# 10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

**CMV Final slide set**
**Post meeting**

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# CMV recommendations ECIL-10 final

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# When to determine CMV status?

- Routine is to do it closely prior to an allogeneic HCT.

- This results in a risk especially for overestimation of CMV seropositivity but also for seronegativity.

# Recommendations for CMV pre-transplant evaluation

- CMV serology in allogeneic HCT candidates should be preferably be done at 2 times:
  - a) At diagnosis of an underlying disease, which might be an indication for an allogeneic HCT and before any blood transfusion is administered (AIIu).
  - If there is no CMV serology result available at the time of diagnosis, any available stored pre-transfusion samples should be tested if possible (BII).
  - b) Before HCT, close to the transplant (AIIu).
- Pre-HCT CMV PCR is recommended (BIIu).
- Clinical judgement has to be used to decide whether to administer anti-CMV prophylaxis in patients with unclear CMV status. These patients need to be monitored as CMV seropositive patients (BII).

# CMV status definitions

## Pre-HCT CMV positive status is defined as:

- Patients with positive pre-transfusion serology at diagnosis of the underlying disease.
- A patient who, prior to HCT, had a positive CMV PCR in blood (or other CMV test like pp65 antigenemia) or from another site including patients with probable or proven CMV disease.
- Patients without a pre-transfusion sample who are seropositive in the pre-HCT sample (as defined by the locally used assay).

## Pre-HCT CMV negative status is defined as:

- Any patient that both pre-transfusion (if applicable) and pre-HCT were CMV seronegative and had no CMV detected by a CMV test before HCT.

## Pre-HCT CMV unclear status is defined as:

- Patients CMV-seronegative at diagnosis of the hematologic disorder but who have CMV indeterminate serology in the pre-HCT evaluation (as defined by the locally used assay).
- Patients without a pre-transfusion serology but who have a CMV indeterminate serology in the pre-HCT sample.

# Recommendations for testing/quantifying cytomegalovirus-DNA loads in plasma and whole blood (screening and monitoring)

- CMV D+R+/D-/R+ and D+/R- allogeneic HCT recipients should be monitored for CMV DNA load in plasma or whole blood by QNAT (AII).

- Monitoring for CMV-DNAemia is recommended for allogeneic HCT recipients receiving letermovir prophylaxis, since failure and need for initiation of antiviral treatment may occur in 10% - 30% of allogeneic HCT (AI).

- Less frequent monitoring-can be considered especially in CMV D-/R- allogeneic HCT recipients undergoing low or standard risk HCT since the risk of primary infection and the incidence of end-organ disease are low if the administration of CMV-safe blood products can be assured (CII).

# Recommendations for testing/quantifying cytomegalovirus-DNA loads in plasma and whole blood (screening and monitoring)

- Monitoring of CMV-DNAemia should be done once at least once weekly for the first 100 days after the transplant (AIIu).

- Extended monitoring for CMV-DNAemia is recommended at least another 3 months in higher-risk patients such as those having undergone mismatched, cord blood, or haploidentical HCT, patients on steroids, ongoing GvHD, and patients with prior episodes of CMV DNAemia (BII).

- Monitoring should be extended in patients with chronic GvHD requiring more intensive systemic immunosuppression, or in those displaying persistent immunodeficiency according to the perceived clinical risk for CMV reactivation and disease (BII).

# Recommendations for testing/quantifying cytomegalovirus-DNA loads in plasma and whole blood (screening and monitoring)

- Monitoring of CMV-DNA load for a given patient should be performed using the same specimen type (plasma or whole blood) and QNAT platform (AIItu).

- CMV-DNA load values for initiating preemptive antiviral therapy should take into account the QNAT platform used, the matrix chosen for CMV-DNA quantification, the associated risk of CMV-disease, and the presence or absence of antiviral prophylaxis (AIIu).

- Significant changes in CMV-DNA load in plasma or whole blood (> 0.5 log10) can assist in making decisions as to when initiate preemptive antiviral treatment (BIIt).

# Recommendations for CMV immune monitoring

- Sequential monitoring of IFN-γ-producing CMV-specific T cells may provide potentially useful information for the management of CMV infection after allo-HCT, that may be used to personalize PET (CIIt).

- The main applications of these assays may include extending or shortening the duration of primary LMV prophylaxis (IIt), withholding therapy for low level viral loads (CII), and to identify patients that may benefit from secondary LMV prophylaxis (CII).

- For future non-interventional or randomized studies assessing the clinical value of monitoring IFN-γ-producing CMV-specific T-cell responses in the management of CMV infection, the use of commercially-available CMV IGRA that were investigated in clinical settings are preferable over laboratory-developed flow cytometry-based immunoassays (CII).

# Prophylaxis in adults; recommendations - 1

- Letermovir is recommended as the strategy of choice for preventing CMV for CMV primary prophylaxis for CMV seropositive adult allo-HCT recipients (AI).
- It is recommended to start as early after allo-HCT as feasible to reduce the risk of early reactivations (BII) but no later than day 28 post-transplantation (AI) Prophylaxis should be continued through at least 100 days post-HCT(AI).
- Extended prophylaxis should be considered in patients at high risk for CMV disease and can continue to at least 200 days after transplantation (BI).
- For some individuals, prophylaxis for longer than 200 days after transplantation can be considered if in the treating physician's judgment, the benefit is stronger than the risk (CII).
- Drug-drug interactions should be considered when giving letermovir prophylaxis (BIIt).

# Prophylaxis in adults; recommendations - 2

- If letermovir prophylaxis is not used as primary prophylaxis for CMV seropositive allo-HCT recipients:
  - Monitoring CMV and use of PET is recommended (AI).
  - Prophylactic valaciclovir could be used (CI).
  - The use of valganciclovir, ganciclovir, iv Ig, or foscarnet as prophylaxis is generally not recommended. (DII).
- There is no controlled data to support primary letermovir prophylaxis in patients with CMV-negative status. regardless of the donor serostatus and it is not recommended (DII).
- So called letermovir blips (single test low level DNA positivity in plasma or whole blood samples occurring especially early during letermovir prophylaxis) are common and it is not recommended to interrupt letermovir prophylaxis unless there are repeated positive samples showing increased viral load (BII).

# Prophylaxis in adults; recommendations – 3

- No recommendation can be given regarding which viral load cut-off should be used to switch to preemptive therapy.

- After discontinuation of prophylaxis, “secondary” prophylaxis with letermovir can be considered in the following situations:
  - After successful treatment (neg qNAT test) of a CMV reactivation (BII) in patients perceived to be at increased risk for CMV disease.
  - In patients, who for some reason has not received primary prophylaxis and who have reactivated CMV that has been successfully treated (BII).

- Letermovir is not indicated for treatment of CMV reactivations or disease due to the high risk for resistance development and possible underdosing since a treatment dose has not been determined (DII).

# First line preemptive therapy

- Preemptive antiviral therapy based on detection of CMV nucleic acid (or antigen) is effective for prevention of CMV disease (AI).
- Either IV ganciclovir or foscarnet can be used for first line preemptive therapy (AI)
- Valganciclovir can be used in place of IV ganciclovir or foscarnet (except in patients with severe GI GVHD); (AII).
- Maribavir can be considered in patients with neutropenia or renal function impairment not appropriate for therapy with valganciclovir (BI) or foscarnet (BII).
- The choice of drug depends on time after HSCT, risk of toxicity, and previous antiviral drug exposure but is not influenced whether a patient has received letermovir prophylaxis (BII).

# Resistance to antiviral drugs during prophylaxis and 1st line preemptive therapy

- Resistance during primary letermovir prophylaxis in HCT recipients is uncommon. Since it is important to detect mutations that may prevent further use of the drug. Genotyping for resistance, if available, could be performed when preemptive therapy is started due to increasing CMV DNA viral load, (BII).

- In case of refractory infections, treatment should be adjusted without waiting for genotyping results (AII).

# Treatment of CMV disease in adults

- No change from ECIL-7 with the exception of maribavir being an alternative for resistant/refractory CMV disease (please, see later in the presentation).

# Pediatric recommendations 1 - prophylaxis

- Letermovir could be used as primary prophylaxis in seropositive recipients of allo-HCT (BIIa provisional).
- Letermovir dosage for pediatric patients ≥ 12 years old and weighing ≥ 35kg should be similar to adults since the exposure is comparable (BIIu). No published data are available on letermovir dosage for children < 12 years old.
- Timing for letermovir use should be similar to the adult HCT setting, as no specific drug-related adverse event/pediatric safety concern has been reported (AIIu).

# Pediatric recommendations 2 - prophylaxis

- Letermovir should be started as in adult setting as early after HCT as feasible to reduce the risk of early reactivations, and no later than 28 days after transplant. The duration of prophylaxis should be at least 14 weeks (AIItu).
- Extended prophylaxis could be considered in pediatric patients at high risk for CMV disease if, in the treating physician's judgement, the benefit is stronger than the risk (CIII). Drug-drug interactions should be considered when giving letermovir prophylaxis (CIIt).
- There is no controlled data to support primary letermovir prophylaxis in CMV-seronegative patients regardless of the donor serostatus and it is not recommended (DIII).

# Prophylaxis of CMV in Pediatric allo-HCT: recommendations

| Drug | Grading | References | Study | Comment |
|---|---|---|---|---|
| Letermovir | BIIa (provisional) | Schulte et al, IDWeek 2023<br>Groll et al., PIDJ 2024 | Children (Phase 2b study) | |
| Valaciclovir | CIIt | Ljungman, Blood 2002 | Children >13 y | Association with preemptive strategy; marrow toxicity |
| Ganciclovir | CIIt | Burns et al, BMT, 2002 | Adults+children | |
| Aciclovir | CII | Burns et al, BMT, 2002 | Adults+children | Less efficient than valaciclovir |
| Foscarnet | DIIt | | No pediatric data | |
| Ivlg | DIII | | No pediatric data | |



Based on: Ljungman et al. LID, 2019

# Pediatric recommendations -3

- Close clinical monitoring for CMV DNAemia with preemptive therapy still remains necessary to detect CMV reactivation (AI).
- Transient self-limiting CMV DNAemia (blips) could be occasionally detected and usually does not represent a reason to drug discontinuation unless there are repeated samples of increasing viral load (CII).
- No recommendation can be given regarding which viral load cut-off should be used to switch to preemptive therapy.
- “Secondary” prophylaxis can be considered in high-risk patients, who did not receive primary prophylaxis and who have reactivated CMV that has been successfully treated (CIII). There are no data available on duration of secondary prophylaxis

# Pediatric recommendations-4 – 1st line treatment (unchanged from ECIL-7)

- Preemptive antiviral therapy based on detection of CMV DNAemia is effective for prevention of CMV disease (AIIu).
- Either iv ganciclovir or foscarnet can be used for first line preemptive therapy (AIIu).
- Valganciclovir can be used in place of iv ganciclovir or foscarnet (except in patients with severe GI GVHD) (AIIu).
- The combination foscarnet + ganciclovir is not recommended (DIII).
- The choice of drug depends on time after HSCT, risk of toxicity, and previous antiviral drug exposure.



Ljungman et al. LID, 2019

# Pediatric recommendations- 5
# Second/third line treatment

- Maribavir can be used for second/third line preemptive therapy for pediatric patients ≥12 years old with a BW of >35 kg* (BIIt). Maribavir is not recommended when encephalitis, meningitis, or retinitis is of concern, since it has poor penetration into the eye and central nervous system (DIIt).
- Letermovir is not indicated for treatment of CMV reactivations or disease for different reasons including high risk for resistance development and underdosing since a treatment dose has not been determined (DIIt).
- Adoptive T-cell therapy could be considered in pediatric patients with post-HSCT refractory cytomegalovirus infection (CIIu).

* FDA approved label. EMA label >18 years.



Ljungman et al. LID, 2019

# Pediatric recommendations-6
# Second/third line treatment (continued; unchanged from ECIL7)

- The alternate drug of ganciclovir/valganciclovir or foscarnet can be considered for second line preemptive therapy (AII). Cidofovir can be considered for second/third line preemptive therapy (5 mg/kg/week) but careful monitoring of the renal function is required (BII).
- The combination of ganciclovir and foscarnet might be considered for second/third line pre-emptive therapy (CII).
- Reduce immunosuppression if possible (BIII).
- Addition of iv immune globulin for preemptive therapy is not recommended (DIII).

# Recommendations for refractory and resistant (R/R) CMV infection/disease - 1

- During salvage therapy, resistance to treatment is frequent and depending on host factors and drug characteristics. More than half of the non-responses (relapse while on therapy or recurrent while off therapy) are driven by emergence of new resistant virus whatever the drug administered.
- Genotyping should be performed in any case of non-response to allowing adjustment of further therapy (AII).
- Genotyping for resistance should include sequencing of all target genes by either Sanger or NGS methods although the emergence capacity of low-level mutants detected by NGS should be confirmed by repeated testing (BIIt).
- Repeated genotyping is recommended if the viral load does not improve within two weeks of appropriate therapy (BIII).
- Genotyping results should be combined with clinical interpretation to guide clinical decision (BIIt).

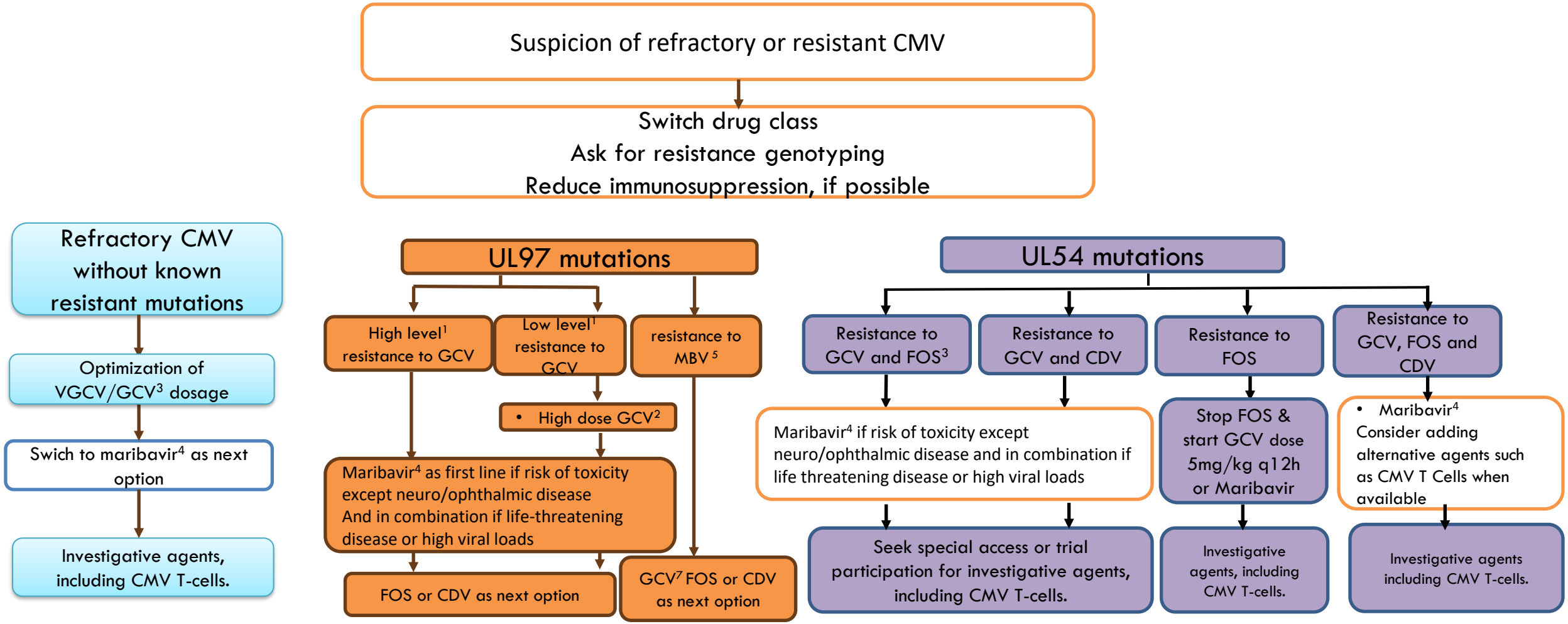
# Recommendations for R/R CMV infection/disease - 2

- Maribavir is effective for treatment of R/R CMV infection and disease and is associated with lower risk for side effects than the other alternatives (AI).
- Maribavir is not indicated for CMV disease involving the CNS and the eyes (DIIt).
- Relapses and recurrences are frequent during treatment of resistant/refractory infection due to commonly occurring resistance development especially in breakthrough infections (I).
- If resistance is suspected, it should be documented by genotyping (AII).
- Change of therapy is recommended before having results of resistance testing available (BII).

# Recommendations for R/R CMV infections/disease - 3

- Foscarnet is an alternative therapy for R/R CMV infections in particular in the CNS and eyes but is associated with significant toxicity (BII).
- Cidofovir is an option for treatment of CMV retinitis (BII).
- CMV-specific T-cells are an option for treatment of R/R CMV infection/disease, if available (BII).
- Letermovir is not indicated for preemptive therapy of CMV infection or treatment of CMV end-organ disease including R/R infections (DIII).
- Combination therapy for R/R CMV infections could be considered (BII). The combination of maribavir with val(ganciclovir) should not be used (DIIt).

# Refractory and resistant CMV algorithm




1. Low-level resistance to GCV : mutations that increase IC50 more than 2-fold and less than 5-fold. High level resistance is more than 5-fold
2. High dose GCV- 7.5mg-10mg/kg q12h as tolerated if CMV disease not present.
3. GCV: Ganciclovir, VGCV: Valganciclovir, FOS: Foscarnet, CID: cidofovir, MBV: Maribavir
4. Maribavir : check for preexisting resistance mutations by resistance genotyping
5. If given as first line treatment
6. Alternative agents: leflunomid or artesunate, donor lymphocytes (under evaluation or other CMV-activated T-cells…)
7. Check for infrequent but possible cross-resistance

# CMV in CAR-T patients: Recommendations - 1

- CMV monitoring is only required in patients being CMV-seropositive before CAR-T (AIIu).
- In CMV-seropositive patients, a viral load determination should be performed before start of lymphodepletion. If the tests show evidence of CMV replication, close monitoring is recommended (BIIu).
- Risk factors for CMV reactivation after CAR-T cell therapy are CRS grade 3-4, receiving corticosteroids >3 days, persistent lymphocytopenia < 200/µl or receiving ≥2 immunosuppressants. Such patients should be regarded as high-risk patients for CMV reactivation.

[1]Lin, R. et al., Blood Advances First Edition 6 June 2004
[2] de la Asunción, C., Clinical Microbiology and Infection 29 (2023)

# CMV in CAR-T patients: Recommendations- 2

- Active monitoring for CMV-DNA-emia testing should be considered between 2 and 6 weeks after cell infusion in high-risk CAR-T recipients (AIIu for high-risk; BIIu for others).
- Preemptive antiviral treatment could be considered in case of “high level”/rapidly increasing level of CMV-DNA-emia (BIIu).
- It is currently unclear whether CAR-T cells directed against different antigens have the same risk for CMV reactivation and therefore the same strategy should be employed (BIII).
- Letermovir prophylaxis is not recommended.

[1]Lin, R. et al., Blood Advances First Edition 6 June 2004
[2] de la Asunción, C., Clinical Microbiology and Infection 29 (2023)

# CMV in Patients receiving T cell engaging antibodies

- Currently there is lack of good data allowing risk assessment regarding CMV reactivation and CMV disease in this patient population. The recommendations should therefore be seen as provisional.
- CMV testing is only required in patients being CMV-seropositive before treatment with bispecific antibodies (AIIu).
- In CMV-seropositive patients, a viral load determination could be performed before start of therapy with bispecific antibodies (CIII).
- If the tests show evidence of CMV replication, close monitoring is recommended (BIIt).
- Risk factors for CMV reactivation after T cell engaging therapy are CRS grade ≥ 2, receiving corticosteroids >3 days, or patients receiving combination therapy with Anti-CD38 Abs, IMiDs and proteosome inhibitor and such patients should be regarded as high-risk patients for CMV reactivation.

# CMV in Patients receiving T cell engaging antibodies:

- It is currently unclear whether T cell engaging antibodies directed against different antigens have the same risk for CMV reactivation and therefore the same strategy should be employed
- Testing for CMV-DNA-emia could be considered in febrile patients who have received bispecific antibodies for > 4 weeks (BIII).
- Antiviral treatment could be considered in case of symptoms and “high level”/rapidly increasing level of CMV-DNA-emia (BIII).