Os cuidados que devo ter no paciente em tratamento com anticorpos biespecificos e pos CAR-T

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President, Brazilian Society of Hematology, Hemotherapy and Cell Therapy (ABHH)

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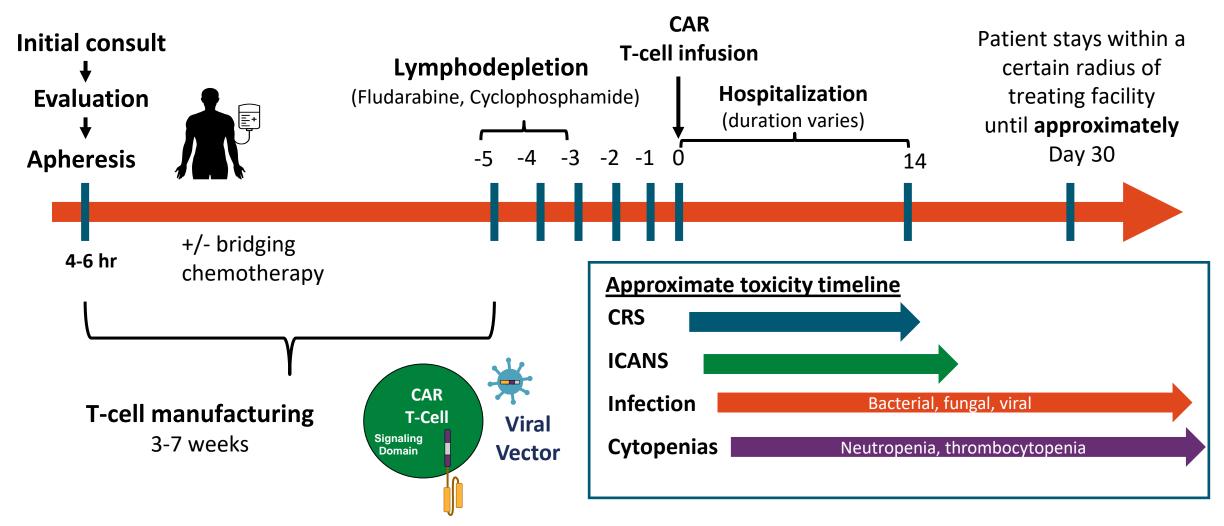
Member of the International Myeloma Working Group



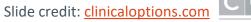
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- Patents and Royalties: not applicable
- Membership on an Entity's Board of Directors or Advisory Committees: Board of Directors Associação Brasileira de Hematologia e HemoterapiaMember of International Myeloma Working Group
- Discussion of off-label drug use: not applicable

CAR T-Cell Treatment Schema



Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29. Cho. Front Immunol. 2018;9:1821. Ciltacabtagene autoleucel PI. Idecabtagene vicleucel PI. Perica. Biol Blood Marrow Transplant. 2018;24:1135.



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CAR T-Cell Therapy: Toxicities

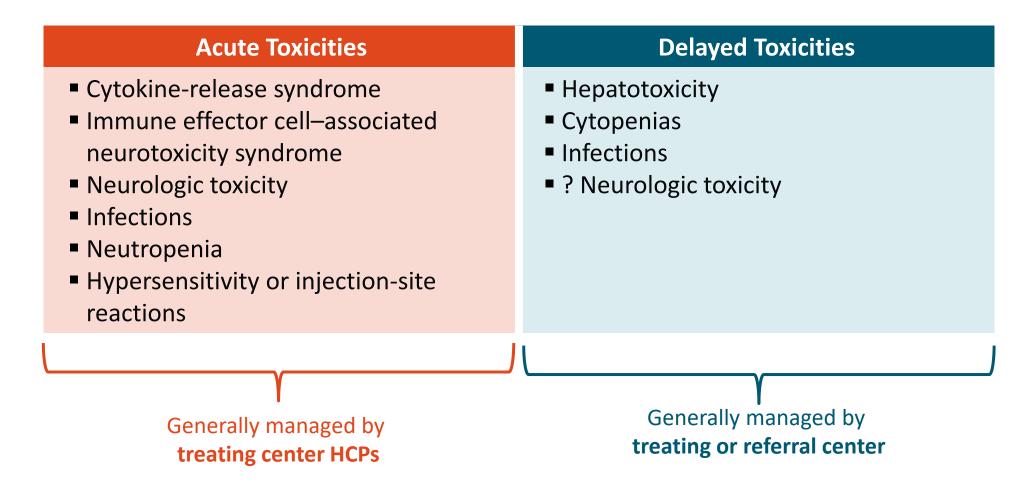
Acute Toxicities ¹	Delayed Toxicities ^{2,3}
 Cytokine-release syndrome Immune effector cell–associated neurotoxicity syndrome Cytopenias Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome 	 B-cell aplasia/ hypogammaglobulinemia Prolonged cytopenias Late infections Long-term neurologic events/ movement and neurocognitive treatment-emergent AEs Transient cardiac toxicities Secondary malignancies?
Generally managed by treating center HCPs	Generally managed by primary hematologists



1. Maus. J Immunother Cancer. 2020;8:e001511. 2. Cohen. Blood Cancer J. 2022;12:32. 3. Chakraborty. Transplant Cell Ther. 2021;27:222. Slide credit: clinicaloptions.com

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Bispecific Antibodies: Toxicities

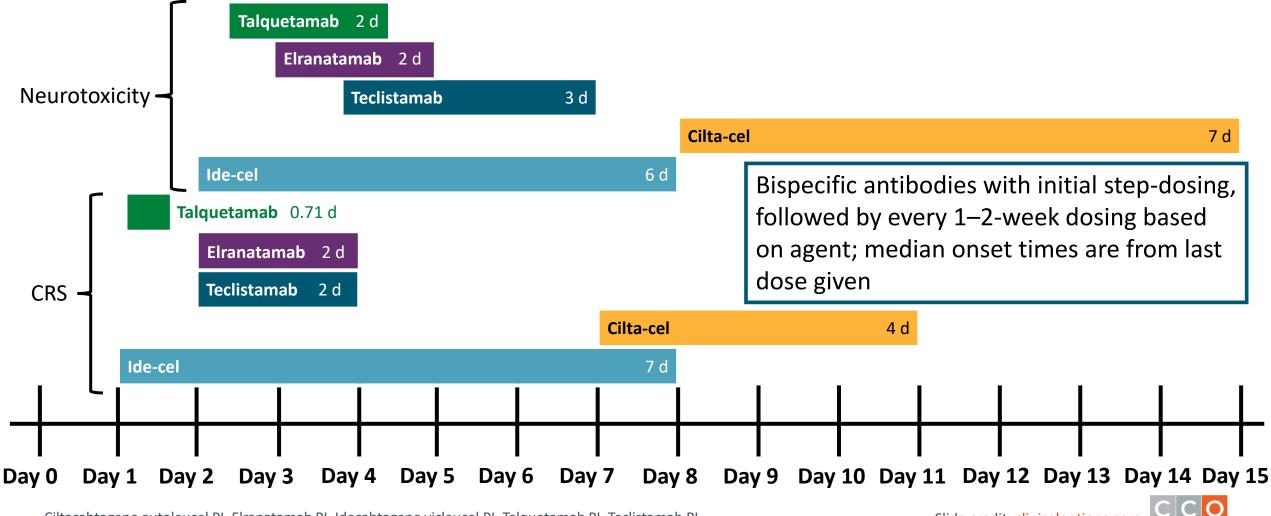


Further long-term follow-up data with bispecific antibodies are necessary

Elranatamab PI. Martin. Cancer. 2023;129:2035. Teclistamab PI.

Slide credit: <u>clinicaloptions.com</u>

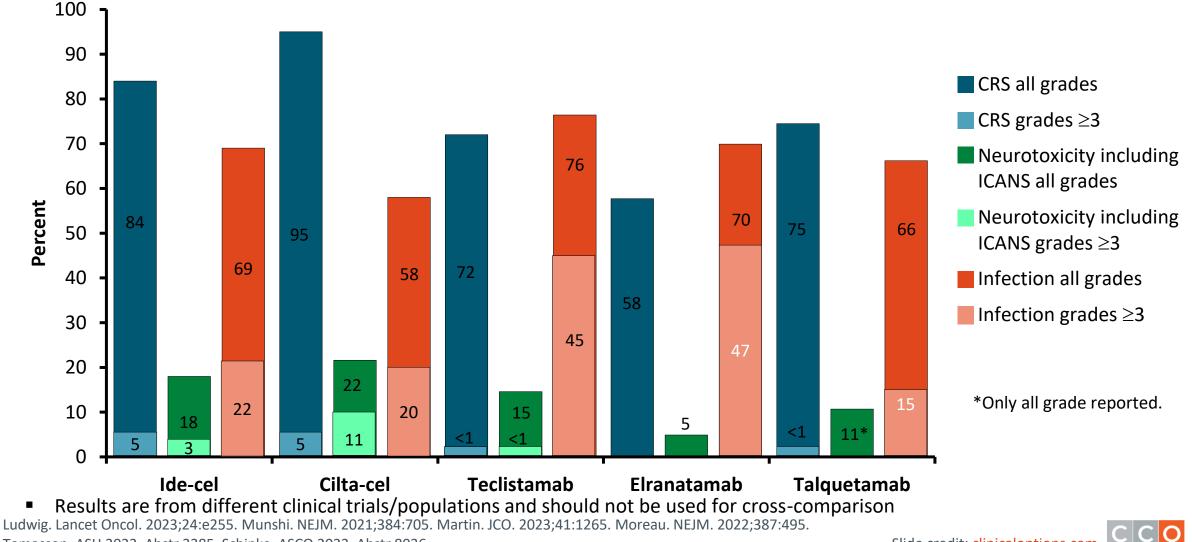
CRS and Neurotoxicity: Median Time to Onset and Duration by CAR T-Cell or Bispecific Antibody Product



Ciltacabtagene autoleucel PI. Elranatamab PI. Idecabtagene vicleucel PI. Talquetamab PI. Teclistamab PI.

Slide credit: <u>clinicaloptions.com</u>

Summary of Selected AE With CAR T-Cell Therapy and Bispecific Antibodies in R/R MM



Tomasson. ASH 2023. Abstr 3385. Schinke. ASCO 2023. Abstr 8036.

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Management of CRS With CAR T-Cell Therapy and Bispecific Antibody Therapy

 Rule out other etiologies: infection, heart failure, pulmonary edema, possibly treat for infection

	CAR T-Cell Therapy	Bispecific Antibody Therapy
Grade	Supportive Care + Intervention	Supportive Care + Intervention
1	± tocilizumab*	Withhold until CRS resolution and administer pretreatment medications prior to next dose
2	Tocilizumab ± corticosteroid	Grade 1 interventions + 48-hr hospitalization following next dose according to institutional and manufacturer guidelines
3	Tocilizumab + corticosteroid	First grade 3 occurrence with duration ≤48 hr: grade 2 interventions + ICU/critical care as needed Recurrent grade 3 or grade 3 with duration >48 hr: grade 4 interventions
4	Tocilizumab + high-dose corticosteroid ICU/critical care	Permanently discontinue; provide ICU/critical care as needed

*High-burden, high-risk products; older; comorbidities; etc.

Brudno. Blood Rev. 2019;34:45. Elranatamab PI. Talquetamab PI. Teclistamab PI.

Other AE With CAR T-Cell and Bispecific Antibody Therapy

- Cytopenias
 - Common with both CAR T-cell therapy and bispecific antibody therapy
 - Additionally, can be caused by lymphodepletion prior to CAR T-cell therapy
 - Consult hematology/oncology regarding potential growth factors
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
 - Rare, and serious complication with CAR T-cell therapy
 - Treatment aimed towards reducing the cytokine hyperactivation
- Hepatotoxicity
 - Monitor liver enzymes



TALQUETAMAB – MonumenTAL-1

AEs (≥30% in any		(g SC QW 143)	0.8 mg/kg (n=	g SC Q2W 145)		r TCR 51)
cohort), n (%)	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Nonhematologic AEs						
CRS ^b	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia ^c	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections ^d	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related ^e	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related ^f	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0
Rash related ^g	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Pyrexia	56 (39.2)	4 (2.8)	40 (27.6)	2 (1.4)	16 (31.4)	0
Dry mouth	38 (26.6)	0	58 (40.0)	0	26 (51.0)	0
Fatigue	35 (24.5)	5 (3.5)	40 (27.6)	1 (0.7)	23 (45.1)	1 (2.0)









Adaptado de Touzeau, et al. EHA 2023. JAAD Case Rep. 2023 Jan; 31: 66–68. Neha Narayan, BA e fotos de caso clínico do autor

THE LANCET Oncology

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, Melitios-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

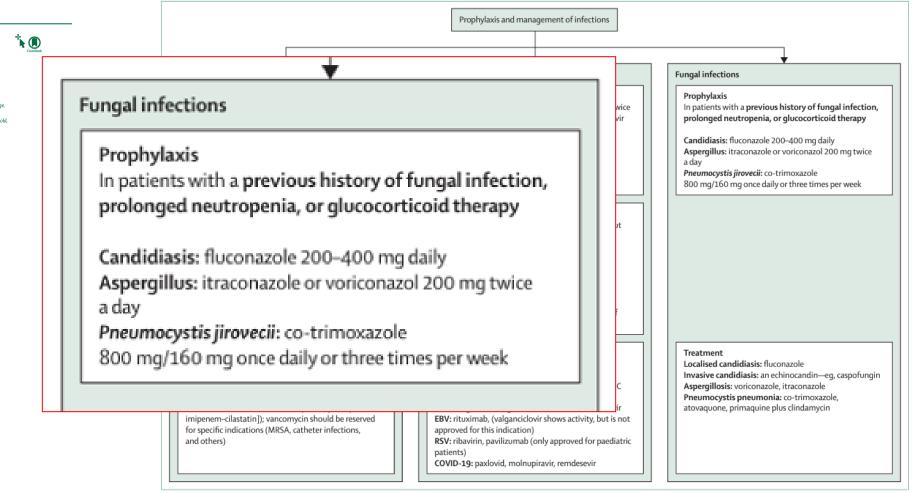
Published: June, 2023 • DOI: https://doi.org/10.1016/S1470-2045(23)00159-6

	Prophylaxis and management of infections	
+	+	*
Bacterial infections	Viral	Fungal 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)	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	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
	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 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)	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	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

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 Dank, Maria-Victaria Mateos, Philippe Moreau, Melitios-Athanasios Dimopoulos, Michel Delforge, Paula Rodriguez-Otero, Jesús San-Miguel, Kwe Yong, Francesca Goy, Hermann Einsele, Roberto Mina, Jo Caers, Christoph Driessen, Pellegrino Musto, Sonja Zwesgman, Monika Engelhardt, Gordon Cook, Katja Weisel, Annemiek Broijl, Meral Belsac, Jelena Bila, Fredrik Schjesvold, Michele Cavo, Roman Fajek, Synille Touzeau, Mario Boccadaro, Pieter Sanneveld



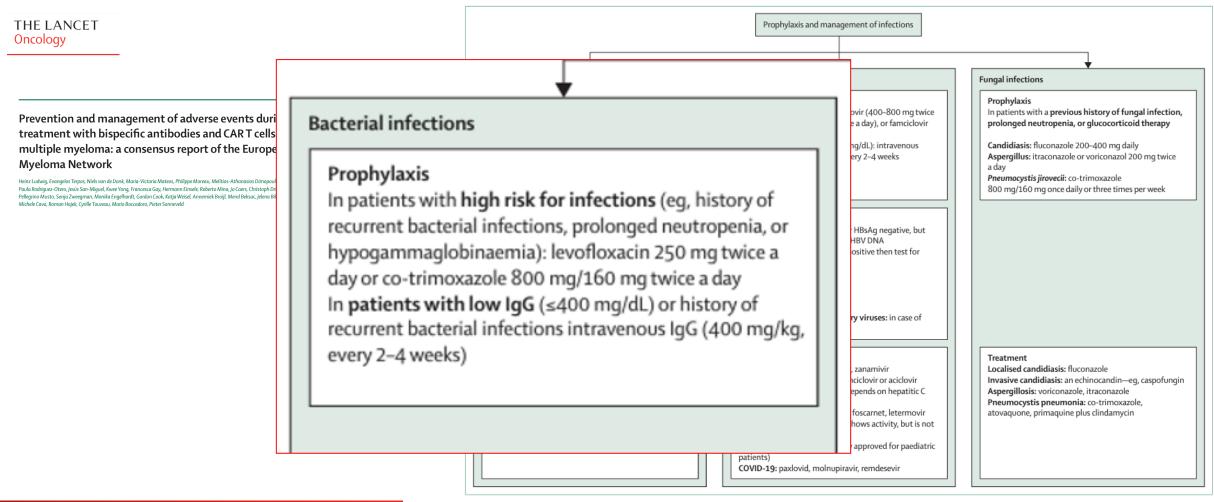
Published: June, 2023 • DOI: https://doi.org/10.1016/S1470-2045(23)00159-6

Figure 3: Recommendations for prevention and management of infections

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	· · · · · · · · · · · · · · · · · · ·	gement of infections
Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in	Viral	
multiple myeloma: a consensus report of the European	Prophylaxis	Fungal infections
Myeloma Network Heinz Ludwig, Evangalos Terpas, Niels van de Donk, Maria-Victoria Mateas, Philippe Moreau, Melitios-Athanasies Dimopoulos, Michel Delforge, Paula Rodriguez-Otero, Jesús San-Miguel, Kwee Yong, Francesca Gay, Hermann Einsele, Roberto Mina, Jo Caers, Christaph Driessen, Pellegrino Musto. Sonjo Zweegman, Monika Engelhardt, Gordon Cook, Karja Webel, Annemiek Broiji, Meral Belsac, Jelena Bila, Fredrik Schjesvold, Michele Caws, Roman Hajek, Cyrille Touzeau, Mario Boccadoro, Pieter Sonneveld	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	iclovir (400–800 mg twice vice a day), or famciclovir Prophylaxis 0 mg/dL): intravenous every 2–4 weeks 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
	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	tory viruses: in case of
	HCV RNA HIV CMV: DNA copies EBV: DNA copies COVID-19: PCR Influenza, RSV, other respiratory viruses: in case of specific symptoms only	vir, zanamivir ganciclovir or aciclovir s depends on hepatitic C vir, foscarnet, letermovir ir shows activity, but is not nly approved for paediatric ravir, remdesevir

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Figure 3: Recommendations for prevention and management of infections



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Figure 3: Recommendations for prevention and management of infections

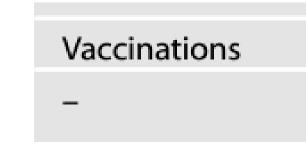
- Follow general guidelines on use of live attenuated vaccines, however it should be noted that live vaccines are contraindicated in MM patients (level IIC)
- Ensure post-stem cell transplant vaccinations have been carried out (level III)
- COVID-19 vaccination recommended as per CDC guidelines, in patients without history of transplant (level III)
- Yearly influenza vaccination, pneumococcal vaccination and varicella zoster vaccination recommended in patients without history of transplant (level III)
- Close contacts should receive seasonal vaccines (level III)
- Health-care providers caring for MM patients should be fully immunized and should receive seasonal vaccines (level III)
- Prior to traveling to endemic areas of infection, patients should receive travel vaccinations and undergo consultation with a disease specialist (level III)

REVIEW ARTICLE OPEN

Check for updates

Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel

Noopur Raje[®]^{1 ⊠}, Kenneth Anderson[®]², Hermann Einsele[®]³, Yvonne Efebera⁴, Francesca Gay⁵, Sarah P. Hammond^{1,2,6}, Alexander M. Lesokhin^{7,8}, Sagar Lonial[®]⁹, Heinz Ludwig[®]¹⁰, Philippe Moreau[®]¹¹, Krina Patel¹², Karthik Ramasamy[®]^{13,14} and Maria-Victoria Mateos[®]¹⁵



Flu; COVID, Pn conjugada, Hib (PNI - CRIEs/UBS) Zoster recombinante; RSV (novas e fora do PNI) Blood Cancer Journal

www.nature.com/bcj

ARTICLE OPEN Effect of Intravenous Immunoglobulin (IVIG) Supplementation on infection-free survival in recipients of BCMA-directed bispecific antibody therapy for multiple myeloma

Meera Mohan ^{1™}, Aniko Szabo ², Heloise Cheruvalath³, Anna Clennon⁴, Vineel Bhatlapenumarthi¹, Anannya Patwari¹, Metodi Balev⁵, Divaya Bhutani⁵, Asis Shrestha⁶, Sharmilan Thanendrarajan⁶, Binod Dhakal ¹, Maurizio Zangari⁶, Anup Trikannad⁶, Sruthi Vellanki⁶, Samer Al-Hadidi ⁶, Suzanne Lentzsch⁵, Frits van Rhee ⁶, Aishee Bag ⁷, Anita D'Souza ¹, Nishi Shah ⁸, Rajshekhar Chakraborty ⁵, Mansi R. Shah⁷ and Carolina Schinke ⁶

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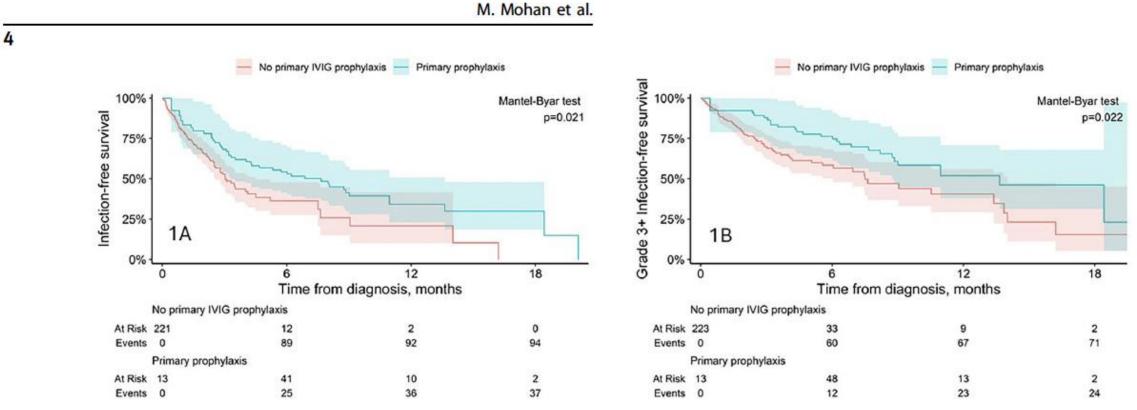


Fig. 1 Infection-free-survival. Infection-free-survival for all-grade infection (A) and \geq grade 3 infection (B) in patients treated with and without primary IVIG.

Meera Mohan, et al Blood Cancer Journal 2025

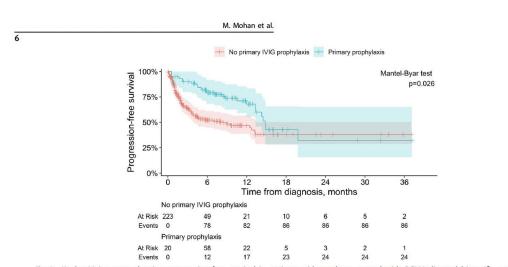


Fig. 2 Kaplan-Meier curve showing progression-free survival in patients with myeloma treated with BCMA-directed bispecific antibody therapy, stratified by IVIG status.

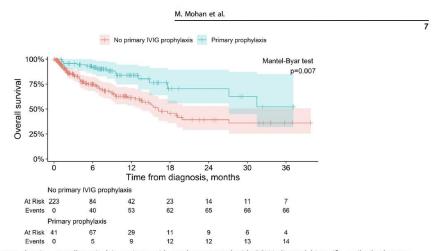


Fig. 3 Kaplan-Meier curve showing overall survival in patients with myeloma treated with BCMA-directed bispecific antibody therapy, stratified by IVIG status.

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Conclusion:

- BCMA and other targets offer great promise
- T-cell redirection with CAR T-cell therapies and bispecific antibodies is now moving into earlier lines of therapy
- Focus on supportive care will allow improved outcomes
- The future will explore alternate dosing schedules, combinations, and sequencing of all these approaches





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