Highlights from
IMS 20th meeting 2023

KATIA MANCUSO

Citopenie (ICAHT) e ipogammaglobulinemia

30-31 gennaio 2024
**BOLOGNA**, Royal Hotel Carlton

T-cell redirecting therapies related toxicities

- CRS, ICANS and HLH are **acute**, class-toxicity events

- Cytopenia, hypogammaglobulinemia, infections are **late-onset** complications

CAR T Cells

T-Cell Engagers

CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector-cell associated neurotoxicity syndrome
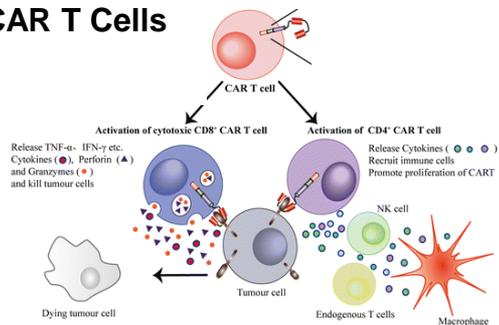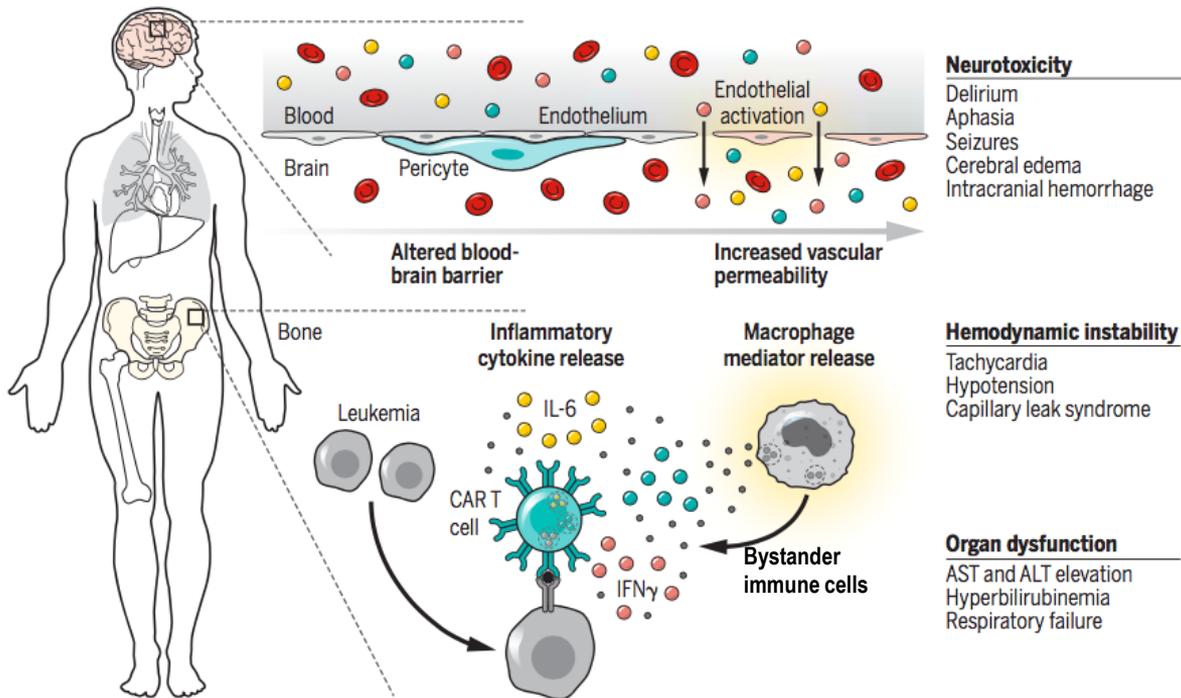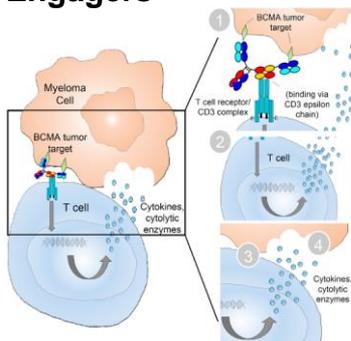
On-target/off tumor: patients treated with CD19/BCMA directed CAR T cells develop B cell aplasia and some degree of hypogammaglobulinemia

B-ALL patients[1]

DLBCL patients[2]

MM patients[3]
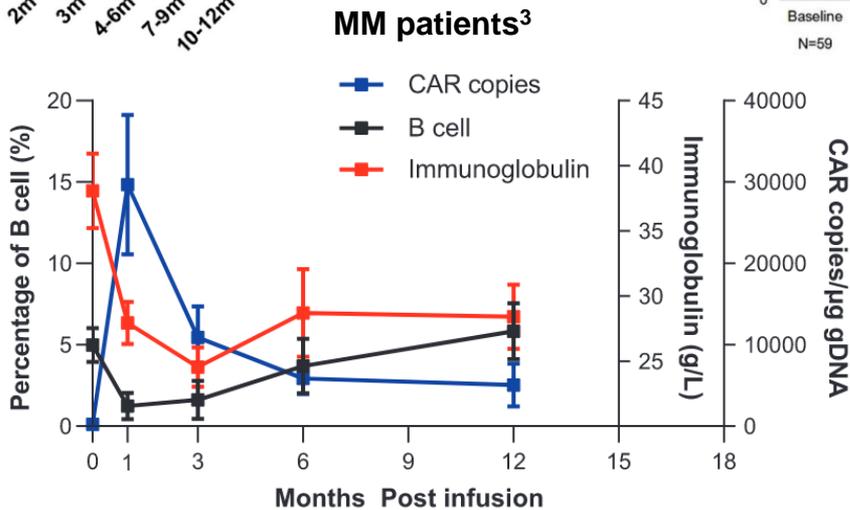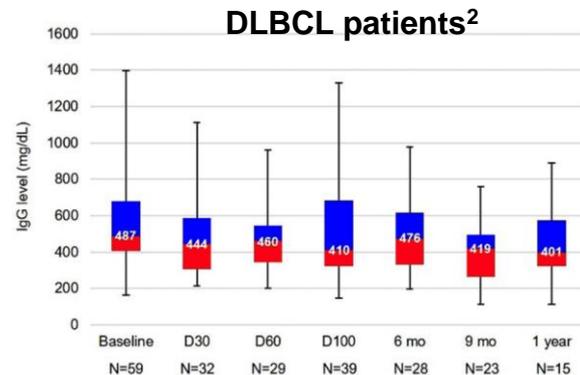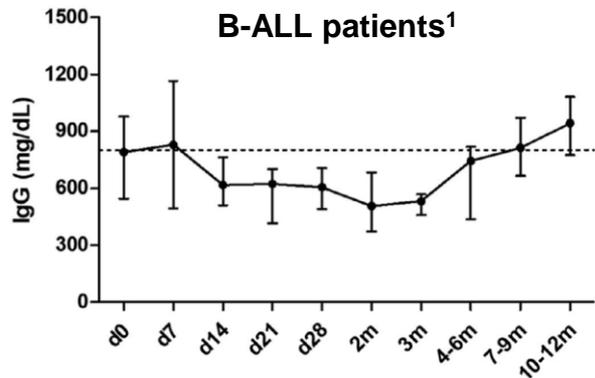
1. Wang Y et al. Int J Lab Hematol 2021
2. Wudhikarn K et al. Blood Cancer J 2020
3. Wang D et al. Blood Cancer J 2021

ICAHT: EHA/EBMT consensus grading and best practice recommendations

➤ Cytopenia following CAR–T was recently termed **I**mmune effector **C**ell-**A**ssociated **H**ematological **T**oxicity (ICAHT)

ICAHT grading	1	2	3	4
Early ICAHT (day 0-30)				
ANC ≤500/µL	<7 d	7-13 d	≥14 d	Never above 500/µL
ANC ≤100/µL	—	—	≥7 d	≥14 d
Late ICAHT (after day +30)*				
ANC	≤1500/µL	≤1000/µL	≤500/µL	≤100/µL

*Measured ≥2 time points, or nontransient neutropenia.

Clinical impact of severe ICAHT (≥3°)

A — Infection Grade by ICAHT Severity: Pooled Analysis

B — Bacterial Infection Grade by ICAHT Severity: Pooled Analysis

	Severe (≥3°) Infection Rate	Severe (≥3°) Bacterial Infection Rate	p
Severe ICAHT (≥3°)	61/125 (49%)	45/125 (36%)	Both
Absent or mild to moderate ICAHT (0-2°)	54/424 (13%)	36/424 (8%)	<0.0001

A — 1-yr Non-Relapse Mortality by ICAHT severity

Severe ICAHT (125)
Severe ICAHT absent (424)
logrank p < 0.0001

B — Causes of Non-Relapse Mortality

31 Deaths
Infection, CRS, ICANS, Accident, Cardiac, Deconditioning

Rejeski K et al. Blood 2023 Sep
Rejeski K et al. Hematology Am Soc Hematol Educ Program 2023 Dec
Rejeski K et al Blood Adv 2024 Jan

CYTOPENIA: SELECTED CLINICAL TRIALS

Drug	CAR-T							Bispecific antibodies			
	Idecabtagene vicleucel			Ciltacabtagene Autoleucel			MCARH109	Teclistamab	Elranatamab	Talquetamab 800 μg sc	Cevostamab
Study	KarMMa	KarMMa-3	RW SOC	CARTITUDE-1	CARTITUDE-4	RW SOC	NCT04555551	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	NCT03275103
Phase study	2	3	//	1B/2	3	//	1	1/2	2	1	1
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	BCMA/CD3	BCMA/CD3	GPRC5D/CD3	FcRH5/CD3
N. of patients	128	245	159	97	208	143	17	165	123	232	160
Neutropenia: All grade	91%	78%	N/A	96%	90%	N/A	100%	71%	49%	36%	18%
Neutropenia: G≥3	80%	76%	N/A	95%	90%	N/A	95%	64%	49%	32%	16%
Thrombo-cytopenia: All grade	63%	54%	N/A	79%	54%	N/A	88%	40%	40%	23%	10%
Thrombo-cytopenia: G≥3	52%	42%	N/A	60%	41%	N/A	65%	64%	24%	11%	6%
Anemia: All grade	70%	66%	N/A	81%	54%	N/A	88%	52%	49%	43%	40%
Anemia: G≥3	60%	51%	N/A	68%	36%	N/A	65%	37%	37%	23%	22%

Median time to recovery from grade ≥3 cytopenias after ide-cel (KarMMa) and cilta-cel (CARTITUDE-1) exposure was 1-4 months

Munshi et al., NEJM 2021; Rodriguez-Otero et. al, NJEM 2023; Hansen et al., JCO 2023; Berdeja et al., NEJM 2021; San Miguel et al., NJEM 2023; Hansen et al., JCO 2023; Mailankody et al., NJEM 2022; Moreau, NEJM 2022; Lesokhin et al., Nature Medicine 2023; Chari et al., NJEM 2022; Trudel et al., Abs 653 63rd ASH 2021

Etiologies of cytopenia post CAR T cell therapy
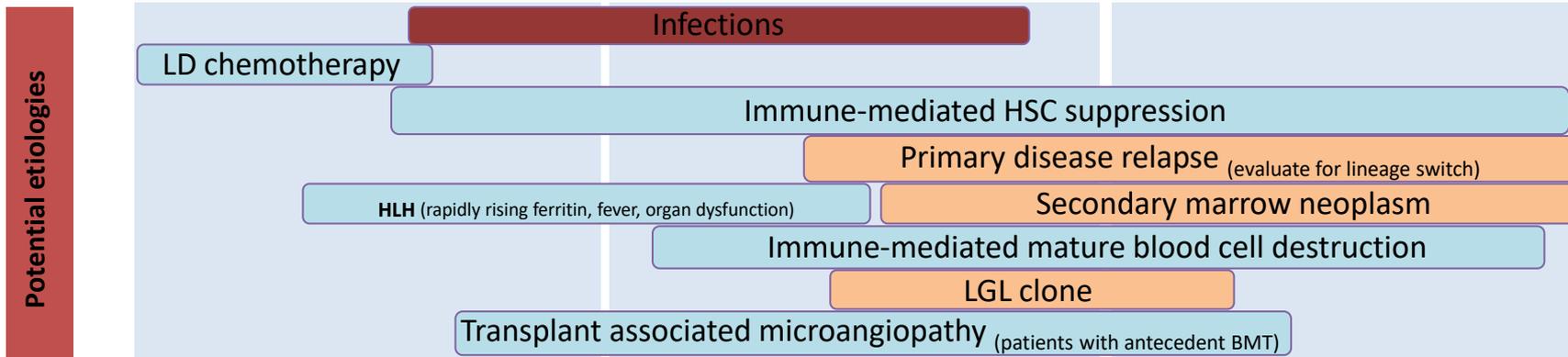
BMT, bone marrow transplant; HSC, hematopoietic stem cell; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome; LGL, large granular lymphocyte; TA-TMA, transplant-associated thrombotic microangiopathy.

Jain T, et al *Blood* 2023;141:2460-2469.

Characterization of prolonged cytopenia after CAR-T

90 RRMM patients after BCMA CAR-T

↓

78 patients evaluable at 4 months cutoff

ADEQUATE HEMATOLOGIC RECOVERY
N=56 (72%)

POOR HEMATOLOGIC RECOVERY
N=22 (28%)

**Anemia ≥3:**
4%
Neutropenia ≥3:
19%
Thrombocytopenia ≥3:
17%
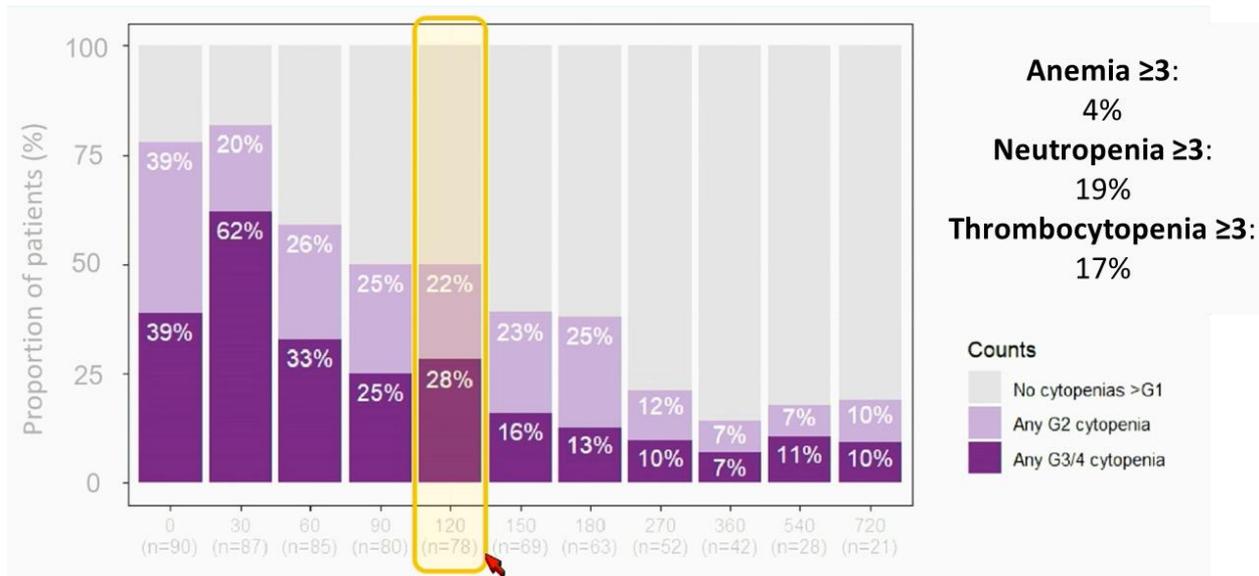
- Older age
- Higher number of prior lines therapy
- Prior of ≥1 ASCT is significantly correlated with poor hematologic recovery

ASCT, autologous stem cell transplantation

Reduced bone marrow reserve due to age and/or treatment-related toxicity may contribute to the decline of hematopoietic function by an unknown mechanism

Baseline parameter predicts long duration of grade ≥3 cytopenias after CAR T cell

- **58 RRMM** (median of 5 lines of therapy)
- 49 (84 %) patients received CAR T cell ide-cel

$R = -0.56, p = 4.3e-05$
baseline Hb = grade≥3 anemia

$R = -0.44, p = 0.0021$
baseline PLT = grade≥3 thrombocytopenia

$R = 0.47, p = 0.00076$
baseline ferritin = grade≥3 anemia

$R = 0.44, p = 0.0021$
baseline ferritin = grade≥3 thrombocytopenia
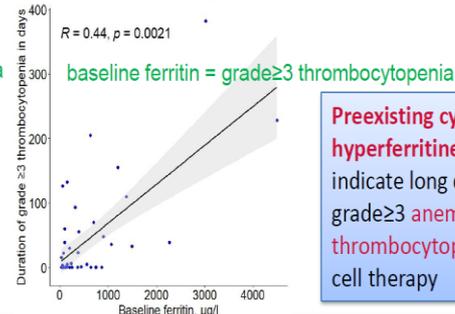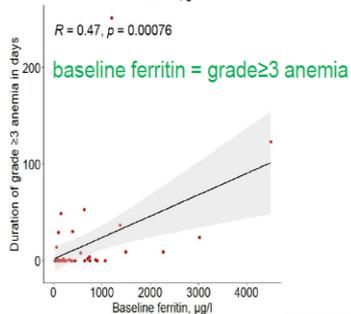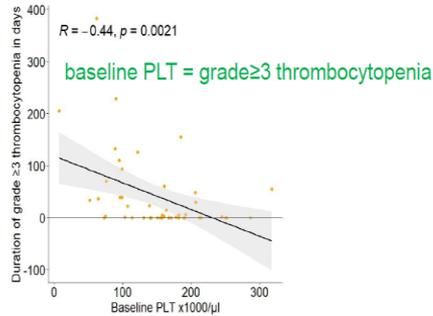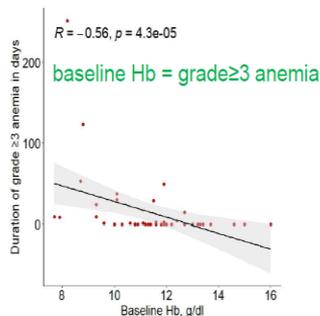
Preexisting cytopenias and **hyperferritinemia** at baseline indicate long duration of grade≥3 anemia and thrombocytopenia after CAR T-cell therapy

$R = -0.39, p = 0.01$
baseline CD4Tcm = grade≥3 anemia

$R = -0.39, p = 0.0095$
baseline CD4Tcm = grade≥3 thrombocytopenia
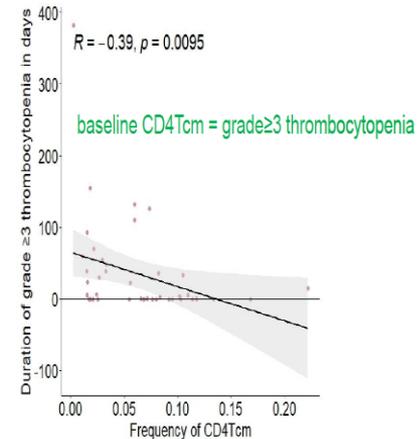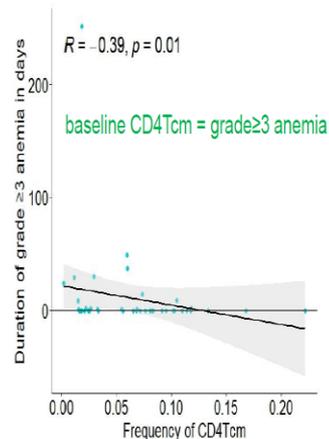
The **frequency of CD4Tcm** at baseline predicts long duration of grade ≥3 anemia and thrombocytopenia after CAR T-cell

Preexisting cytopenias, **hyperferritinemia** and **low frequency of CD 4 T cell memory** indicate long duration of grade 3 cytopenias after CAR T cell

Cellular Dynamics Following CAR T Cell Therapy Are Associated with Response, Resistance and CRS in RRMM

- **27 RRMM** patients treated with **Ide-cel**
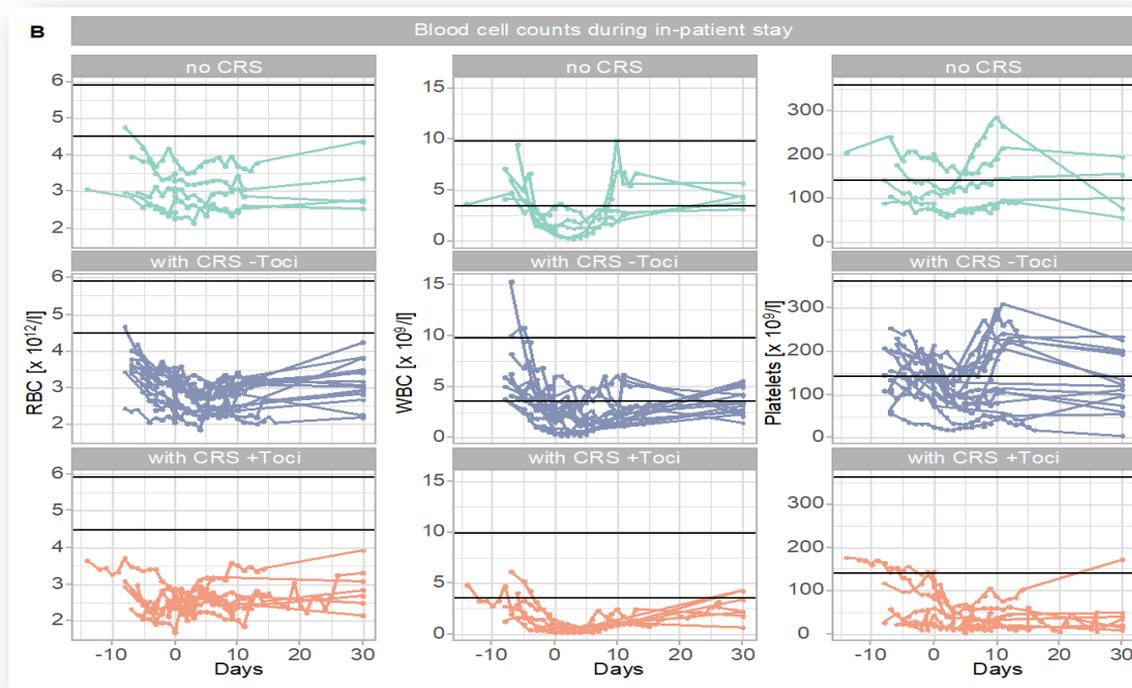
CRS and cytopenias are connected to each other

CAR-HEMATOTOX score as a prognostic model of <u>toxicity</u> and response in patients receiving BCMA-directed CAR-T

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

• Leniency time period for lab values: 3 days

| Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml

Low: 0-1   High: ≥2

Low risk (HT 0-1)

Risk profile

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

High risk (HT 2-7)

|	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

The CAR-HEMATOTOX score identifies patients at risk for severe hematotoxicity

Rejeski K et al. Hematology Am Soc Hematol Educ Program 2023 Dec
Rejeski et al. Journal of Hematology & Oncology (2023) 16:88

CAR-HEMATOTOX score as a prognostic model of toxicity and <u>response</u> in patients receiving BCMA-directed CAR-T

The CAR-HEMATOTOX score identifies patients at **risk for severe infectious** complications

The CAR-HEMATOTOX score identifies patients at risk for **poor treatment outcomes**
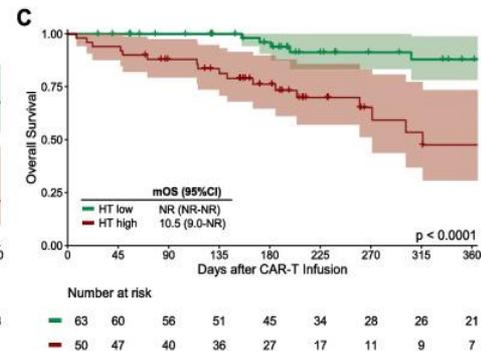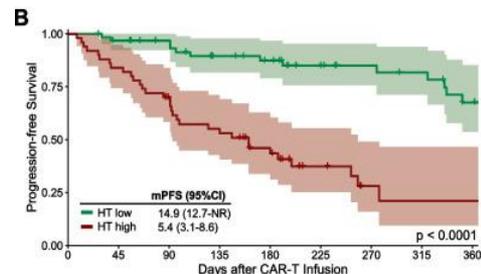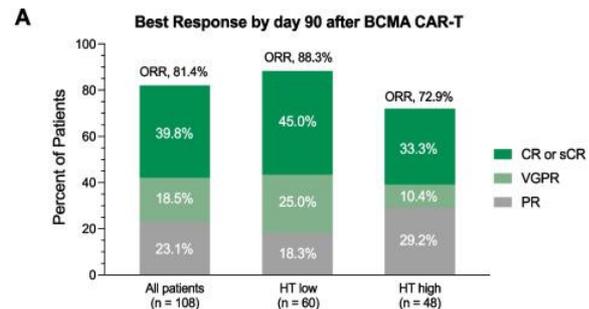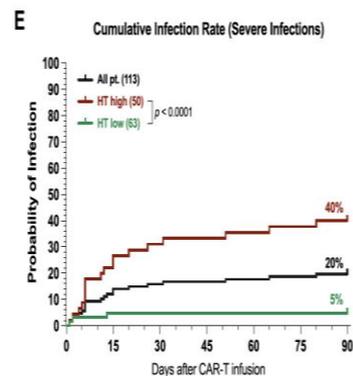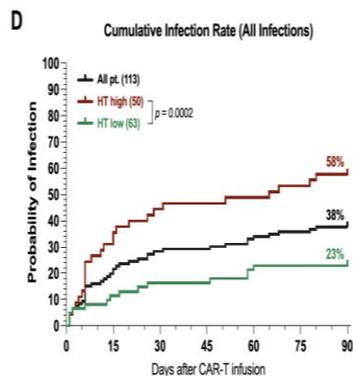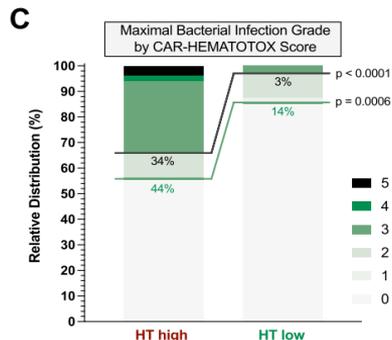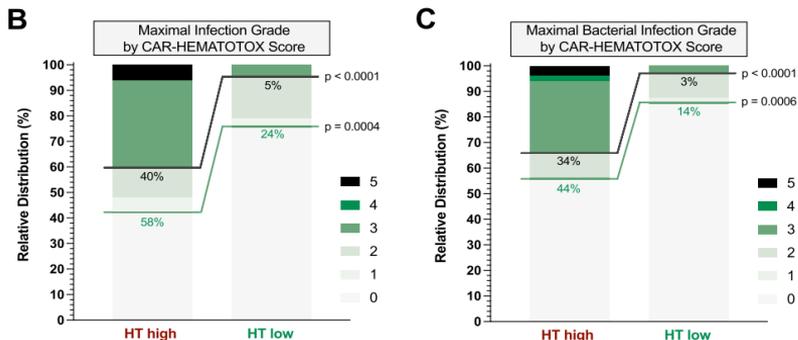
Recognizing, defining, and managing CAR-T hematologic toxicities

DIAGNOSTIC WORKUP

Diagnostic category	Included diagnostic tests	When to initiate	Additional comments
Basis workup (tier 1)	• Check medication list for myelotoxic co-medications • Rule out active infections: blood cultures, procalcitonin • Vitamin deficiency: B12, folic acid • Consider secondary HLH/MAS: serum ferritin	In case of severe neutropenia (ANC <500/μL) beyond day +7 after CAR-T infusion	Low threshold to perform (minimal workup)
Advanced workup in case of severe ICAHT (tier 2)	• Bone marrow aspiration and biopsy • Advanced viral studies (parvovirus B19, CMV)	Grade 3 or higher ICAHT beyond day +14	Especially in patients with underlying marrow infiltration
Clinical suspicion for therapy-related myeloid neoplasm	Immunohistochemistry, flow cytometry, cytogenetics; next-generation sequencing (myeloid panel)	In case of persistent bone marrow aplasia beyond 1 month; unclear and/or new-onset cytopenia; cytopenia refractory to therapeutic measures	t-MN after CAR-T therapy is an emerging field of study*

ANC, absolute neutrophil count; CMV, cytomegaly virus; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICAHT, immune effector cell-associated hematotoxicity; t-MN, therapy-related myeloid neoplasm.

*Incidence rate as high as 6% of t-MN after CAR T-cell infusion (see Gurney et al., EHA 2023; abstract number S263[87]).

Treatment algorithm for immune effector cell associated hematotoxicity
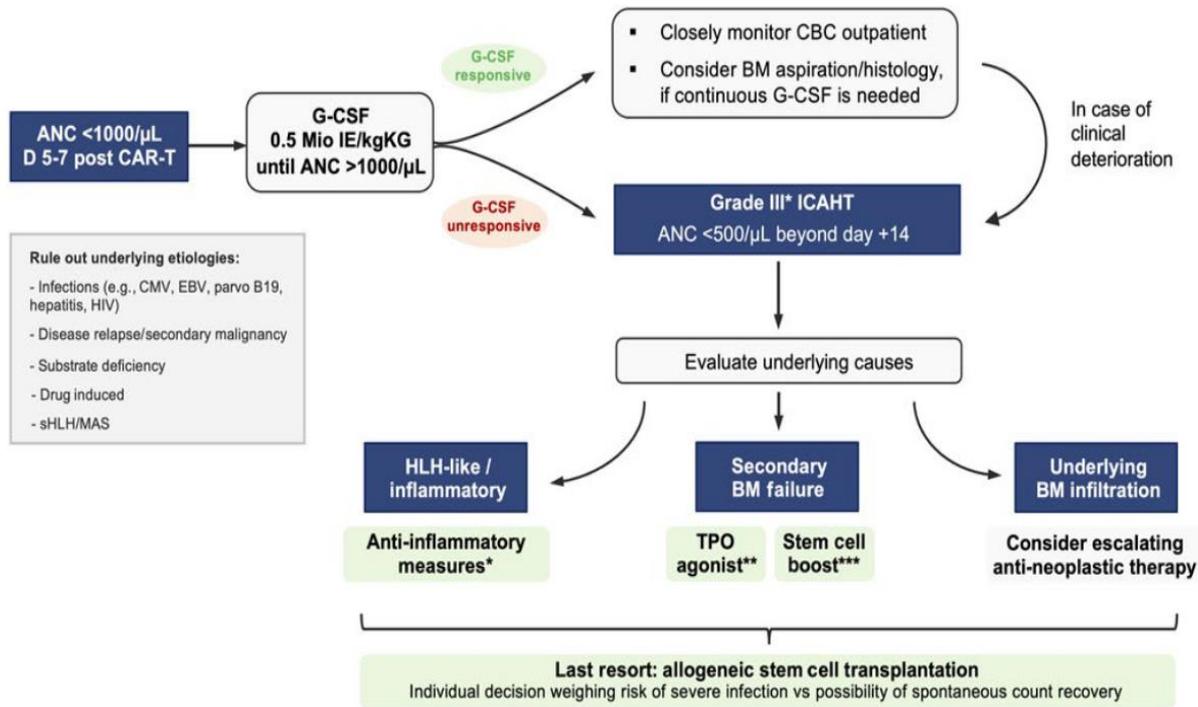
Figure 2. Treatment algorithm for immune effector cell associated hematotoxicity. *Consider dexamethasone-pulse (20 mg over 4 days) or anticytokine-therapy (e.g., anakinra or tocilizumab). **Consider eltrombopag (e.g., 50 mg×7 days). ***If available, contact apheresis unit.

Rejeski et al. Blood 2023
Galli et al. Bone marrow transplant 2020
Lievin et al. Bone marrow transplant 2022
Miller et al. Blood Cancer J 2022

Rejeski K et al. Hematology Am Soc Hematol Educ Program 2023 Dec

INFECTIONS and HYPOGAMMAGLOBULINEMIA: SELECTED CLINICAL TRIALS

Drug	CAR-T							Bispecific antibodies			
	Idecabtagene vicleucel			Ciltacabtagene Autoleucel			MCARH109	Teclistamab	Elranatamab	Talquetamab 800 µg sc	Cevostamab
Study	KarMMa	KarMMa-3	RW SOC	CARTITUDE-1	CARTITUDE-4	RW SOC	NCT04555551	MajesTEC-1	MagnetisMM-3	MonumenTAL-1	NCT03275103
Phase study	2	3	//	1B/2	3	//	1	1/2	2	1	1
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	BCMA/CD3	BCMA/CD3	GPRC5D/CD3	FcRH5/CD3
N. of patients	128	245	159	97	208	143	17	165	123	232	160
Infections: All grade	88%	58%	N/A	58%	62%	N/A	18%	76%	70%	34%	42.5%
Infections: G>3	22%	24%	N/A	20%	27%	N/A	12%	45%	40%	7%	19%
Hypogammaglobulinemia	21%	N/A	N/A	N/A	43%	N/A	N/A	75%	75%	71%	N/A

Munshi et al., NEJM 2021; Rodriguez-Otero et. al, NJEM 2023; Hansen et al., JCO 2023; Berdeja et al., NEJM 2021; San Miguel et al., NJEM 2023; Hansen et al., JCO 2023; Mailankody et al., NJEM 2022; Moreau, NEJM 2022; Lesokhin et al., Nature Medicine 2023; Chari et al., NJEM 2022; Trudel et al., Abs 653 63rd ASH 2021;

N/A: not available; G: grade; N: number

Hypogammaglobulinemia in retrospective studies of BCMA CAR T-cell therapy
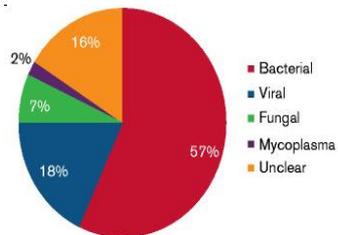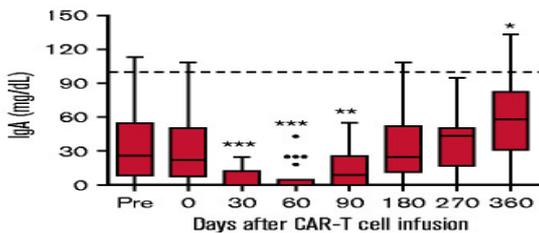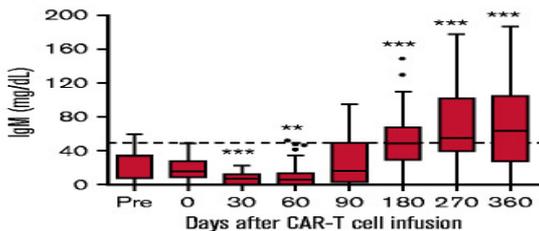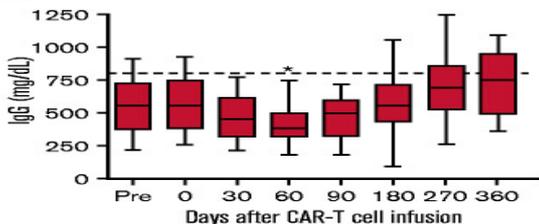
Infection microorganism
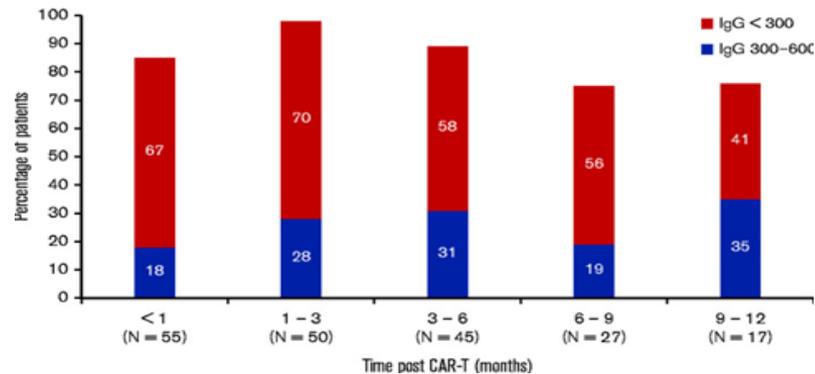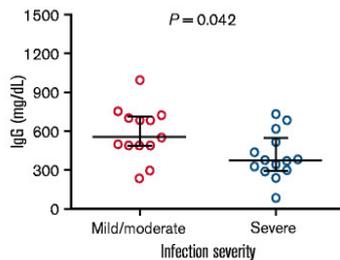
Supplemental Table 3. Severity of hypogammaglobulinemia at time of infections post CAR-T.

	IgG < 300	IgG 300-600	IgG > 600	Total (N= 47)
Infection (any severity), n (%)	28 (60)	9 (19)	10 (21)	47 (100)
Bacterial, n (%)	12 (26)	3 (6)	4 (9)	19 (40)
Viral, n (%)	14 (30)	6 (13)	5 (11)	25 (53)
Fungal, n (%)	2 (4)	0 (0)	1 (2)	3 (6)
Infection (low severity), n (%)	25 (53)	9 (19)	9 (19)	43 (91)
Bacterial, n (%)	10 (21)	3 (6)	3 (6)	16 (34)
Viral, n (%)	14 (30)	6 (13)	5 (11)	25 (53)
Fungal, n (%)	1 (2)	0 (0)	1 (2)	2 (4)
Infection (high severity), n (%)	3 (6)	0 (0)	1 (2)	4 (9)
Bacterial, n (%)	2 (4)	0 (0)	1 (2)	3 (6)
Viral, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Fungal, n (%)	1 (2)	0 (0)	0 (0)	1 (2)

Wang Y. et al. Blood Adv. 2021

Kambhampathi et al. Blood Advances 2022

Hypogammaglobulinemia in retrospective studies with BiTes
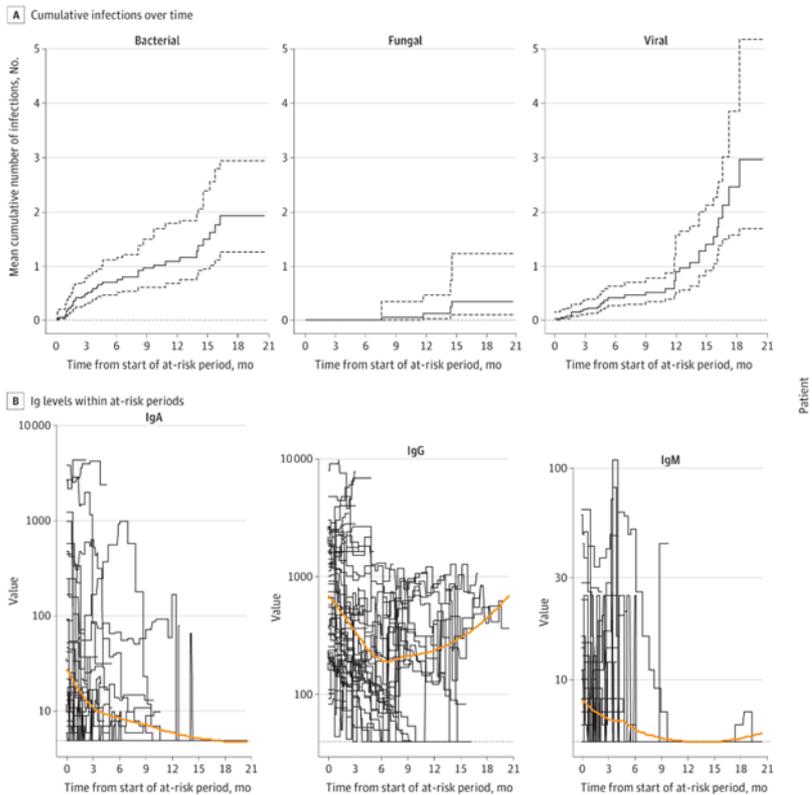
Lancman et al, Blood 2022
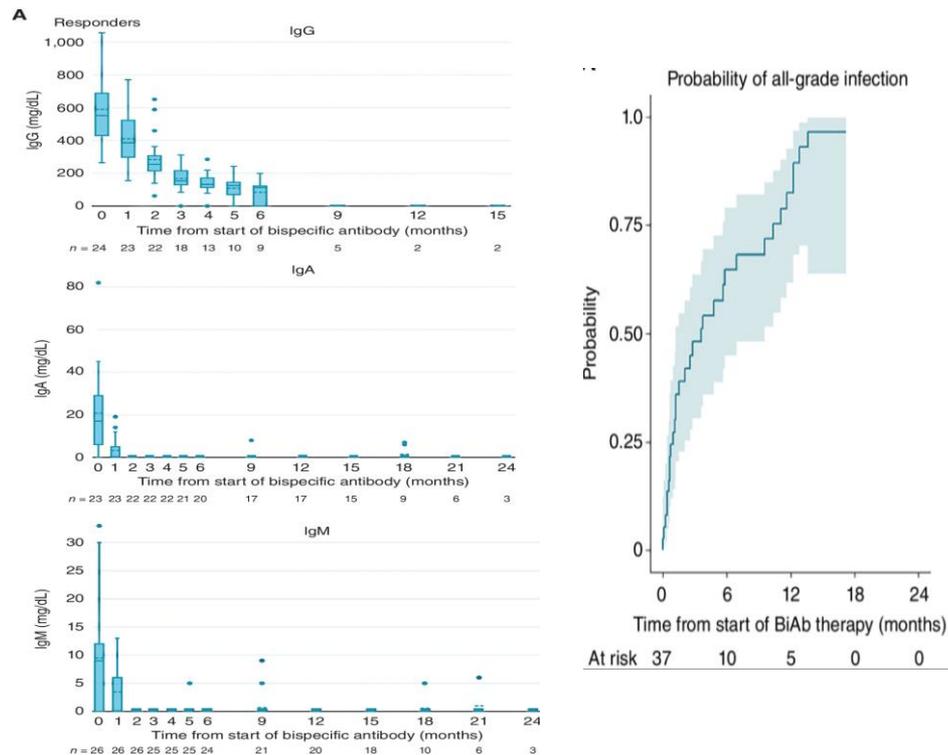
Hammons et al, JAMA Open 2022

Teclistamab impairs humoral immunity in patients with heavily pretreated myeloma: importance of immunoglobulin supplementation
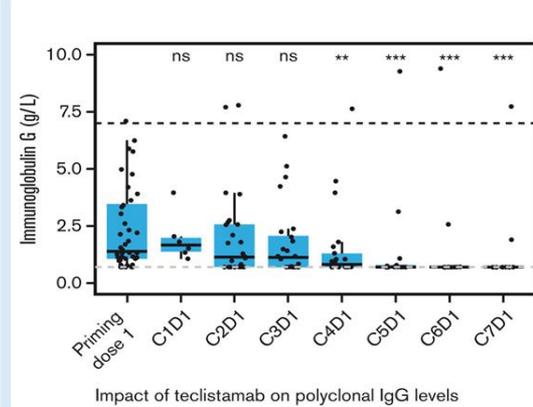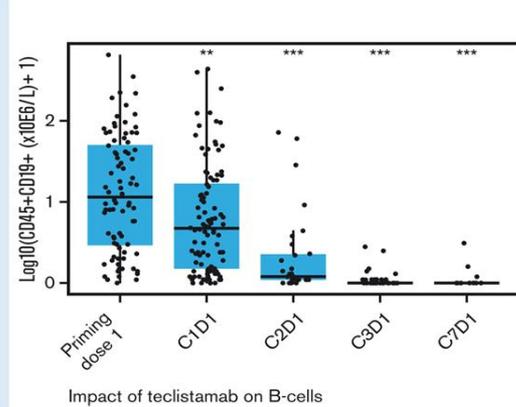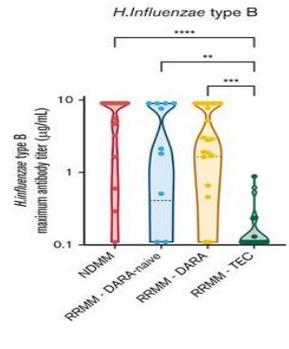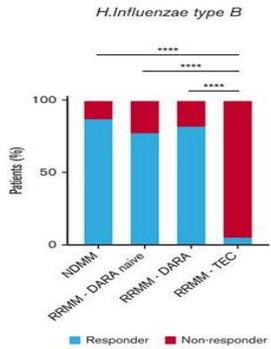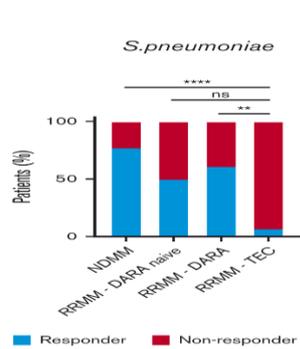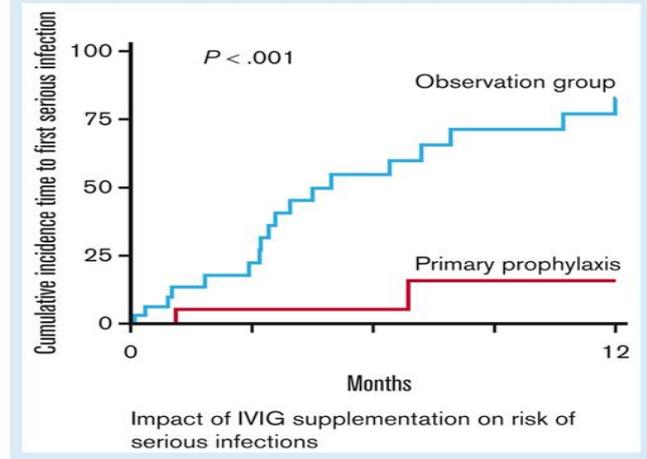
Hematologic toxicity and infections in MajesTEC-1

Any grade neutropenia
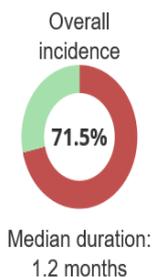
Grade 3/4 neutropenia

G-CSF use

Overall incidence

**71.5%**

Median duration: 1.2 months

Overall incidence

65.5%

Median duration: 0.8 months[a]

Median time to onset[a]

2.3 months

Prophylaxis and management

54.5%
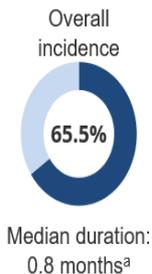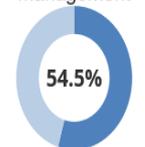
Growth factors should be considered for grade ≥3 neutropenia with infection/fever and grade 4 neutropenia

Where possible, growth factors should not be given during the teclistamab step-up dosing schedule or during CRS, because of the potential for increased CRS severity due to temporal myeloid cell stimulation[1-3]

Hypogammaglobulinemia

70.9% of patients had ≥1 IgG value <400 mg/dL

of patients received ≥1 dose of IgG replacement **46.1%**
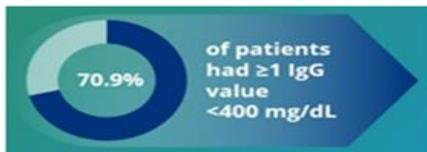
Infections occurred in 126 patients (76%; grade 3/4: 45%)

Appropriate use of IgG replacement is recommended during treatment[1-4]

✓ IgG replacement should be administered every 3–6 weeks to maintain serum IgG ≥400 mg/dL

✓ After reaching a steady state, IgG levels should be measured every 3 months[5]

✓ Administer IgG replacement per institutional guidelines:
- For life-threatening infections (especially due to encapsulated bacteria)
- For serious or recurrent/chronic infections
- Prophylactically based on physician-assessed clinical benefit

Van de Donk N, et al. Athens IMS 2023
Nooka et al. Cancer 2023 Nov

Clinical management of infection in T-cell redirecting therapies

Prophylaxis and management of infections

Bacterial infections

Prophylaxis
In patients with **high risk for infections** (eg, history of recurrent bacterial infections, prolonged neutropenia, or hypogammaglobinaemia): levofloxacin 250 mg twice a day or co-trimoxazole 800 mg/160 mg twice a day
In **patients with low IgG** (≤400 mg/dL) or history of recurrent bacterial infections intravenous IgG (400 mg/kg, every 2–4 weeks)

Treatment
Dependent on infectious agent, if identified **without neutropenia**: levofloxacin, amoxicillin calvulamate
Concomitant neutropenia: broad spectrum antibiotics, third generation cephalosporin (eg, ceftriaxone, cefotaxime, ceftazidime, or carbopenem [meropenem, imipenem–cilastatin]); vancomycin should be reserved for specific indications (MRSA, catheter infections, and others)

Viral

Prophylaxis
In all patients (VZV, HSV): aciclovir (400–800 mg twice a day), valaciclovir (500 mg twice a day), or famciclovir (250 mg twice a day)
In patients with low IgG (≤400 mg/dL): intravenous immunoglobulin 400 mg/kg, every 2–4 weeks

Screen
Hepatitis B: If HBs A positive (or HBsAg negative, but anti-HBc positive), then test for HBV DNA
Hepatitis C: HCV antibodies, if positive then test for HCV RNA
HIV
CMV: DNA copies
EBV: DNA copies
COVID-19: PCR
Influenza, RSV, other respiratory viruses: in case of specific symptoms only

Treatment
Influenza: oseltamivir, baloxavir, zanamivir
VZV: therapeutic doses of valganciclovir or aciclovir
Hepatitis C: selection of drugs depends on hepatitic C genotype
CMV: valganciclovir, ganciclovir, foscarnet, letermovir
EBV: rituximab, (valganciclovir shows activity, but is not approved for this indication)
RSV: ribavirin, pavilizumab (only approved for paediatric patients)
COVID-19: paxlovid, molnupiravir, remdesevir

Fungal infections

Prophylaxis
In patients with a **previous history of fungal infection, prolonged neutropenia, or glucocorticoid therapy**

Candidiasis: fluconazole 200–400 mg daily
Aspergillus: itraconazole or voriconazol 200 mg twice a day
Pneumocystis jirovecii: co-trimoxazole 800 mg/160 mg once daily or three times per week

Treatment
Localised candidiasis: fluconazole
Invasive candidiasis: an echinocandin—eg, caspofungin
Aspergillosis: voriconazole, itraconazole
**Pneumocystis pneumonia:** co-trimoxazole, atovaquone, primaquine plus clindamycin

Figure 3: Recommendations for prevention and management of infections
CMV=cytomegalovirus. EBV=Epstein-Barr virus. HBc=hepatitis core antigen. HBs=hepatitis B surface antigen. HBV=hepatitis B virus. HCV=hepatitis C virus. HSV=herpes simplex virus. MRSA=methicillin-resistant *Staphylococcus aureus*. RSV=respiratory syncytial virus. VZV=varicella zoster virus.

Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network

Heinz Ludwig, Evangelos Terpos, Niels van de Donk, Maria-Victoria Mateos, Philippe Moreau, Meletios-Athanasios Dimopoulos, Michel Delforge, Paula Rodriguez-Otero, Jesús San-Miguel, Kwee Yong, Francesca Gay, Hermann Einsele, Roberto Mina, Jo Caers, Christoph Driessen, Pellegrino Musto, Sonja Zweegman, Monika Engelhardt, Gordon Cook, Katja Weisel, Annemiek Broijl, Meral Beksac, Jelena Bila, Fredrik Schjesvold, Michele Cavo, Roman Hajek, Cyrille Touzeau, Mario Boccadoro, Pieter Sonneveld

EMN expert panel

Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group

Noopur S Raje, Elias Anaissie, Shaji K Kumar, Sagar Lonial, Thomas Martin, Morie A Gertz, Amrita Krishnan, Parameswaran Hari, Heinz Ludwig, Elizabeth O'Donnell, Andrew Yee, Jonathan L Kaufman, Adam D Cohen, Laurent Garderet, Ashutosh F Wechalekar, Evangelos Terpos, Navin Khatry, Ruben Niesvizky, Qing Yi, Douglas E Joshua, Tapan Saikia, Nelson Leung, Monika Engelhardt, Mohamad Mothy, Andrew Branagan, Ajai Chari, Anthony J Reiman, Brea Lipe, Joshua Richter, S Vincent Rajkumar, Jesús San Miguel, Kenneth C Anderson, Edward A Stadtmauer, Rao H Prabhala, Phillip L McCarthy, Nikhil C Munshi

IMWG

Recommendations on prevention of infections during chimeric antigen receptor T-cell and bispecific antibody therapy in multiple myeloma

Meera Mohan[1] | Rajshekhar Chakraborty[2] | Susan Bal[3] | Anoma Nellore[4] | Muhamed Baljevic[5] | Anita D'Souza[1] | Peter G. Pappas[4] | Jesus G. Berdeja[6] | Natalie Callander[7] | Luciano J. Costa[3]

COMMIT expert panel

IMWG manuscript under revision (Rodriguez-Otero et al.)

Ludwig H et al. Lancet Oncology 2023
Raje N et al. Lancet Hematol 2022
Mohan M et al. BJH 2023

CONCLUSION

• ICAHT and hypogammaglobulinemia are common complications of CAR T-cell and BsAb therapy.

• Profound/prolonged cytopenias and hypogammaglobulinemia are important drivers of increased infection risk.

• CAR–HEMATOTOX scoring system enables pretherapeutic risk assessment and presents the potential for risk-adapted management.

• Management of cytopenias following novel immunotherapies is supportive: G-CSF is the mainstay of treatment. Clinical management of G-CSF refractory ICAHT can be challenging.

• Prophylactic administration of IVIG is recommended in patients with low IgG concentrations (< 400 mg/dl +/- recurrent infections).

• Future studies will need to elucidate pathophysiology and predictors of these toxicities, and to develop evidence-based management strategies (e.g., HT-adapted strategies for anti-infective prophylaxis and early G-CSF use, optimal duration and dosing of IVIG replacement, etc.)

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