, there is a strong correlation between antibody and T cell responses (Einarsdottir et al Blood Advances 2021, Buggert et al, Immunity 2022)



- Responses can be retained up to 6 months after first vaccination (Buggert et al; Immunity 2022)



Impact of anti-CD20 on COVID-19 Vaccination in Hematological Malignancy Patients.

- Hematological Malignancy Patients (Jimenez Blood Advances 2022, Ehmsen Cancer Cell 2022)
  - Methods: mRNA 2doses 28d
  - Humoral response lymphoid malignancies and MM 67%
    - Lymphoma patients: 52.7-67%.
    - Predictor of non-response
      - current or treatment during the last 6 months
      - Therapy with anti-CD20 monoclonal antibodies during the last 6 months
  - Allo-SCT population 80.6% (50 of 62).
    - only ex vivo CD34 selection associated with a lower humoral immunogenicity
  - Cellular Response
    - Lymphoid malignancies:
      - Lymphoma: 34-75% (54 of 72), MM 49-87.3% (48 of 55) CLL 46-83% (39 of 47)
      - treatment with anti-CD20 therapy 71.1% (27 of 38)
      - Treatment anti-CD20 + Chemotherapy: 50% (9 of 18).
    - Allo-SCT 72.9% (43 of 59).
      - 10 (62.5%) of 16 cellular nonresponders on treatment with immunosuppressive drugs for GVHD.

Efficacy and safety data of a 3rd dose of Covid vaccine in non-transplanted hematology patients

- A 3rd dose of vaccine significantly increases the anti-S Ab and the Nab titers, and the T-cell response even in poor responders to 2 doses *(Aleman Cancer cell 2022; Greenberger Cancer cell 2021; Lee BJM 2021; Mai Eur J Cancer 2022; Fendler Cancer cell 2022)*
- The response rate to dose 3 is between 30-53% in non-responders (*seroconversion)* to dose 2, and between 75-90% in responders (*seroelevation*) to dose 2, although the Ab titers are lower than in healthy individuals *(Mai Eur J Cancer 2022; Reimann BJH 2021; Re Research Square 2022).* Overall, two thirds of HM patients benefit from dose 3.
- The response to dose 3 is associated by previous response to dose 2, age, type of underlying disease (better in MM than in CLL), interval between dose 2/dose 3 (better response if longer interval), antiCD20 Abs within the last 12 months, and anti-CD38 or anti-BCMA drugs *(Fendler Cancer cell 2022; Thompson J Patient Cent Res Rev 2022; Re Research Square 2021; Greenberger Cancer cell 2021; Aleman Cancer cell 2022; Enssle Cancer cell 2022)*
- As for the healthy population, the response to VOC in HM pts is sub-optimal when compared to the response to WT *(Fendler Cancer cell 2022; Enssle Cancer cell 2022)*

Efficacy and safety data of a 4th dose of Covid vaccine in non-transplanted hematology patients

- A dose 4 administered > 3 months after dose 3 is safe in immunocompromised patients *(Hause MMWR 2022)* and increases the anti-S and nAb titers in HM patients with Ab titers close to the ones or higher than observed early after dose 3 *(Ntanasis-Stamopoulos Hemasphere 2022; Ehmsen Cancer cell August 2022)*
- The response to dose 4 was poor in MM patients treated with anti-BCMA *(Ntanasis-Stamopoulos Hemasphere 2022)* and in LPD patients treated with antiCD20 or BTK-inhibitors *(Ehmsen Cancer cell 2022)*
- In a series including 256 HM pts (101 MM and 118 CLL), the rate of seronegative HM patients decreased from after dose 2 (43%) to after dose 3 (24%) to after dose 4 (13%) *(Ehmsen Cancer cell August 2022)*
- As the kinetics of Ab waning after dose 3 is influenced by the underlying disease and/or the ongoing treatment, the time between dose 3 and dose 4 should be individually adapted by assessing anti-S IgG titers regularly after dose 3, especially in patients with an expected low response *(Ehmsen Cancer cell April 2022)* in order to optimize the timing of dose 4

Breakthroughs after vaccination – allo HCT

- Chaekal et al (Transplant Cell Ther 2022) reported 1 case of delta variant and 8 of omicron. None of the cases were severe. One hospitalized. Five of 8 were treated.
- Ljungman et al (EBMT 2022; manuscript) reported 24 patients infected prior to omicron. 14 incomplete vaccinated (< 14 days post dose 2) and 10 with complete 2 dose schedule. 3 deaths; 1 completely vaccinated
- Beerlage et al (Transplant Infect Dis 2022) reported 1 patient after 1st dose and 2 patients after 2nd dose of whom 1 had a severe disease and needed treatment
- Maillard et al (Blood 2022) reported 4 breakthrough cases; 1 severe infection requiring hospitalization

Comments on revised guidelines

You can send your comments about the Vaccination group revised guidelines before Octobre 31st to the group leader:

- Per Ljungman: per.ljungman@ki.se