Highlights from
IMS 20th meeting 2023

CORRADO GIRMENIA

Complicanze infettive: prevenzione e terapia

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

Infection-control strategies in MM

- Epidemiology and prophylaxis of bacterial, fungal and viral infections
- Vaccination schedules and COVID-19 prevention in MM populations
- Focus on anti-BCMA treatments

Infection-control strategies in MM

- **Epidemiology and prophylaxis of bacterial, fungal and viral infections**
- **Vaccination schedules and COVID-19 prevention in MM populations**
- **Focus on anti-BCMA treatments**

Multiple myeloma and infections: a population-based study on 9253 multiple myeloma patients

haematologica | 2015; 100(1)

Cecilie Blimark,[1] Erik Holmberg,[2] Ulf-Henrik Mellqvist,[1] Ola Landgren,[3] Magnus Björkholm,[4] Malin Hultcrantz,[4] Christian Kjellander,[4] Ingemar Turesson,[5] and Sigurdur Y. Kristinsson[4,6]

Table 2. Relative risk of selected infections after diagnosis of myeloma compared to matched controls.

Disease	Total			One-year follow up		
	Myeloma (n=9 253)	Controls (n=34 931)	HR* (95%CI)	Myeloma	Controls	HR (95%CI)
Any infection (combined)**	3781	6519	7.1 (6.8-7.4)	1626	672	11.6 (10.6-12.7)
Specific infections						
Bacterial***	3361	5792	7.1 (6.8-7.4)	1388	574	11.5 (10.4-12.7)
Pneumonia	2150	3504	7.7 (7.2-8.1)	770	279	12.7 (11.1-14.6)
Osteomyelitis	37	100	3.5 (2.4-5.2)	19	12	6.9 (3.4-14.3)
Septicemia	1336	960	15.6 (14.3-17.1)	464	69	29.9 (23.2-38.6)
Pyelonephritis	152	570	2.9 (2.4-3.5)	50	51	4.3 (2.9-6.4)
Cellulitis	164	564	3.0 (2.5-3.6)	47	58	3.7 (2.5-5.4)
Meningitis	51	28	16.6 (10.2-27.1)	12	3	17.3 (4.9-61.3)
Endocarditis	35	73	5.3 (3.4-8.1)	12	6	8.7 (3.3-23.1)
Viral****	607	556	10.0 (8.9-11.4)	215	54	17.6 (13.1-23.8)
Influenza	150	245	6.1 (4.9-7.6)	52	22	10.5 (6.4-17.3)
Herpes zoster	282	171	14.8 (12.1-18.2)	92	16	25.8 (15.2-43.8)

*HR: hazard ratio, CI: confidence interval. *Cox proportional hazard models were used to compare total and one-year risks of infection in myeloma patients compared to controls. Adjusted (by sex, age at diagnosis and year of diagnosis) HRs and 95%CIs were estimated. **Pneumonia, osteomyelitis, septicemia, pyelonephritis, cellulitis, meningitis, endocarditis, cystitis, CMVEBV, empyema, encephalitis, gonorrhea, hepatitis A-C, HSV, herpes zoster, HIV, intestinal infections, Lyme disease, malaria, mononucleosis, myocarditis, otitis, pharyngitis/nasopharyngitis, pericarditis, sinusitis, syphilis, tonsillitis, tuberculosis. ***Pneumonia, cellulitis, cystitis, empyema, endocarditis, gonorrhea, meningitis, osteomyelitis, otitis, pharyngitis/nasopharyngitis, pyelonephritis, septicemia, sinusitis, syphilis, tonsillitis and tuberculosis. ****HIV, HSV, herpes zoster, hepatitis (A-C), CMV, EBV, mononucleosis, encephalitis, pericarditis, myocarditis and influenza.*

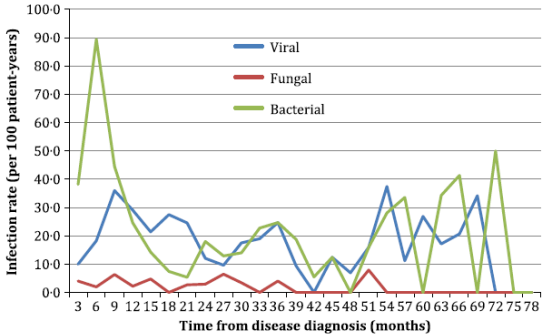
bjh research paper

Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy

Benjamin W. Teh,[1,2] Simon J. Harrison,[2,3] Leon J. Worth,[1] Tim Spelman,[4] Karin A. Thursky[1,4] and Monica A. Slavin[1,4]

British Journal of Haematology, 2015, **171**, 100–108

- Overall, infections occurred in **95% of** MM patients, accounting for **1.33 per patient-year**.
- The respiratory tract (**42.4%**), blood (13.0%) and skin, soft tissue (12.2%) were the most frequent sites of infection.
- There was a bimodal peak in incidence of bacterial and viral infections following disease diagnosis.



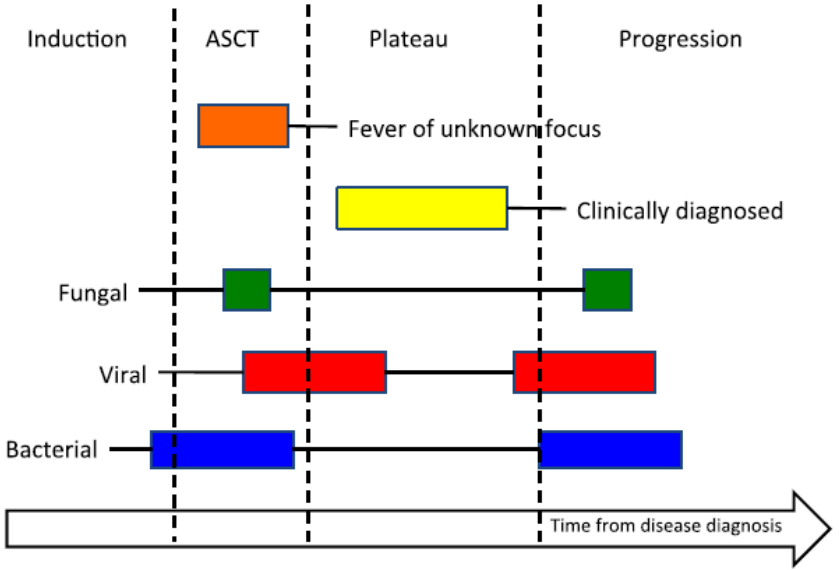


Fig 3. Defined risk periods for infection following myeloma diagnosis, by type of infection. ASCT, autologous haematopoietic stem cell transplant.

Antimicrobial prophylaxis in multiple myeloma patients

- Bacterial prophylaxis in the era of MDR
- Fungi and P.jirovecii prophylaxis
- Viral infections prophylaxis

TEAMM Trial Management Group and Trial Investigators (2019). Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Drayson, M. T., et al.The Lancet. Oncology, 20(12), 1760-1772.

	Events/patients		12-week events		HR (95% CI)
	Levofloxacin group	Placebo group	Observed – expected	Variance	
Estimated glomerular filtration rate (mL/min)					
>50	67/369 (18%)	109/369 (30%)	-24·0	43·9	0·58 (0·43-0·78)
≤50	28/120 (23%)	25/119 (21%)	0·5	13·2	1·04 (0·60-1·77)
Stratified	95/489 (19%)	134/488 (27%)	-23·5	57·2	0·66 (0·51-0·86)
Interaction between two groups p=0·06					
High-dose CT with planned stem-cell transplantation					
Yes	61/266 (23%)	74/266 (28%)	-7·6	33·7	0·80 (0·57-1·12)
No	34/223 (15%)	60/222 (27%)	-15·7	23·4	0·51 (0·34-0·77)
Stratified	95/489 (19%)	134/488 (27%)	-23·3	57·1	0·66 (0·51-0·86)
Interaction between two groups p=0·10					
Age (years)					
≤65	41/208 (20%)	53/201 (26%)	-7·4	23·5	0·73 (0·49-1·09)
>65	54/281 (19%)	81/287 (28%)	-16·1	33·7	0·62 (0·44-0·87)
Stratified	95/489 (19%)	134/488 (27%)	-23·5	57·2	0·66 (0·51-0·86)
Interaction between two groups p=0·55					
Performance status					
ECOG 0-1	70/373 (19%)	88/361 (24%)	-11·7	39·5	0·74 (0·54-1·01)
ECOG 2-4	24/106 (23%)	44/117 (38%)	-11·1	17·0	0·52 (0·32-0·84)
Stratified	94/479 (20%)	132/478 (28%)	-22·8	56·4	0·67 (0·51-0·87)
Interaction between two groups p=0·22					
International Staging System					
Stage I	21/100 (21%)	32/116 (28%)	-4·3	13·2	0·72 (0·42-1·24)
Stage II	36/188 (19%)	46/165 (28%)	-9·0	20·3	0·64 (0·42-0·99)
Stage III	25/121 (21%)	37/130 (28%)	-5·8	15·5	0·69 (0·42-1·13)
Stratified	82/409 (20%)	115/411 (28%)	-19·1	49·0	0·68 (0·51-0·90)
Heterogeneity between three groups p=0·95					
Test for trend over three groups p=0·91					
Co-trimoxazole					
No	71/316 (22%)	99/316 (31%)	-16·6	42·4	0·68 (0·50-0·91)
Yes	22/159 (14%)	32/155 (21%)	-6·3	13·5	0·63 (0·37-1·07)
Stratified	93/475 (20%)	131/471 (28%)	-22·9	55·9	0·66 (0·51-0·86)
Interaction between two groups p=0·80					
Unstratified	**95/489 (19%)**	**134/488 (27%)**	**-23·5**	**57·2**	**0·66 (0·51-0·86)**

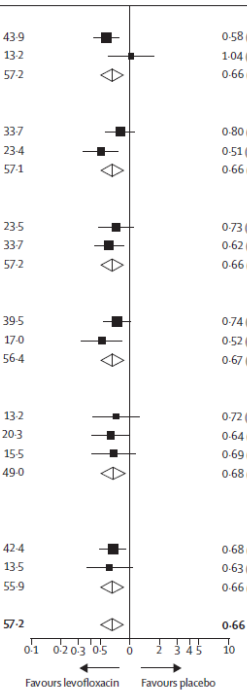


Figure 3: **Forest plots of time to febrile episode or death in various subgroups**
ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

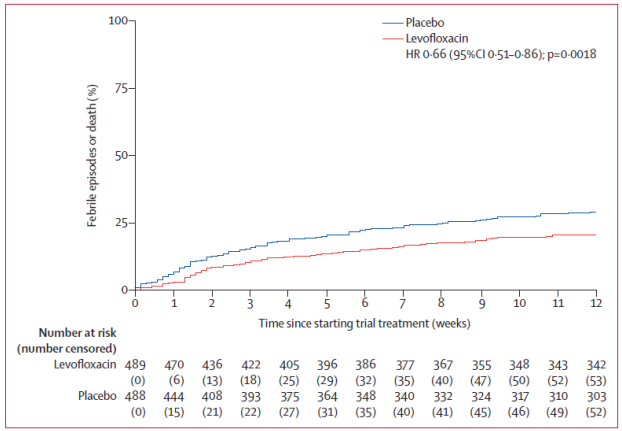
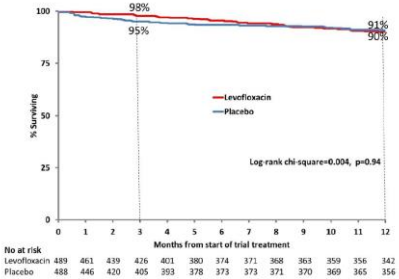


Figure 2: Kaplan-Meier graph of time to febrile episode or death

Table S5: Reported potentially pathogenic or invasive isolates from local laboratories by treatment arm

Species	Levofloxacin	Placebo	Total
Total Gram negative	**6 (18%)**	**27 (82%)**	**33**
Enterobacteriaciae	4	14	18
Pseudomonas Spp.	0	5	5
Other Gram negative	2	8	10

Figure S2: Overall survival up to 12 months



Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Associazione Microbiologi Clinici Italiani (AMCLI). Incidence, Risk Factors and Outcome of Pre-engraftment Gram-Negative Bacteremia After Allogeneic and Autologous Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey.

Girmenia C, et al. Clin Infect Dis. 2017 Nov 13;65(11):1884-1896

	Auto-SCT in Multiple Myeloma	Auto-SCT in other diseases
Total transplants	846	778
No fever or infection	463 (55%)	225 (29%)
FUO only	181 (21.4%)	276 (35%)
Clin. documented infections only *	39 (4.6%)	49 (6.3%)
Microb. documented infections*	162 (19,2%)	218 (28%)
Gram-positive infections*	88 (10.4%)	110 (14.1%)
Gram-negative infections*	68 (8.0%)@	90 (11.6%)
Fungal infections*	2 (0.2%)	7 (0.9%)
Viral diseases*	1 (0.1%)	3 (0.4%)

*cases with one or more infections; @Gram-neg infections 8% in I and 10% in II auto-SCT in MM

Gruppo Italiano Trapianto di Midollo Osseo (GITMO) and Associazione Microbiologi Clinici Italiani (AMCLI). Incidence, Risk Factors and Outcome of Pre-engraftment Gram-Negative Bacteremia After Allogeneic and Autologous Hematopoietic Stem Cell Transplantation: An Italian Prospective Multicenter Survey.

Girmenia C, et al. Clin Infect Dis. 2017 Nov 13;65(11):1884-1896

Risk factors for pre-engraftment Gram negative infections: Multivariate analysis

Allo-HSCT		Auto-HSCT	
Variable	**HR (95% CI), p**	Variable	**HR (95% CI), p**
Age (+10y)	1.16 (1.06-1.27), 0.001	Age (+10y)	1.20 (1.06-1.36), 0.004
Other diseases vs acute leukemia	0.65 (0.46-0.92), 0.01	Lymphoma vs other diseases	1.86 (1.30-2.66), <0.001
Donor MMR MMU CB	 4.14 (2.31-7.42), <0.001 2.92 (1.47-5.81), 0.002 3.50 (1.32-9.29), 0.01	Antibacterial prophylaxis vs no prophylaxis	0.50(0.34-0.75), <0.001
Ex vivo T-cell depletion	0.13 (0.03-0.53). 0.004		
Days of pre-engraftment neutropenia	1.02 (1.01-1.03), <0.001		

Antibacterial prophylaxis with ciprofloxacin for patients with multiple myeloma and lymphoma undergoing autologous haematopoietic cell transplantation: a quasi-experimental single-centre before-after study.

Yeshurun M, et al. Clin Microbiol Infect. 2018 Jul;24(7):749-754.

Methods: This is a quasi-experimental, retrospective, before-after study. We compared the incidence of bacterial-related complications among 356 patients with multiple myeloma (MM) ($n = 202$) and lymphoma ($n = 154$) who underwent AHCT with ($n = 177$) or without ($n = 179$) ciprofloxacin prophylaxis between 03/2007 and 10/2012 and between 10/2012 and 07/2016, respectively, at a single centre.

Table 2
Infection-related complications

	No prophylaxis ($N = 179$)	Ciprofloxacin prophylaxis ($N = 177$)	p value
Bacteraemia *N* (%)			
Multiple myeloma ($N = 202$)	14/98 (14.3)	4/104 (3.8)	0.009
Lymphoma ($N = 154$)	13/81 (16)	4/73 (5.4)	0.008
All ($N = 356$)	27/179 (15)	8/177 (4.5)	<0.0001
Febrile neutropaenia *N* (%)			
Multiple myeloma ($N = 202$)	84/98 (85.7)	79/104 (76)	0.004
Lymphoma ($N = 154$)	77/81 (95.1)	68/73 (93.2)	0.64
All ($N = 356$)	161/179 (90.4)	147/177 (83.1)	0.002
Pneumonia *N* (%)			
Multiple myeloma ($N = 202$)	8/98 (8.2)	7/104 (6.7)	0.7
Lymphoma ($N = 154$)	14/81 (17.3)	4/73 (5.5)	0.02
All ($N = 356$)	22/179 (12.3)	11/177 (6.2)	0.04
CDAD *N* (%)			
Multiple myeloma ($N = 202$)	4/98 (4.1)	2/104 (1.9)	0.37
Lymphoma (N = 154)	8/81 (9.9)	3/73 (4.1)	0.16
All ($N = 356$)	12/179 (6.7)	5/177 (2.8)	0.08
Mortality by day 30 post-HCT	2/179 (1.1)	4/177 (2.3)	0.4

CDAD, *Clostridium difficile*-associated diarrhoea.

Table 3
Multivariate analysis of factors predicting bacteraemia, pneumonia, and febrile neutropaenia in the study population

Factor	OR[a] (CI), p value		
	Bacteraemia	Pneumonia	Febrile neutropaenia
Age	1.0 (0.99–1.02), p = 0.9	0.98 (0.95–1.01), p = 0.3	0.99 (0.99–1), p = 0.36
Duration of neutropaenia	1.08 (1.02–1.14), p = 0.06	1.14 (1.08–1.76) p < 0.0001	1.16 (1.04–1.3), p = 0.007
Bacterial prophylaxis	0.19 (0.075–0.47), p < 0.0001	0.37 (0.16–0.85), p = 0.02	0.54 (0.28–1.03), p = 0.06

Ludwig Heinz (Orcid ID: 0000-0002-3302-8726)
Kumar Shaji (Orcid ID: 0000-0001-5392-9284)

Am J Hematol, 2022

Revised version: Prevention of infections including vaccination strategies in multiple myeloma

Short title: Prevention of infections in multiple myeloma

- Antibiotic prophylaxis at start of first line therapy should be considered in carefully selected patients with increased risk for infections.
- Likewise antibiotic prophylaxis may be considered in heavily pretreated patients with active disease scheduled for immunosuppressive rescue therapy although scientific evidence for this indication is scarce

Antimicrobial prophylaxis in multiple myeloma patients

- Bacterial prophylaxis in the era of MDR
- Fungi and P.jirovecii prophylaxis
- Viral infections prophylaxis

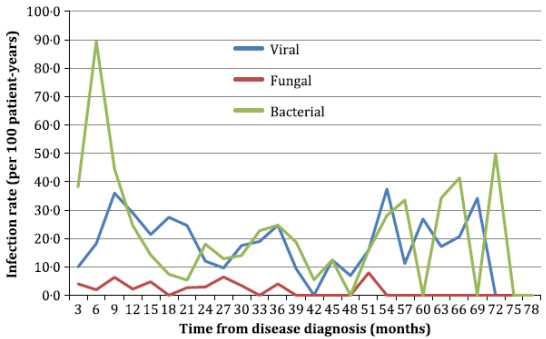
bjh research paper

Risks, severity and timing of infections in patients with multiple myeloma: a longitudinal cohort study in the era of immunomodulatory drug therapy

Benjamin W. Teh,[1,2] Simon J. Harrison,[2,3] Leon J. Worth,[1] Tim Spelman,[4] Karin A. Thursky[1,4] and Monica A. Slavin[1,4]

British Journal of Haematology, 2015, **171**, 100–108

There was a bimodal peak in incidence of bacterial and viral infections following disease diagnosis.



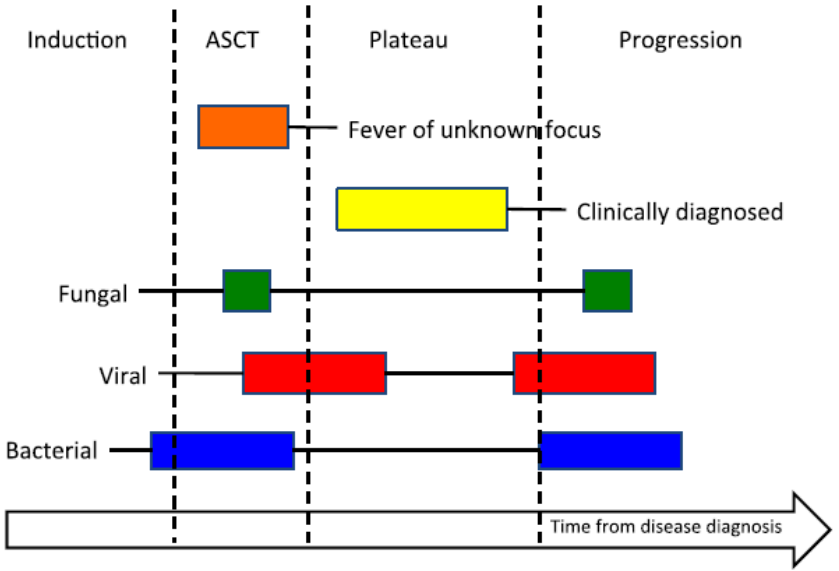


Fig 3. Defined risk periods for infection following myeloma diagnosis, by type of infection. ASCT, autologous haematopoietic stem cell transplant.

Ludwig Heinz (Orcid ID: 0000-0002-3302-8726)
Kumar Shaji (Orcid ID: 0000-0001-5392-9284)

Am J Hematol, 2022

Revised version: Prevention of infections including vaccination strategies in multiple myeloma

Short title: Prevention of infections in multiple myeloma

- Fungal prophylaxis may be considered in patients with prolonged neutropenia such as those receiving cellular therapies. Effective drugs are fluconazole, micafungin or vorinoconazole and posaconazole.
- Co-trimoxazole is recommended for PJP prophylaxis in patients with pro*l*onged immunosuppression and/or cytopenia. With present conventional therapies the incidence of *P.jirovecii* infections is much lower than in previous times with use of high dose and continuous dexamethasone.

Antimicrobial prophylaxis in multiple myeloma patients

- Bacterial prophylaxis in the era of MDR
- Fungi and P.jirovecii prophylaxis
- Viral infections prophylaxis

Ludwig Heinz (Orcid ID: 0000-0002-3302-8726)
Kumar Shaji (Orcid ID: 0000-0001-5392-9284)

Am J Hematol, 2022

Revised version: Prevention of infections including vaccination strategies in multiple myeloma

Short title: Prevention of infections in multiple myeloma

- Prophylaxis against *Herpes zoster* reactivation with acyclovir is recommended for patients treated with proteasome inhibitors, particularly in those receiving bortezomib but also in patients treated with anti-CD38 antibodies and in those after ASCT. Prophylaxis should be maintained in parallel with treatment with the above-cited drugs.
- Data on the duration of antiviral prophylaxis after discontinuation of proteasome-inhibitors or CD38 antibodies are scarce

Infection-control strategies in MM

- Epidemiology and prophylaxis of bacterial, fungal and viral infections
- Vaccination schedules and COVID-19 prevention in MM populations
- Focus on anti-BCMA treatments

Ludwig Heinz (Orcid ID: 0000-0002-3302-8726)
Kumar Shaji (Orcid ID: 0000-0001-5392-9284)

Am J Hematol, 2022

Revised version: Prevention of infections including vaccination strategies in multiple myeloma

Short title: Prevention of infections in multiple myeloma

Vaccination in MM patients

- All patients should be vaccinated against the key 4 pathogens: **Influenza, pneumococci, herpes zoster and COVID-19**
- Depending on the individual risk profile other vaccinations are recommended.
  - Patients with functional or anatomical asplenia should be vaccinated against Haemophilus influenza and Meningococci.
  - Patients living in or travelling to areas endemic for hepatitis A and B and not immune against this pathogens should be vaccinated with the respective vaccines
  - Patients after HSCT or CAR-T cell therapy should be tested against tetanus, diphtheria and pertussis. In case of no inadequate antibody response vaccination should be considered. The same applies to measles, mumps and rubella. But vaccination with the latter vaccines should only be considered in patients with full immuno-reconstitution as these are attenuated live vaccines
  - It should be kept in mind that immune response to vaccination in multiple myeloma patients is frequently suboptimal.

Table 2. Recommendations for vaccination for all patients with multiple myeloma

Infections	Vaccine type	Recommendation	Doses	Supported by	Comments
Influenza	Quadrivalent or trivalent high dose or adjuvanted seasonal vaccine)	All patients, non-immune family members, close contacts and HCWs	2, or 1 in case of documented seroprotection after the 1st dose, yearly	WHO, CDC NCCN	CDC recommends high-dose flu vaccine in people 65 years of age or older
Pneumococci[1]	PCV13, or PCV15 followed by PPSV23, or PCV20 only	All patients	1	CDC, IDSA, NCCN	Conjugated vaccine to a mutant diphtheria toxin induces T cell response
	PPSV23	>2 months, or 6-12 months after PCV13 or PCV15	1-3 Repeat in 3 years after 1st dose		Polysaccharide vaccine, less immunogenic than PCV
	Meningococcal B capsular polysaccharide-free recombinant vaccine targeting serogroup B (4CMenB)	All patients	1		Includes 3 core recombinant proteins plus one of the outer membrane
Herpes zoster	Recombinant VZV glycoprotein E vaccine (Shingrix®)	All patients with MM	2	EMN	Antibody response in 80.4%
	Live-attenuated VZV vaccine[2] (Zostavax®) if the recombinant vaccine is not available	All patients with MM	4	EMN	Estimated vaccine efficacy: 63%
SARS-CoV2 (COVID-19)	mRNA-1273 BNT162b2	All patients with MM non-immune family members, close contacts and HCWs	2 plus a 3rd dose >4 mos after the 2nd dose, plus a 4th dose 4-6 mos thereafter	EMN CDC WHO	Anti-spike antibody response increased to 88% and 91% in those without and with measurable antibodies after 2nd dose
	Ad26.COV2, Adenovirus vector-based vaccine		2, presently no data on efficacy of additional doses available		
	Novavax Protein-based		2, presently no data on efficacy of additional doses available		

[1] PVC 15 and PCV 20 are new recently approved vaccines, data on how well these vaccines work in real world are not available. [2] only in case recombinant VZV glycoprotein E vaccine is not available, CDC-Center of Disease Control, NCCN- National Comprehensive Cancer Network, IDSA- Infectious Disease Society of America, EMN- European Myeloma Network

In Italia sono disponibili vaccini antinfluenzali quadrivalenti che contengono 2 virus di tipo A (H1N1 e H3N2) e 2 virus di tipo B.

https://www.salute.gov.it/portale/influenza/dettaglioFaqInfluenza.jsp?lingua=italiano&id=103

Vaccino inattivato quadrivalente su colture cellulari (Flucelvax Tetra)

- Il vaccino contiene 2 virus di tipo A (H1N1 e H3N2) e 2 virus di tipo B cresciuti su colture cellulari, ed autorizzato per l'uso in bambini e adulti di età superiore ai 2 anni.

Vaccino inattivato quadrivalente adiuvato (Fluad Tetra)

- Uno dei prodotti quadrivalenti contiene l'adiuvante MF59, un'emulsione olio-in-acqua composta da squalene come fase oleosa. L'adiuvante ha lo scopo di facilitare l'adeguata risposta immunitaria partendo da una minore quantità di antigene. Gli altri prodotti inattivati non contengono un adiuvante.
  È indicato nei soggetti di età pari o superiore a 65 anni.

Vaccino ad alto dosaggio (Efluelda)

- Si tratta di un vaccino *split* quadrivalente che contiene due virus di tipo A (H1N1 e H3N2) e due virus di tipo B contenente 60 mcg di emoagglutinina (HA) per ciascun ceppo virale per garantire una maggiore risposta immunitaria e quindi una maggiore efficacia, indicato nei soggetti di età pari o superiore a 60 anni.

Vaccino vivo attenuato (Fluenz Tetra)

- Il vaccino vivo attenuato è un vaccino quadrivalente, che viene somministrato con *spray* intranasale e autorizzato per l'uso in persone di età compresa tra 2 e 18 anni. I ceppi influenzali contenuti nel quadrivalente sono attenuati in modo da non causare influenza e sono adattati al freddo e sensibili alla temperatura, in modo che si replichino nella mucosa nasale piuttosto che nel tratto respiratorio inferiore.
  Il vaccino è stato introdotto per la prima volta in Italia nell'ambito della campagna antinfluenzale 2020-2021; è stato somministrato ai bambini tra 2 e 6 anni e, in seguito, anche ai bambini e adolescenti da 6 anni compiuti fino ai 18 anni.

Vaccino quadrivalente a DNA ricombinante (Supemtek)

- Il vaccino quadrivalente è prodotto tramite la tecnologia del DNA ricombinante che si basa sulla produzione di una proteina di un agente infettivo senza utilizzare il microrganismo selvaggio, mediante tecniche di ingegneria genetica che frammentano il DNA corrispondente e lo esprimono in diversi vettori di espressione "in vitro". È indicato dai 18 anni di età.

Efficacy of single *versus* boost vaccination against influenza virus in patients with multiple myeloma

Michael Hahn,[1] Paul Schnitzler,[2] Brunhilde Schweiger,[3] Christina Kunz,[4] Anthony D. Ho,[1] Hartmut Goldschmidt,[1] and Michael Schmitt[1]

haematologica 2015; 100:e286

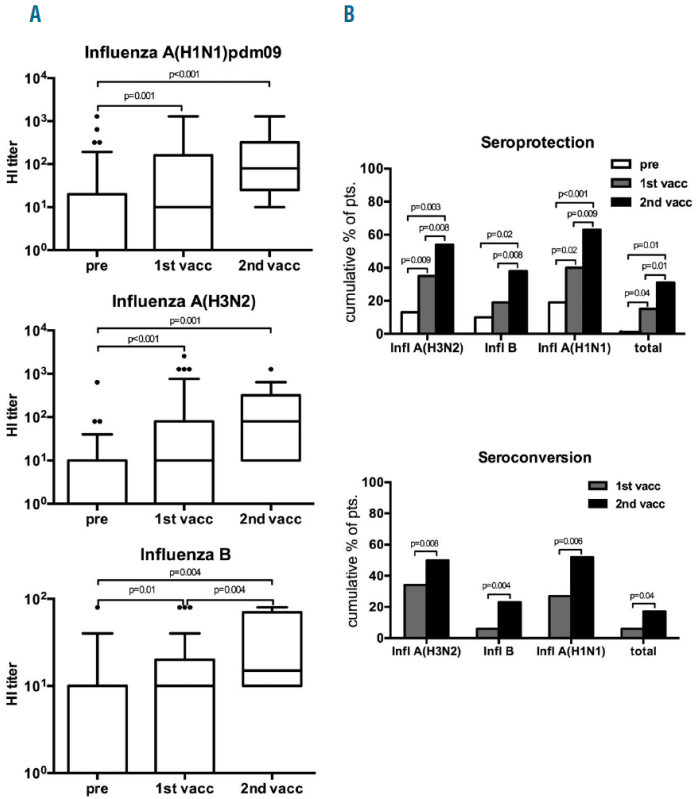


Figure 1. (A) Antibody titers against different influenza virus strains after sequential vaccination in myeloma patients. Box plots depict the increase of antibody titers against the different influenza strains. Differences of HI titers between two time points were analyzed using the signed-rank Wilcoxon test. Statistically significant *P*-values are shown in the plots. (B) Immune response to double vaccination against seasonal influenza. Bar charts depict seroprotection (upper panel) and seroconversion (lower panel) rates before, after the first and second vaccinations. Differences were analyzed by pairwise McNemar test. *P*-values are shown.

Table 2. Response to vaccination.

Cumulative seroprotection

	A(H1N1)	A(H3N2)	B/Yamagata	All strains
Pre vacc	19% (9/48)	13% (6/48)	10% (5/48)	0% (0/48)
1st vacc	40% (19/48)	35% (17/48)	19% (9/48)	15% (7/48)
2nd vacc	63% (30/48)	54% (26/48)	38% (18/48)	31% (15/48)

Cumulative seroconversion

	A(H1N1)	A(H3N2)	B/Yamagata	All strains
1st vacc	27% (13/48)	34% (16/48)	6% (3/48)	6% (3/48)
2nd vacc	52% (25/48)	50% (24/48)	23% (11/48)	17% (8/48)

Upper panel: percentages and absolute numbers of patients displaying seroprotection against single influenza strains as well as total seroprotection before the first vaccination and after the first and second vaccinations. Lower panel: percentages and absolute numbers of patients who seroconverted in response to the first and second vaccinations.

Double vaccination against influenza in MM patients seems to enhance protection and should be systematically studied. A larger and stratified cohort of patients would be needed for systematic assessment of associations between immunization results and clinical parameters. Furthermore, clinical effectiveness should also be studied, particularly with regards to the impact on influenza incidence, morbidity and mortality.

Differences and Temporal Changes in Risk of Invasive Pneumococcal Disease in Adults with Hematological Malignancies: Results from a Nationwide 16-Year Cohort Study

Clinical Infectious Diseases® 2021;72(3):463–71

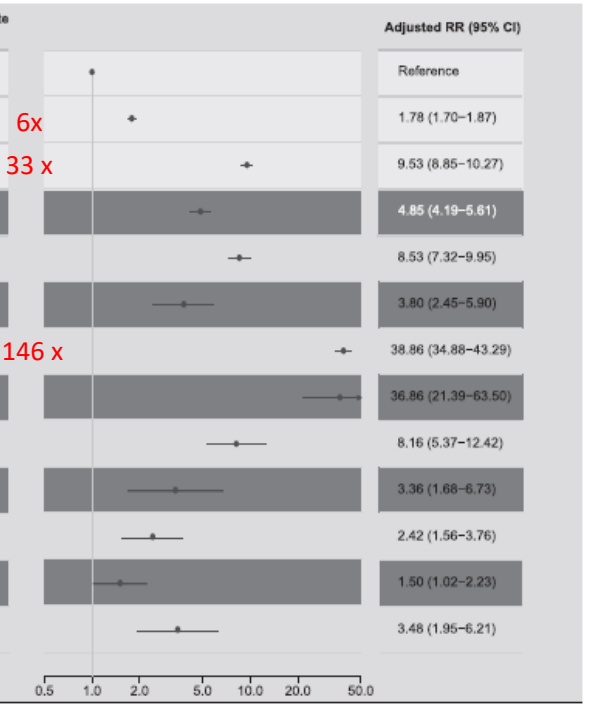
Michael Asger Andersen,[1,2] Carsten Utoft Niemann,[1] Klaus Rostgaard,[2] Tine Dalby,[3] Rasmus Sørrig,[1] Daniel M. Weinberger,[4] Henrik Hjalgrim,[1,2] and Zitta Barrella Harboe[3,5]

[1]Department of Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, [2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark, of Bacteria, Parasites and Fungi, Statens Serum Institut, Copenhagen, Denmark, [4]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connec and [5]Department of Pulmonary and Infectious Diseases, Hospital of Nordsjælland, University of Copenhagen, Copenhagen, Denmark

Patients with hematological malignancies (HM) are among those with the highest risk of IPD, with incidences ranging between **13–50** times higher when compared with the background population, and with HM patients accounting for up to **10%** of all IPD episodes in adults. We explored temporal changes in the risk of IPD and associated mortality in adults with HM, compared to the risk in patients with non- Hematological cancers and cancer-free individuals during 16 years in Denmark.

Table 1. Incidence and Case Fatality Rates of Invasive Pneumococcal Diseases in Patients With and Without Hematological Malignancies, Denmark 2000–2016

Disease	Person-years	Events (n)	Incidence (/100,000 PY) (95% CI)	Case Fatality Rate (%)	Adjusted RR (95% CI)
No malignancy	81428279	10303	12.7 (12.4–12.9)	14	Reference
Nonhematological malignancy	3361648	2382	70.9 (68.1–73.8)	26	1.78 (1.70–1.87)
Hematological malignancy	178616.45	742	415.4 (386.6–446.4)	16	9.53 (8.85–10.27)
Non–Hodgkin lymphoma	70093	184	262.5 (227.2–303.3)	21	4.85 (4.19–5.61)
Chronic lymphocytic leukemia	36655	163	444.7 (381.4–518.5)	11	8.53 (7.32–9.95)
Hodgkin lymphoma	18179	20	110 (71–170.5)	10	3.80 (2.45–5.90)
Multiple myeloma	17824	331	1857.1 (1667.4–2068.3)	18	38.86 (34.88–43.29)
Acute lymphoblastic leukemia	2197	13	591.8 (343.6–1019.2)	31	36.86 (21.39–63.50)
Acute myeloid leukemia	7213	23	318.9 (211.9–479.8)	4	8.16 (5.37–12.42)
Chronic myeloid leukemia	6344	8	126.1 (63.1–252.1)	12	3.36 (1.68–6.73)
Myelodysplastic syndrome	10164	20	196.8 (127–305)	20	2.42 (1.56–3.76)
Myeloproliferative neoplasm	33832	24	70.9 (47.5–105.8)	0	1.50 (1.02–2.23)
Other types of leukemias	6319	11	174.1 (96.4–314.4)	0	3.48 (1.95–6.21)



PY, number of events, crude incidence rates, and case-fatality rates are shown for all groups. RR for IPD in individuals with a hematological malignancy are adjusted for age, gender, calendar year, morbidity, and type of malignancy. Persons with more than one malignancy count multiple times for person years, events, and incidences.
Abbreviations: CI, confidence interval; IPD, invasive pneumococcal disease; PY, person years; RR, rate ratio.

Received: 5 December 2018 | Revised: 24 April 2019 | Accepted: 2 May 2019
DOI: 10.1002/cam4.2253

ORIGINAL RESEARCH

Cancer Medicine Open Access WILEY

Response to pneumococcal vaccination in multiple myeloma

Loïc Renaud[1] | Susanna Schraen[2] | Guillemette Fouquet[1] | Stephanie Guidez[3] | Hélène Demarquette[1] | Morgane Nudel[1] | Emilie Cayssials[4] | Claire Bories[1] | Charles Herbaux[1] | Thomas Systchenko[3] | Jean-Luc Faucompré[2] | Antoine Machet[3] | Florence Sabirou[3] | Antony Levy[3] | Arthur Bobin[3] | Valentine Richez[4] | Niels Moya[3] | Cécile Gruchet[3] | Deborah Desmier[3] | Zoe van de Wyngaert[1] | Benjamin Carpentier[1] | Salomon Manier[1] | Thierry Facon[1] | Stephen Harding[5] | Xavier Leleu[3]

	IgG (mg/L)	IgG2 (mg/L)	IgA (U/mL)	IgM (U/mL)
ASCT				
Pre	110.5	52.74	26.32	28.8
Post	14	7.8	2.97	3.7
Fold decrease	7.9	6.8	12.9	7.7
P	0.008	0.008	0.008	0.008
No ASCT				
Postvaccination	95.47	48.76	32.77	34.57
Late postvaccination	34.34	17.10	4.13	8.48
Fold decrease	2.8	2.9	7.9	4.1
P	0.001	0.002	0.04	6.10 e-5
ASCT vs no ASCT				
P	0.03	0.03	0.27	0.64

TABLE 3 Geometric mean concentration of anti-PCP IgG, IgG2, IgA, and IgM in 8 patients with multiple myeloma pre- and post-autologous stem cell transplantation and in 15 patients after vaccination and several months later

In conclusion, we demonstrated myeloma has the ability to demonstrate a response to pneumococcal vaccine, independently of preexisting hypogammaglobulinemia and disease response and possibly of treatment induced immunodepression, with an expected drop of response overtime and immediately following autologous transplantation. This response tends to be associated with protection against pneumococcal infection. Further studies in a larger group of patients is warranted to validate this data.

Pneumococcal Vaccine Timing for Adults

Make sure your patients are up to date with pneumococcal vaccination.

CDC recommends pneumococcal vaccination for

- Adults 65 years old and older
- Adults 19 through 64 years old with certain underlying medical conditions or other risk factors:
  - Alcoholism
  - Cerebrospinal fluid leak
  - Chronic heart/liver/lung disease
  - Chronic renal failure*
  - Cigarette smoking
  - Cochlear implant
  - Congenital or acquired asplenia*
  - Congenital or acquired immunodeficiencies*
  - Diabetes
  - Generalized malignancy*
  - HIV infection*
  - Hodgkin disease*
  - Iatrogenic immunosuppression*
  - Leukemia*
  - Lymphoma*
  - Multiple myeloma*
  - Nephrotic syndrome*
  - Sickle cell disease or other hemoglobinopathies*
  - Solid organ transplants*

* Considered an immunocompromising condition

Pneumococcal vaccines

PCV13: 13-valent pneumococcal conjugate vaccine (Prevnar13®)
PCV15: 15-valent pneumococcal conjugate vaccine (Vaxneuvance™)
PCV20: 20-valent pneumococcal conjugate vaccine (Prevnar20®)
PPSV23: 23-valent pneumococcal polysaccharide vaccine (Pneumovax®)

For those who have never received a pneumococcal vaccine or those with unknown vaccination history

Administer one dose of PCV15 or PCV20.

If **PCV20** is used, their pneumococcal vaccinations are complete.

PCV20

If **PCV15** is used, follow with one dose of PPSV23.

- The recommended interval is at least 1 year.
- The minimum interval is 8 weeks and can be considered in adults with an immunocompromising condition*, cochlear implant, or cerebrospinal fluid leak.
- Their pneumococcal vaccinations are complete.

PCV15 → At least 1 year apart (8 weeks can be considered) → PPSV23

For those who previously received PPSV23 but who have not received any pneumococcal conjugate vaccine (e.g., PCV13, PCV15, PCV20)

You may administer one dose of PCV15 or PCV20.

Regardless of which vaccine is used (PCV15 or PCV20):

- The minimum interval is at least 1 year.
- Their pneumococcal vaccinations are complete.

PPSV23 → At least 1 year apart → PCV15 or PCV20

NCIRDig410 | 04/01/22

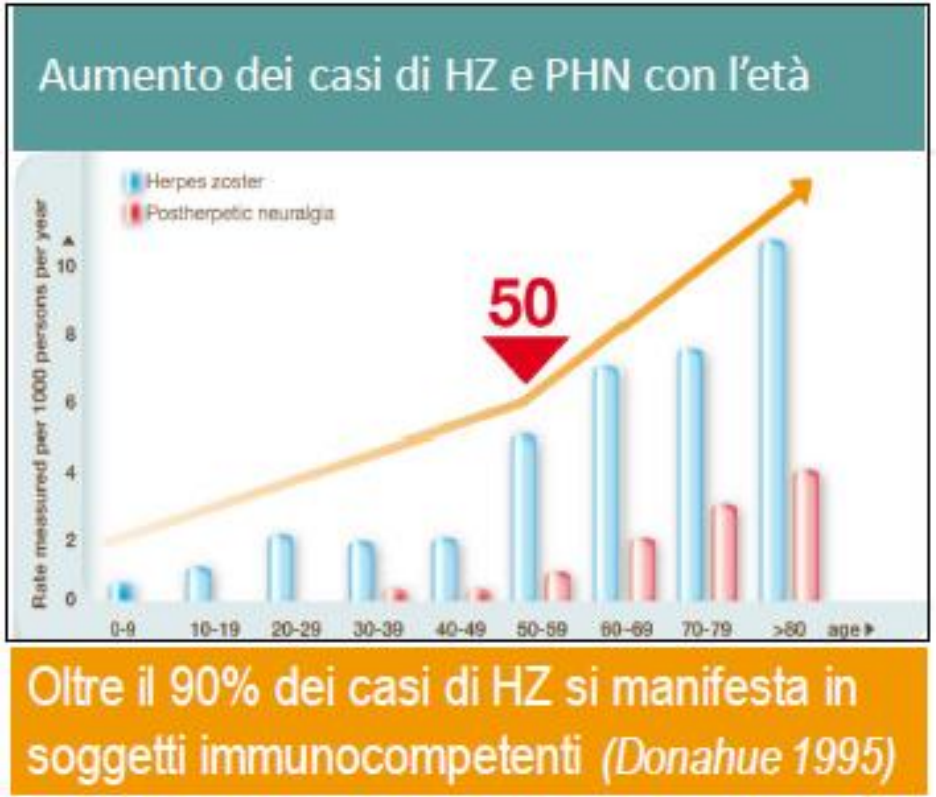
www.cdc.gov/pneumococcal/vaccination.html

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Herpes zoster: incidenza e complicanze

Sintomi e diagnosi dell'Herpes Zoster
l'Herpes Zoster compare prevalentemente a livello toracico, anche se ci possono essere altre localizzazioni, e interessa tipicamente un solo lato del corpo
La malattia ha inizio con una fase iniziale (prodromica) pruriginosa e dolorosa, seguita dalla comparsa di vescicole piene di liquido. Le lesioni possono continuare per circa 7 giorni, al termine dei quali si formano le croste, che spariscono in 3 settimane. Le vescicole dell'Herpes Zoster possono comparire anche sul viso, interessando l'occhio e il nervo ottico
Altri sintomi comprendono: • febbre • mal di testa • bruciore • disturbi di stomaco
La diagnosi dell'infezione è clinica e non necessita solitamente di test di laboratorio. L'Herpes Zoster è solitamente accertato (diagnosticato) sulla base della comparsa del dolore e delle tipiche vescicole (eruzione cutanea) su un solo lato del corpo. Sono anche disponibili esami di laboratorio, qualora il medico li ritenga opportuni

Le complicanze dell'Herpes Zoster
• nevralgia post-erpetica, la più comune, con un'incidenza che aumenta parallelamente con l'età: causa un dolore molto forte a livello del nervo coinvolto, che perdura per almeno 90 giorni dopo l'eruzione cutanea; la durata della nevralgia post-erpetica è variabile da pochi mesi ad anni o, addirittura, per tutta la vita con impatto negativo e disabilitante sulla qualità della vita stessa del paziente
• sindrome di Ramsay Hunt, quando l'infezione coinvolge il nervo facciale, vicino all'orecchio causando paralisi facciale e perdita dell'udito
• infezione degli occhi e perdita della vista, quando l'infezione coinvolge il nervo trigemino con conseguente infiammazione del nervo ottico, glaucoma, ulcere e cicatrici sulla superficie dell'occhio; questa complicanza può portare a perdita della vista
• infezione batterica delle vescicole
• cicatrici permanenti
• infezione di polmoni, fegato, meningi, encefalo



BJC
British Journal of Cancer (2017) 116, 1643–1651 | doi: 10.1038/bjc.2017.124 BJC OPEN

Keywords: herpes zoster; malignancy; cancer; CPRD; haematology; oncology; shingles

Herpes zoster risk after 21 specific cancers: population-based case–control study

Erik Hansson[1], Harriet J Forbes[1], Sinéad M Langan[1], Liam Smeeth[1] and Krishnan Bhaskaran*[,1]

[1]Department of Non-Communicable Diseases Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

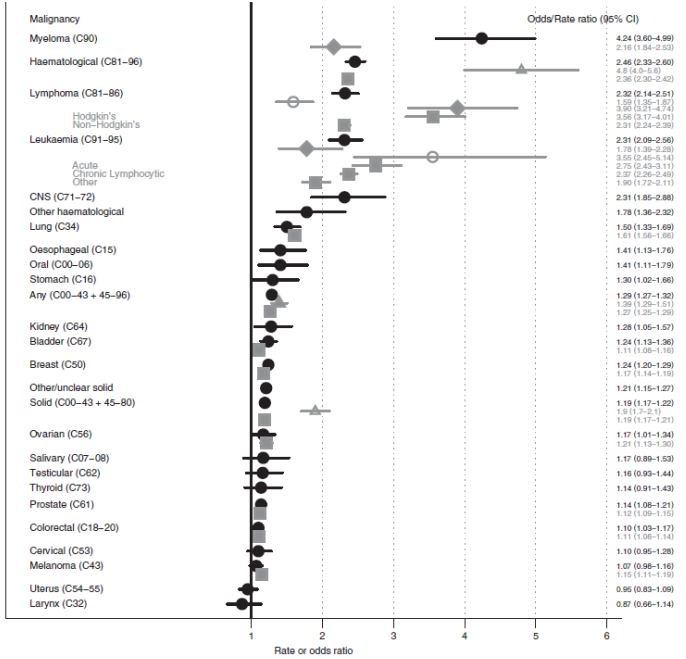
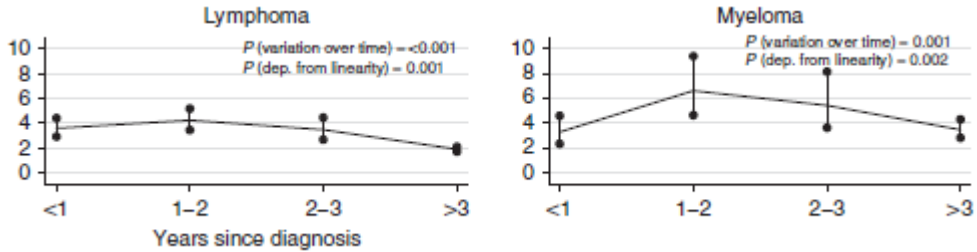


Figure 2. Odds ratios of zoster for different malignancy diagnoses adjusted for potential confounders, compared to previous studies. Black filled circles—present study estimates. Previous studies in grey: Filled triangle—(Liu *et al*, 2015), square—(Yenikomshian *et al*, 2015), hollow triangle—(Habel *et al*, 2013) hollow circle—(Heymann *et al*, 2008), diamond—(Forbes *et al*, 2014).

Table 2. Prevalence of malignancies among cases and controls, and association between prevalent/previous malignancy and incident zoster

	Controls	Cases	Model 1[a]		Model 2[b]		Model 3[c]	
Malignancy type	*N* (%)	*N* (%)	OR (with 95% CI)	*P*	OR (with 95% CI)	*P*	OR (with 95% CI)	*P*
No malignancy	683331 (93.3)	175952 (91.6)	1 (–)		1 (–)		1 (–)	
Malignancy (C00–43 + 45–96)	48704 (6.7)	16129 (8.4)	1.30 (1.27–1.33)	<0.001	1.29 (1.27–1.32)	<0.001	1.29 (1.27–1.32)	<0.001
Any haematological (C81–96)	3725 (0.5)	2393 (1.2)	2.49 (2.35–2.64)	<0.001	2.46 (2.33–2.60)	<0.001	2.42 (2.28–2.56)	<0.001
Lymphoma (C81–86)	1979 (0.3)	1213 (0.6)	2.35 (2.17–2.54)	<0.001	2.32 (2.14–2.51)	<0.001	2.28 (2.11–2.47)	<0.001
Myeloma (C90)	356 (0)	367 (0.2)	4.27 (3.63–5.02)	<0.001	4.24 (3.60–4.99)	<0.001	4.05 (3.43–4.77)	<0.001
Leukaemia (C91–95)	1198 (0.2)	713 (0.4)	2.34 (2.11–2.59)	<0.001	2.31 (2.09–2.56)	<0.001	2.29 (2.07–2.54)	<0.001
Other haematological (C96/88)	192 (0)	100 (0.1)	1.83 (1.40–2.38)	<0.001	1.78 (1.36–2.32)	<0.001	1.75 (1.34–2.29)	<0.001

[a]adjusted for matching factors only, that is, age, sex, practice and calendar time.
[b]adjusted additionally for diabetes, SLE, IBD, RA, COPD, depression, asthma, renal failure, HIV, OID, inhaled corticosteroid treatment, BMI, smoking and alcohol use.
[c]Adjusted additionally for covariates potentially on the causal pathway that is, GP prescribed oral corticosteroids and other immunosuppression, and HSCT. See Supplementary Appendix B for estimates of the other covariates.



Herpes zoster risk and burden of disease in immunocompromised populations: a population-based study using health system integrated databases, 2009–2014

Muñoz-Quiles *et al. BMC Infectious Diseases* (2020) 20:905
https://doi.org/10.1186/s12879-020-05648-6

Cintia Muñoz-Quiles[1*†], Mónica López-Lacort[1†], Javier Díez-Domingo[1,2] and Alejandro Orrico-Sánchez[1]

Table 2 Incidence rates of HZ (per 1000 persons - year) by age groups and IC condition in the Valencia Region in 2009–2014

IC condition	Incidence rate of HZ per 1000 PY (95% CI)							
	18–29	30–39	40–49	50–59	60–69	70–79	≥ 80	Overall
Population	2.32 (2.27–2.37)	2.46 (2.42–2.51)	2.93 (2.88–2.98)	5.88 (5.80–5.96)	8.63 (8.53–8.74)	9.82 (9.69–9.95)	10 (9.83–10.16)	5.02 (4.99–5.04)
HSCT	42.37 (21.89–74.02)	38.94 (24.11–59.53)	50.13 (35.81–68.26)	69.24 (54.08–87.33)	61.82 (47.5–79.1)	51.99 (24.93–95.61)	0	56.07 (48.86–64.04)
SOT	6 (3.61–9.37)	6.23 (4.58–8.29)	7.31 (5.83–9.05)	14.89 (12.87–17.14)	17.02 (14.93–19.32)	14.21 (12.06–16.62)	17.26 (13.83–21.29)	12.65 (11.8–13.54)
HN	4.96 (4.1–5.94)	4.53 (3.77–5.41)	5.86 (4.97–6.87)	13.95 (12.5–15.52)	18.03 (16.46–19.7)	20.06 (18.37–21.85)	18.44 (16.46–20.6)	11.99 (11.48–12.52)

Table 4 Incidence rates of HZ complications (per 100,000 persons - year), overall and by age groups and IC condition

IC condition	Incidence rate of HZ complications per 100,000 PY (95% CI)							
	18–29	30–39	40–49	50–59	60–69	70–79	≥ 80	Overall
Population	0.35 (0.18–0.59)	0.75 (0.53–1.04)	1.09 (0.81–1.44)	1.34 (0.99–1.77)	4.34 (3.63–5.15)	10.89 (9.6–12.31)	21.35 (19.08–23.81)	3.63 (3.39–3.88)
HSCT	310.46 (7.86–1729.79)	161.25 (4.08–898.45)	759.63 (305.41–1565.13)	161.39 (19.55–583)	232.54 (47.95–679.57)	0 (0–1492.1)	0 (0–25,474.82)	300.77 (164.43–504.63)
SOT	0 (0–112.66)	38.5 (7.94–112.52)	41.92 (13.61–97.83)	35.98 (11.68–83.97)	90.74 (49.61–152.25)	50.33 (18.47–109.55)	36.08 (4.37–130.34)	50.16 (34.94–69.76)
HN	4.13 (0.1–23)	10.68 (2.2–31.22)	40.77 (20.35–72.95)	15.49 (4.22–39.65)	47.43 (25.93–79.58)	51.98 (29.09–85.73)	52.86 (25.35–97.22)	31.8 (24.15–41.11)

Table 5 Recurrence rates of HZ (per 100 persons - year), overall and by age groups and IC condition

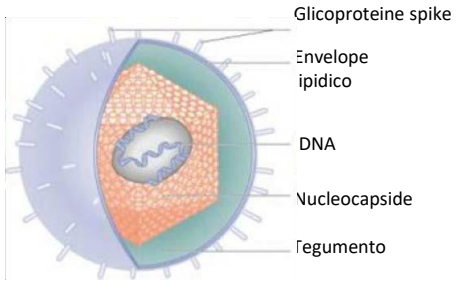
IC condition	Recurrence rate of HZ per 100 PY (95% CI)							
	18–29	30–39	40–49	50–59	60–69	70–79	≥ 80	Overall
Population	0.99 (0.9–1.09)	1.13 (1.05–1.21)	1.19 (1.11–1.27)	1.31 (1.25–1.38)	1.7 (1.63–1.77)	2.2 (2.12–2.28)	2.71 (2.6–2.83)	1.66 (1.63–1.69)
HSCT	7.38 (1.52–21.56)	2.33 (0.28–8.4)	5.05 (2.18–9.95)	5.39 (2.87–9.22)	5.48 (3.07–9.04)	13.84 (4.49–32.31)		5.5 (4.03–7.34)
SOT	2.83 (0.58–8.26)	2.87 (1.15–5.92)	3.12 (1.7–5.23)	2.94 (1.94–4.28)	2.62 (1.8–3.68)	3.55 (2.38–5.1)	3.27 (1.74–5.59)	3.01 (2.5–3.58)
HN	3.32 (1.93–5.31)	1.89 (1.01–3.23)	2.04 (1.21–3.23)	3.27 (2.45–4.27)	3.08 (2.42–3.85)	4.16 (3.39–5.04)	4.03 (3.08–5.18)	3.35 (3.01–3.73)

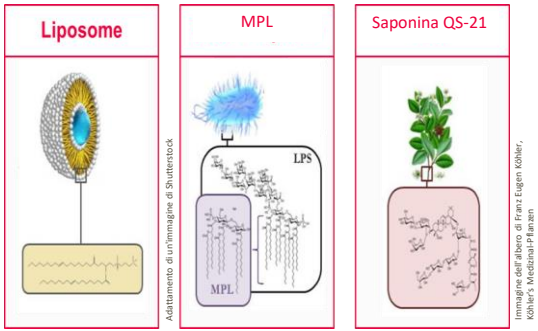
Composizione del vaccino RZV

Vaccino RZV

Antigene
Glicoproteina E (gE) - 50 µg

Sistema adiuvante
$AS01_B$: QS-21* e MPL – 50 µg ciascuno





*Adiuvante QS-21 concesso in licenza da Antigenics Inc, una società interamente controllata da Agenus Inc., società del Delaware, Stati Uniti; gE, glicoproteina; MPL, 3-O-desacyl-4'-monofosforil lipide A; QS-21, Quillaja saponaria Molina, frazione 21

1. Lal H et al., N Eng J Med 2015, 372: 2087-96; 2. Cunnigham A et al, N Eng J Med 2016,75:1019-32

RCT	ZOE-50 (Zoster-006)	ZOE-70 (Zoster-022)
Schedula	2 dosi (intervallo 2 mesi)	
Obiettivi primari	VE_{HZ} in soggetti ≥50 aa	VE_{HZ} in soggetti ≥70 aa
Obiettivi primari (pooled analysis)	VE_{PHN} in ≥70 aa VE_{HZ} in ≥70 aa	

Tabella 1: Efficacia di Shingrix verso HZ (mTVC)

Età	Shingrix			Placebo			
(anni)	Numero di soggetti valutati	Numero di casi HZ	Tasso di incidenza per 1000 anni persona	Numero di soggetti valutati	Numero di casi HZ	Tasso di incidenza per 1000 anni persona	Efficacia del vaccino (%) [95% IC]
ZOE-50*							
≥ 50	7.344	6	0,3	7.415	210	9,1	**97,2** [93,7; 99,0]
50-59	3.492	3	0,3	3.525	87	7,8	**96,6** [89,6; 99,4]
≥ 60	3.852	3	0,2	3.890	123	10,2	**97,6** [92,7; 99,6]
60-69	2.141	2	0,3	2.166	75	10,8	**97,4** [90,1; 99,7]
Analisi aggregata ZOE-50 e ZOE-70**							
≥ 70	8.250	25	0,8	8.346	284	9,3	**91,3** [86,8 ; 94,5]
70-79	6.468	19	0,8	6.554	216	8,9	**91,3** [86,0; 94,9]
≥ 80	1.782	6	1,0	1.792	68	11,1	**91,4** [80,2; 97,0]

Tabella 2: Efficacia di Shingrix contro la PHN (mTVC)

Età (anni)	Shingrix			Placebo			Efficacia del vaccino (%) [95% IC]
	Numero di soggetti valutati	Numero di casi di PHN*	Tasso di incidenza per 1000 anni persona	Numero di soggetti valutati	Numero di casi di PHN	Tasso di incidenza per 1000 anni persona	
ZOE-50**							
≥ 50	7.340	0	0,0	7.413	18	0,6	**100** [77,1; 100]
50-59	3.491	0	0,0	3.523	8	0,6	**100** [40,8; 100]
≥ 60	3.849	0	0,0	3.890	10	0,7	**100** [55,2; 100]
60-69	2.140	0	0,0	2.166	2	0,2	**100**§ [< 0; 100]
Analisi aggregata ZOE-50 e ZOE-70***							
≥ 70	8.250	4	0,1	8.346	36	1,2	**88,8** [68,7; 97,1]
70-79	6.468	2	0,1	6.554	29	1,2	**93,0** [72,4; 99,2]
≥ 80	1.782	2	0,3	1.792	7	1,1	**71,2**§ [< 0; 97,1]

Effect of Recombinant Zoster Vaccine on Incidence of Herpes Zoster After Autologous Stem Cell Transplantation
A Randomized Clinical Trial

Adriana Bastidas, MD; Javier de la Serna, MD; Mohamed El Idrissi, MSc; Lidia Oostvogels, MD; Philippe Quittet, MD; Javier López-Jiménez, MD, PhD; Filiz Vural, MD; David Pohlreich, MD; Tsila Zuckerman, MD; Nicolas C. Issa, MD; Gianluca Gaidano, MD, PhD; Je-Jung Lee, MD; Sunil Abhyankar, MD; Carlos Solano, MD, PhD; Jaime Perez de Oteyza, MD, PhD; Michael J. Satlin, MD; Stefan Schwartz, MD; Magda Campins, MD, PhD; Alberto Rocci, MD, PhD; Carlos Vallejo Llamas, MD, PhD; Dong-Gun Lee, MD, PhD; Sen Mui Tan, MD; Anna M. Johnston, MBBS; Andrew Grigg, MBBS, FRACP, MD; Michael J. Boeckh, MD, PhD; Laura Campora, MD; Marta Lopez-Fauquet, PhD; Thomas C. Heineman, MD, PhD; Edward A. Stadtmauer, MD; Keith M. Sullivan, MD; for the ZOE-HSCT Study Group Collaborators

JAMA. 2019;322(2):123-133.

Participants were randomized to receive 2 doses of either recombinant zoster vaccine (n = 922) or placebo (n = 924) administered into the deltoid muscle; **the first dose was given 50 to 70 days after transplantation and the second dose 1 to 2 months thereafter.**

Table 2. Incidence Rates and Incidence Rate Ratios for First or Only Herpes Zoster Episode During the Study

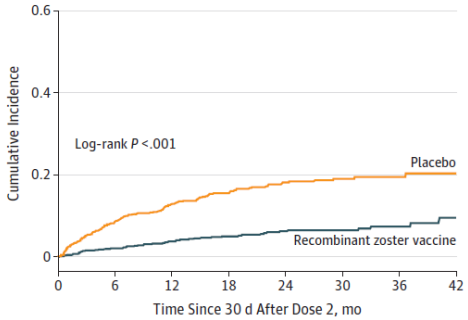
	Recipients, No.	Confirmed Cases, No.	Cumulative Follow-up Period, y[a]	Herpes Zoster Incidence Rate Per 1000 Person-Years	Incidence Rate Ratio (95% CI)[b]
Modified Total Vaccinated Cohort (Primary End Point)[c]					
Recombinant zoster vaccine	870	49	1633.1	30.0	0.32 (0.22-0.44)
Placebo	851	135	1431.9	94.3	
Total Vaccinated Cohort (Sensitivity Analysis for Primary End Point)[c]					
Recombinant zoster vaccine	922	70	2017.5	34.7	0.36 (0.27-0.48)
Placebo	924	172	1798.8	95.6	

[a] Cumulative follow-up period is the sum of follow-up periods (censored at the first occurrence of a confirmed herpes zoster episode and at the occurrence of treatment for relapse [modified total vaccinated cohort only]). For any participant who developed herpes zoster, subsequent follow-up data were excluded from analysis. Participants were followed up for herpes zoster episodes from the first vaccine dose to a minimum of 13 months after the second dose.

[b] $P < .001$ (2-sided; conditional to the number of cases); no adjustments were made.

[c] The total vaccinated cohort included all participants who received at least the first study dose. The modified total vaccinated cohort included all participants who received 2 doses of the same study vaccine; participants developing a herpes zoster episode sooner than 1 month after receiving the second vaccine dose were excluded from the analysis.

Figure 2. Cumulative Incidence of Herpes Zoster Overall (Modified Total Vaccinated Cohort)



No. at risk								
Placebo	851	704	604	464	337	209	112	40
Recombinant zoster vaccine	870	779	682	537	396	268	141	49
No. with ≥1 herpes zoster episode								
Placebo	0	69	100	117	130	133	134	135
Recombinant zoster vaccine	0	17	30	38	44	45	47	49

Injection site reactions were recorded in 86% of vaccine and 10% of placebo recipients, of which pain was the most common, occurring in 84% of vaccine recipients (grade 3: 11%). Unsolicited and serious adverse events, potentially immune-mediated diseases, and underlying disease relapses were similar between groups at all time points.

68.2% vaccine efficacy

89.3% reduction of postherpetic neuralgia

Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis

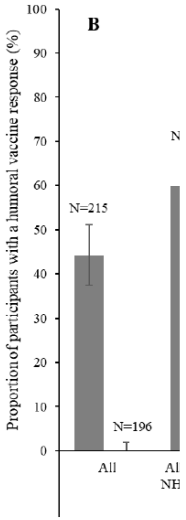
Lancet Infect Dis 2019; 19: 988–1000

*Alemnew F Dagnew, Osman Ilhan, Won-Sik Lee, Dariusz Woszczyk, Jae-Yong Kwak, Stella Bowcock, Sang Kyun Sohn, Gabriela Rodriguez Macías, Tzeon-Jye Chiou, Dimas Quiel, Mickael Aoun, Maria Belen Navarro Matilla, Javier de la Serna, Samuel Milliken, John Murphy, Shelly A McNeil, Bruno Salaun, Emmanuel Di Paolo, Laura Campora, Marta López-Fauqued, Mohamed El Idrissi, Anne Schuind, Thomas C Heineman, Peter Van den Steen, Lidia Oostvogels, on behalf of the Zoster-039 study group**

At month 2, 142 (**65.4%**) of 217 participants in the vaccine group and one (**0.5%**) of 198 participants in the placebo group had a humoral vaccine response.

Excluding pts with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukaemia, at month 2, 119 (**80.4%**) of 148 participants had a humoral vaccine response to adjuvanted recombinant zoster vaccine, compared with one (**0.8%**) of 130 participants in the placebo group.

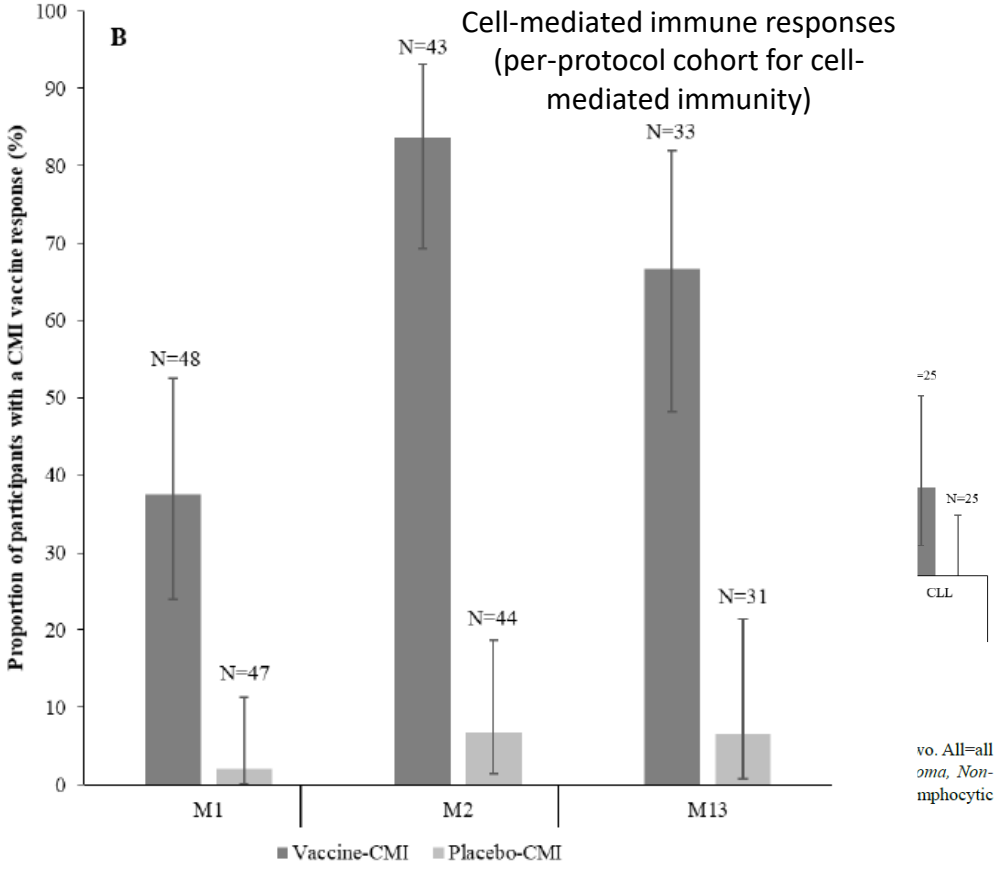
At **month 13** in the vaccine group, 86 (**52.1%**) of 165 participants in the vaccine group had a humoral vaccine response, compared with five (3.6%) of 140 participants in the placebo group.



(B) Proportion of participa

N=total number of particip participants. All excluding *Hodgkin T-cell Lymphom* Leukaemia.

Cell-mediated immune responses (per-protocol cohort for cell-mediated immunity)

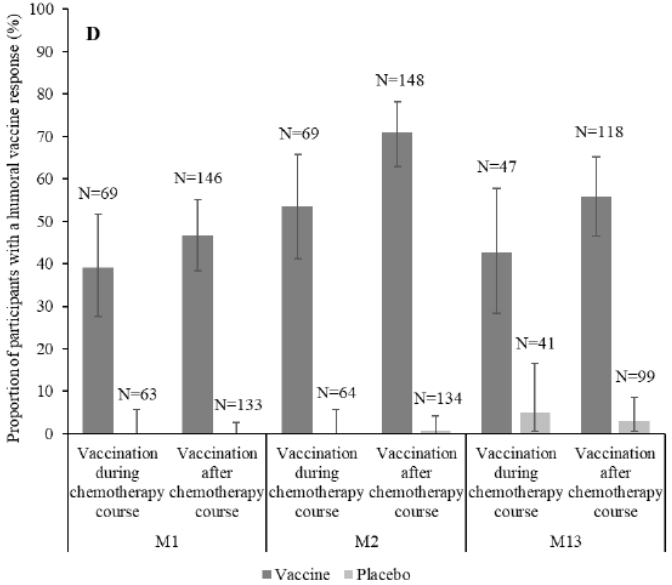


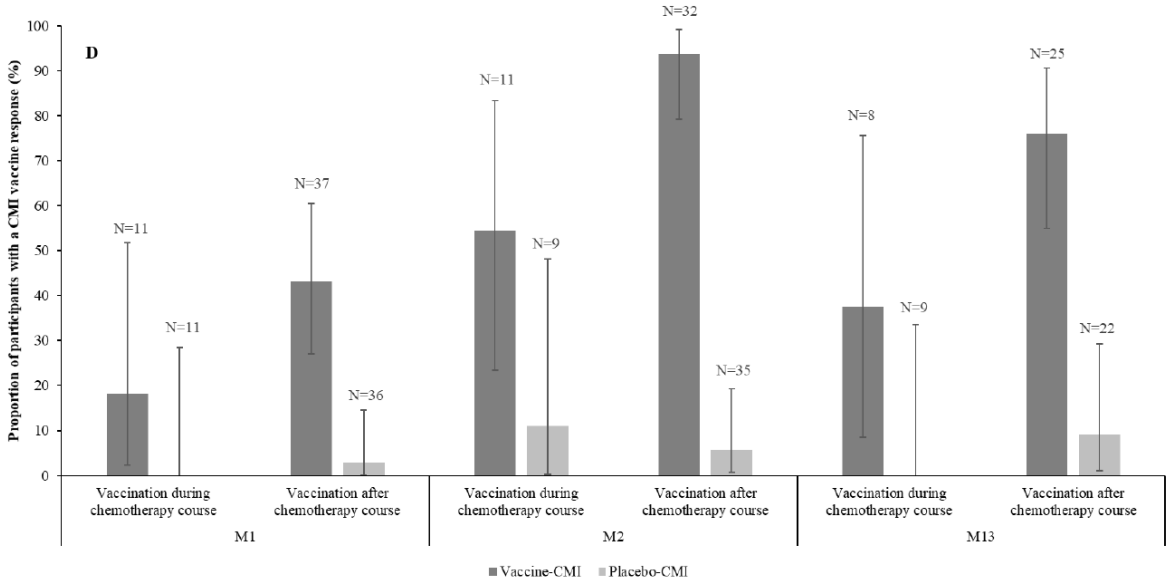
vo. All=all *oma, Non-* mphocytic

Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis

Lancet Infect Dis 2019; 19: 988–1000

*Alemnew F Dagnew, Osman Ilhan, Won-Sik Lee, Dariusz Woszczyk, Jae-Yong Kwak, Stella Bowcock, Sang Kyun Sohn, Gabriela Rodriguez Macías, Tzeon-Jye Chiou, Dimas Quiel, Mickael Aoun, Maria Belen Navarro Matilla, Javier de la Serna, Samuel Milliken, John Murphy, Shelly A McNeil, Bruno Salaun, Emmanuel Di Paolo, Laura Campora, Marta López-Fauqued, Mohamed El Idrissi, Anne Schuind, Thomas C Heineman, Peter Van den Steen, Lidia Oostvogels, on behalf of the Zoster-039 study group**





A post-hoc analysis revealed that the incidence of HZ was 8·5 per 1000 person-years in the vaccine group and 66·2 per 1000 person-years in the placebo group, resulting in **87·2%** (95% CI 44·3–98·6; p=0·0021) efficacy against HZ. Median follow-up was 11·1 months (IQR 10·3–12·2) from 30 days after dose 2.

Adjuvanted recombinant zoster vaccine decreases herpes zoster-associated pain and the use of pain medication across 3 randomized, placebo-controlled trials

PAIN 164 (2023) 741–748

Joon Hyung Kim[a,*], Robert Johnson[b], Martina Kovac[a], Anthony L. Cunningham[c,d], Mohamed Amakrane[e], Keith M. Sullivan[f], Alemnew F. Dagnew[a], Desmond Curran[e], Anne Schuind[a]

Table 1

Reduction in the duration of clinically significant herpes zoster-associated pain in participants with confirmed herpes zoster.

Study	RZV			Placebo			VE (%)	95% CI	*P*
	N	n	T (d)	N	n	T (d)			
ZOE-50	9	7	146	254	221	6705	26.9	(−59.6, 66.5)	0.432
ZOE-70	23	18	628	223	198	9633	28.4	(−17.7, 56.4)	0.188
ZOE-HSCT*	49	37	892	135	120	6275	38.5	(11.1, 57.5)	0.010

The associated hazard ratio for reduction of the duration of clinically significant HZ-associated pain in the ZOE-HSCT study has been published previously.[1]

* This analysis excluded pain linked to a confirmed HZ case after relapse of the pre-existing malignant disease.

CI, confidence interval; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; n, number of participants with at least 1 confirmed HZ episode and at least 1 d of clinically significant HZ-associated pain; N, number of participants with at least 1 confirmed HZ episode; RZV, recombinant zoster vaccine; T, sum of follow-up period (for participants without clinically significant pain, T is 1; for participants with clinically significant pain, T is the duration of clinically significant pain) expressed in d; VE, vaccine efficacy (adjusted by age strata and regions in the ZOE-50 and ZOE-70 studies); ZOE, Zoster Efficacy Study.

Table 2

Mean and median duration of clinically significant herpes zoster-associated pain and difference between the recombinant zoster vaccine and placebo groups.

Study	RZV			Placebo			Placebo-RZV*	
	N	Duration (d)		N	Duration (d)		Difference (d)	*P*
		Mean (SD)	Median (min, max)		Mean (SD)	Median (min, max)	Mean (SD)	
ZOE-50	7	20.6 (26.8)	11.0 (3.0, 78.0)	221	30.2 (52.0)	15.0 (1.0, 464.0)	9.6	0.6267
ZOE-70	18	34.6 (45.5)	13.5 (1.0, 162.0)	198	48.5 (101.4)	19.0 (1.0, 834.0)	13.9	0.5653
ZOE-HSCT†	37	23.8 (31.9)	14.0 (1.0, 178.0)	120	52.2 (127.8)	24.0 (1.0, 1025.0)	28.4	0.1835
Total (pooled)‡	62	26.6 (35.7)	12.5 (1.0, 178.0)	539	41.8 (92.6)	17.0 (1.0, 1025.0)	15.2	0.1992

* This column describes calculated difference between the RZV and placebo group.

† This analysis excluded pain linked to a confirmed HZ case after relapse of the pre-existing malignant disease.

‡ These results refer to the pooled data of ZOE-50, ZOE-70, and ZOE-HSCT studies, where *P* values were calculated using the Student two-sample *t* test.

HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; max, maximum; min, minimum; N, number of participants with at least 1 confirmed HZ episode with clinically significant HZ-associated pain; RZV, recombinant zoster vaccine; ZOE, Zoster Efficacy Study.

Towards a personalized preventive strategy of herpes zoster infection in patients with hematological diseases or submitted to hematopoietic stem cell transplant: a position paper from an ad hoc Italian expert panel

C.Girmenia, F.Ciceri, P.Corradini, A.Cuneo, F.D'Ancona, P.Musto,A.M. Risitano, M.Teresa Voso, A. Venditti, G. Barosi.

Haematologica, 2024

Herpes zoster prevention in multiple myeloma

- MM is at high risk for HZ in general and particularly during proteosome inhibitors treatment and both AVP and vaccination are recommended.
- Acyclovir at a dose of 400 mg per day is an appropriate anti HZ viral prophylaxis in malignant and non malignant HD and in subjects undergoing autologous and allogeneic HSCT.
- In patients with MM not eligible for auto-HSCT aRZV is recommended possibly at the onset of disease before start of hematologic treatment. AVP is also recommended during proteosome inhibitors treatment at least until one month after the second vaccine dose.
- In patients with MM eligible for auto-HSCT the Expert Panel agrees to delay aRZV administration two months after transplant, while AVP should be administered from the onset of induction treatment to one month after the second vaccine dose.

COVID-19 Vaccination Response and Its Practical Application in Patients With Chronic Lymphocytic Leukemia

HemaSphere

HemaSphere (2023) 7:1(e811).

Mazyar Shadman[1,2], Catherine Liu[2,3,4], Katherine Eakle[5], Hwai J. Hiew[6], Juliana M.L. Biondo[5], Paolo Ghia[7], Anthony R. Mato[8]

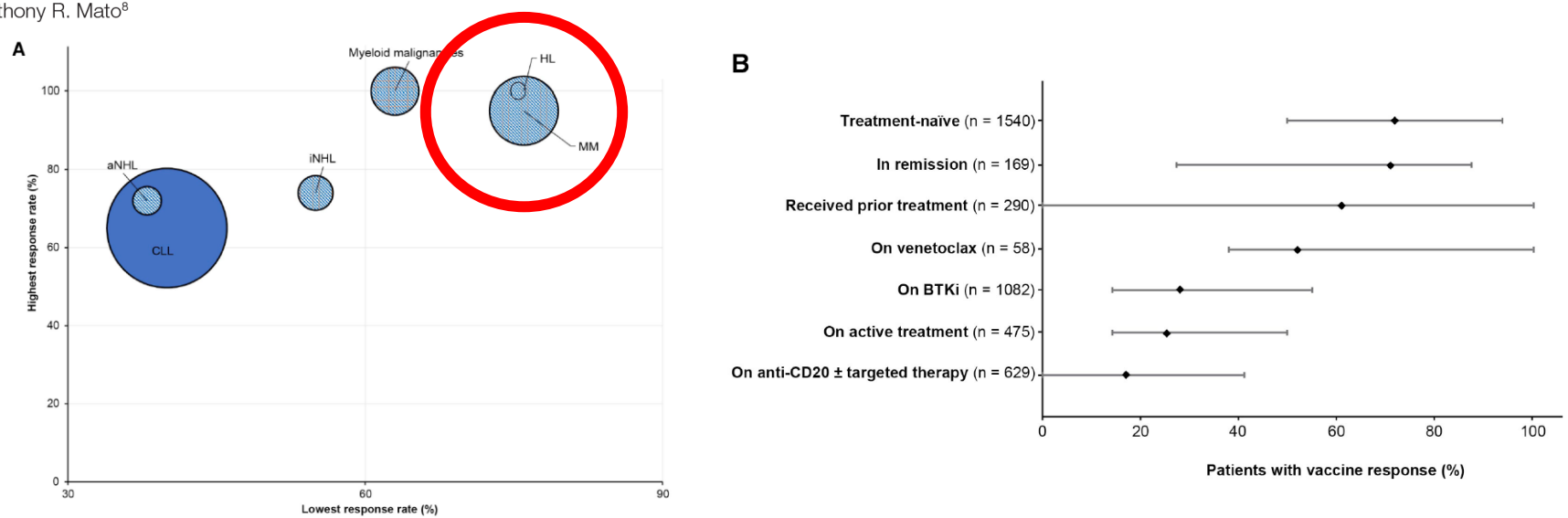


Figure 2. Vaccine antibody responses by disease area (A)[a] and treatment status and type (B)[b]. [a]The data for other hematologic malignancies represent only data present in those references that were included for the CLL analysis, and are not a comprehensive evaluation of response rates in those malignancies. The visual shows the range of vaccine responses for each disease area, with the lowest response rate within the range shown on the x-axis and the highest response on the y-axis. The size of the bubbles represent the number of patients within that disease area across all studies; [b]Diamond represents median; bar represents range. Median (range) % responders by treatment status or treatment type: treatment-naive, 72 (50–94); active treatment, 25.3 (14–50); prior treatment, 61 (0–100); remission, 71 (27.2–87.5); venetoclax, 52 (38–100); BTKi, 28 (14.3–55); anti-CD20, 17 (0–41). AML/MDS = acute myeloid leukemia/myelodysplastic syndromes; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; CR = complete remission; HL = Hodgkin lymphoma; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NHL = non-Hodgkin lymphoma; TN = treatment-naive; ven = venetoclax.

Infection-control strategies in MM

- Epidemiology and prophylaxis of bacterial, fungal and viral infections
- Vaccination schedules and COVID-19 prevention in MM populations
- Focus on anti-BCMA treatments

Infections in relapsed/refractory MM patients treated with daratumumab and isatuximab : phase III trials

Author, year	Therapy	Grade 3-5 infections	
		Study group	Control group
Palumbo, 2016	Daratumumab, bortezomib and dexamethasone vs bortezomib and dexamethasone . Median previous lines 2	Overall infections: 21.4% Pneumonia 8.2%	Overall infections: 19% Pneumonia: 9.7%
Dimopoulos, 2016	Daratumumab, lenalidomide and dexamethasone vs lenalidomide and dexamethasone Median previous lines 1	Overall infections: 28.3% Pneumonia. 7.8%	Overall infections: 22.8% Pneumonia: 8.2%
Dimopoulos, 2020	Carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone Median previous lines 2	Overall infections: 28.9% Pneumonia 13.3%	Overall infections: 12.4% Pneumonia 8.5%
Dimopoulos 2021	Daratumumab plus pomalidomide and dexamethasone vs pomalidomide and dexamethasone Median previous lines 2	Overall infections: 24% Pneumonia: 11%	Overall infections: 20% Pneumonia: 6%
Sonneweld 2022	Daratumumab, Bortezomib, and Dexamethasone vs Bortezomib, and Dexamethasone Median previous lines 2	Overall infections:16.1 % Pneumonia: 10.7%	Overall infections:11.8 % Pneumonia: 10.1%
Moreau 2021	Isatuximab, carfilzomib, and dexamethasone versus carfilzomib, and dexamethasone Median previous lines 2	Overall infections:26% Pneumonia: 21%	Overall infections:17% Pneumonia: 14%
Richardson 2022	Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone Median previous lines 3	Overall infections:45% Pneumonia: 23%	Overall infections: 28% Pneumonia: 21%

Infectious risk in MM patients under anti-BCMA treatments

BELANTAMAB MEFODOTIN

CAR-T

BISPECIFIC MONOCLONAL ANTIBODIES

Real-world experience with belantamab mafodotin therapy for relapsed/refractory multiple myeloma: A multicentre retrospective study

Tamir Shragai[1,2] | Hila Magen[2,3] | Noa Lavi[4,5] | Moshe Gatt[6,7] | Svetlana Trestman[1] | Miri Zektser[8] | Chezi Ganzel[7,9] | Osnat Jarchowsky[2,10] | Tamar Berger[2,11] | Tamar Tadmor[5,12] | Merav Leiba[13,14] | Katrin Hertzog-Tzarfaty[15] | Netanel Horowitz[4,5] | Michael Shapira[16] | David Varssano[2,17] | Yoav Berger[18] | Shahar Frenkel[7,19] | Mark Krauthammer[2,17] | Irit Avivi[1,2] | Efrat Luttwak[1,2] | Yael C. Cohen[1,2] | for the Israeli myeloma study group

Br J Haematol. 2023;200:45–53.

Dose were delayed due to ocular toxicity in 82 cases (70.7%), haematological toxicity in 11 cases (9.5%) and infections in four (**3.5%**) cases.

Infectious complications were not uncommon, highlighting the need for close surveillance and early intervention as needed. The two cases of hepatitis B reactivation are worrisome, and repeated testing prior to initiation of treatment should be consided.

TABLE 3 Treatment-emergent adverse events (non-ocular).

	All grades *n* (%)	Grade 3–5[a] *n* (%)
Thrombocytopenia	29 (27.4)	19 (17.9)
Infection	12 (11.3)	8 (7.5)
Anaemia	12 (11.3)	4 (3.8)
Hypersensitivity/infusion reaction	8 (7.5)	3 (2.8)
Neutropenia	8 (7.5)	5 (4.7)
Transaminitis	5 (4.7)	1 (0.9)
Dry eyes	5 (4.7)	0
Fever	4 (3.8)	1 (0.9)
TLS	2 (1.9)	1 (0.9)
Cholangitis/elevated bilirubin	2 (1.9)	2 (1.9)
CMV reactivation	2 (1.9)	2 (1.9)
AKI	2 (1.9)	1 (0.9)
Nausea/vomiting	2 (1.9)	1 (0.9)
Diarrhoea	2 (1.9)	1 (0.9)
Confusion	2 (1.9)	0
Hepatitis B reactivation	2 (1.9)	0
Dermatitis	1 (0.9)	0
Other[b]	11 (10.3)	6 (5.6)

Abbreviations: AKI, acute kidney injury; CMV, cytomegalovirus; TLS, tumour lysis syndrome.

[a]Two grade 5 adverse events were reported (pneumonia and sepsis).

[b]Other adverse effects included (one event each): cough, fatigue, gastritis, general deterioration, gamma glutamyl transferase increase, hypotension, impaired hearing, listeria cerebritis, peripheral neuropathy, pneumonitis, sialadenitis.

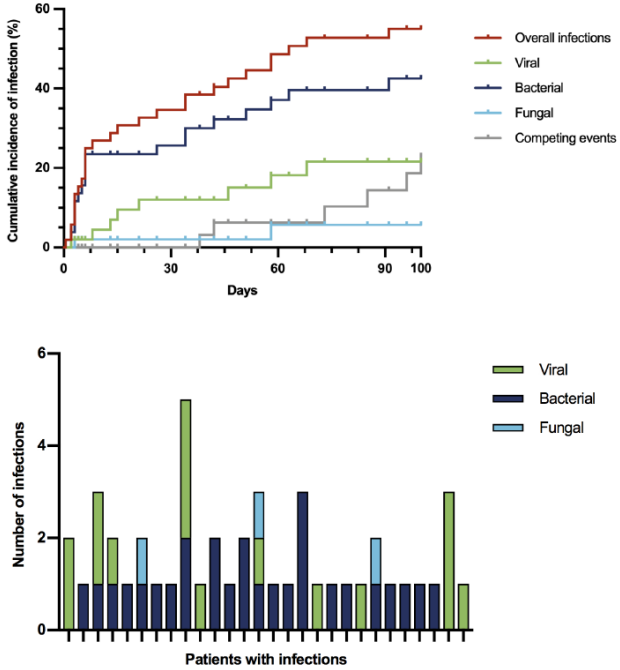
Early cytopenias and infections after standard of care idecabtagene vicleucel in relapsed or refractory multiple myeloma

Jennifer M. Logue[1], Lauren C. Peres[2], Hamza Hashmi[3], Christelle M. Colin-Leitzinger[2], Alexandria M. Shrewsbury[1], Hitomi Hosoya[4], Rebecca M. Gonzalez[1], Christina Copponex[1], Krista H. Kottra[1], Vanna Hovanky[4], Bita Sahaf[4], Sunita Patil[4], Aleksandr Lazaryan[1], Michael D. Jain[1], Aliyah Baluch[5], Olga V. Klinkova[5], Nelli Bejanyan[1], Rawan G. Faramand[1], Hany Elmariah[1], Farhad Khimani[1], Marco L. Davila[1], Asmita Mishra[1], Brandon J. Blue[6], Ariel F. Grajales-Cruz[6], Omar A. Castaneda Puglianini[1], Hien D. Liu[1], Taiga Nishihori[1], Ciara L. Freeman[1], Jason B. Brayer[6], Kenneth H. Shain[6], Rachid C. Baz[6], Frederick L. Locke[1], Melissa Alsina[1], Surbhi Sidana[4]*, and Doris K. Hansen[1]*

blood advances 2022

Figure 4. Cumulative incidence of infection and infection density

Cumulative incidence of infection and infection prevalence within 100 days following ide-cel infusion. (A) Cumulative incidence of first infection by type of infection (viral, bacterial, and fungal) among the total cohort (N = 52) over 100 days post ide-cel infusion. Patients were censored at the time of last follow-up (maximum of 100 days). Competing events were defined as disease relapse or progression and death. Two patients had concurrent bacterial and fungal infections. (B) Number of infections among the 28 patients with any infection annotated by type of infection (viral, bacterial, and fungal).



48. **Table 3. Incidence of cytopenias and severe cytopenias in the first 90 days following ide-cel**

49.

	Apheresis N = 52	Day -5 N = 52	Day 0 N = 52	Day 7 N = 52	Day 14 N = 51	Day 21 N = 51	Day 30 N = 51	Day 90 N = 47
Leukopenia – n (%)								
Any grade	32 (62%)	23 (44%)	51 (98%)	50 (96%)	42 (82%)	47 (92%)	42 (82%)	26 (55%)
Grade ≥ 3	5 (10%)	6 (12%)	40 (77%)	41 (79%)	23 (45%)	29 (57%)	18 (35%)	6 (13%)
Neutropenia – n (%)								
Any grade	20 (38%)	20 (38%)	41 (79%)	48 (92%)	38 (75%)	39 (76%)	32 (63%)	17 (36%)
Grade ≥ 3	2 (4%)	5 (10%)	28 (54%)	42 (81%)	26 (51%)	26 (51%)	20 (39%)	5 (11%)
Anemia – n (%)								
Any grade	44 (85%)	46 (88%)	48 (92%)	50 (96%)	47 (92%)	44 (86%)	46 (90%)	33 (70%)
Grade ≥ 3	4 (8%)	13 (25%)	18 (35%)	16 (31%)	10 (20%)	12 (24%)	15 (29%)	7 (15%)
Thrombocytopenia – n (%)								
Any grade	32 (62%)	30 (58%)	41 (79%)	48 (92%)	42 (82%)	48 (94%)	46 (90%)	31 (66%)
Grade ≥ 3	4 (8%)	6 (12%)	16 (31%)	27 (52%)	22 (43%)	28 (55%)	26 (51%)	13 (28%)
Any cytopenia – n (%)								
Any grade	48 (92%)	48 (92%)	52 (100%)	51 (98%)	51 (100%)	50 (98%)	50 (98%)	41 (87%)
Grade ≥ 3	11 (21%)	16 (31%)	42 (81%)	49 (94%)	35 (69%)	38 (75%)	33 (65%)	19 (40%)

50.

51. Numbers and percentage of patients with any grade and grade ≥ 3 leukopenia, neutropenia, anemia, thrombocytopenia and any cytopenia from apheresis to day 90. Any grade cytopenias: Anemia with hemoglobin (Hb) < 11.4 g/dL, Neutropenia with absolute neutrophil count (ANC) < 1800/uL, Thrombocytopenia with platelets (Plt) <143,000/uL; Grade 3 cytopenias: Anemia with Hb < 8 g/dL, Neutropenia with ANC < 1000/uL, Thrombocytopenia with Plt < 50,000/uL.

Received: 7 June 2023 | Revised: 30 August 2023 | Accepted: 10 September 2023
DOI: 10.1111/tid.14157

REVIEW ARTICLE

Infections after chimeric antigen receptor (CAR)-T-cell therapy for hematologic malignancies

Eleftheria Kampouri[1,2] | Jessica S. Little[3,4] | Kai Rejeski[5,6] | Oriol Manuel[2] | Sarah P. Hammond[4,7] | Joshua A. Hill[1,8,9]

Bacterial infections predominate early after CD19, while a more equal distribution between bacterial and viral causes is seen after BCMA CAR-T-cell therapy, and fungal infections are universally rare.

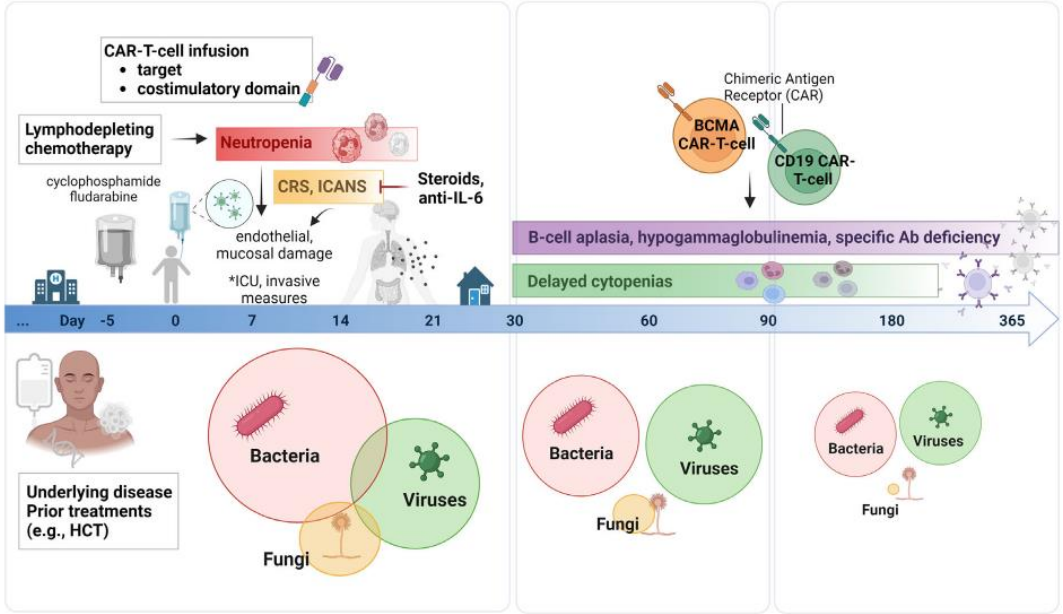
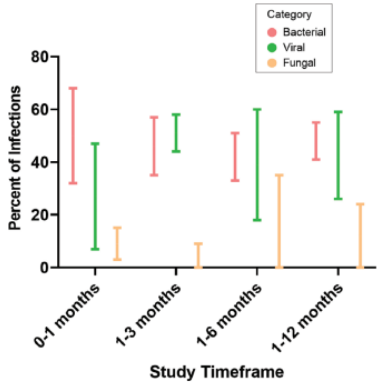


FIGURE 1 Infection risk and epidemiology during different time intervals after chimeric antigen receptor (CAR)-T-cell therapy. The size of the bubble represents the relative approximated frequency for each type of infection (bacterial, viral, and fungal). Neutropenia and delayed cytopenias are now referred to as early and late immune effector cell-associated hematotoxicity (ICAHT). CRS, cytokine release syndrome; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-6, interleukin 6. *Source*: Created with BioRender.com.



Timeframe	Bacterial cause	Viral cause	Fungal cause	References
0–1 month	32%–68%	7%–47%	3%–15%	35-38,40,49, 50,57,59,79
1–3 months	35%–57%	44%–58%	0%–9%	35,38,59
1–6 months	33%–51%	18%–60%	0%–35%	37,46,49
1–12 months	41%–55%	26%–59%	0%–24%	40,49,59

FIGURE 4 Relative frequency of infection types (bacterial, viral and fungal) as percentage of all infections after CD19 CAR-T-cell therapy during different time intervals. The percentages and references are included in the table given below the figure.

ESMO Volume 33 ■ Issue 3 ■ 2022 ANNALS OF ONCOLOGY

SPECIAL ARTICLE

Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

Table 12. Infection prophylaxis post-CAR-T

	EBMT/EHA recommendation	Comments
Neutropenia	G-CSF to shorten duration of neutropenia from day +14 or after resolution of CRS or ICANS Can consider starting earlier, e.g. day 5,[a] if patient is at high risk of infection, e.g. ALL, post-allo-HCT, high-dose steroids. For persistent neutropenia ($<0.5 \times 10^9$/l) following day +28, consider G-CSF	Avoid if patient has CRS or ICANS
Antibacterial prophylaxis	Not routinely recommended[b]	Can be considered in case of prolonged neutropenia and should be based on local guidelines, e.g. with levofloxacin or ciprofloxacin
Anti-viral	Valaciclovir 500 mg bid or aciclovir 800 mg bid	Start from LD conditioning until 1-year post-CAR T-cell infusion AND until $CD4^+$ count $>0.2 \times 10^9$/l
Anti-pneumocystis	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until 1-year post-CAR-T cell infusion AND until $CD4^+$count $>0.2 \times 10^9$/l Where there is prolonged myelosuppression, postpone start after ANC $>0.5 \times 10^9$/l	Can be started later depending on centre guidelines In case of co-trimoxazole allergy (or cytopenias precluding use of co-trimoxazole), pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered
Systemic anti-fungal prophylaxis	Not recommended routinely; consider posaconazole (300 mg/day) or fluconazole (200 mg/day) or micafungin (50 mg i.v./day) in patients with severe (ANC $<0.5 \times 10^9$/l) or prolonged (>14 days) neutropenia and/or in patients on long-term or high-dose (>72 h) corticosteroids or in patients post-allo-HCT	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
i.v. Immunoglobulin	Routine in children. Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	Clinical evidence does not support routine use in adults following allo-HCT

CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma

blood® 16 DECEMBER 2021 | VOLUME 138, NUMBER 24

Kai Rejeski,[1-3] Ariel Perez,[4] Pierre Sesques,[5] Eva Hoster,[1,6] Carolina Berger,[7] Liv Jentzsch,[8] Dimitrios Mougiakakos,[9] Lisa Frölich,[1,3] Josephine Ackermann,[1] Veit Bücklein,[1,2] Viktoria Blumenberg,[1,2] Christian Schmidt,[1] Laurent Jallades,[5] Boris Fehse,[7] Christoph Faul,[8] Philipp Karschnia,[3,10] Oliver Weigert,[1,3] Martin Dreyling,[1] Frederick L. Locke,[4] Michael von Bergwelt-Baildon,[1,3] Andreas Mackensen,[9] Wolfgang Bethge,[8] Francis Ayuk,[7] Emmanuel Bachy,[5] Gilles Salles,[5] Michael D. Jain,[4] and Marion Subklewe[1-3]

Baseline 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		

Figure 4. CAR-HEMATOTOX. Determined before lymphodepletion, the score comprises 5 markers of hematotoxicity with additional weighting of the baseline platelet count and ferritin levels. The score discriminates between a high (CAR-HEMATOTOX score ≥2) and low (CAR-HEMATOTOX score 0-1) risk for hematotoxicity.

The score implicates bone marrow reserve and inflammation prior to CAR T-cell therapy as key features associated with delayed cytopenia and will be useful for risk-adapted management of hematotoxicity.

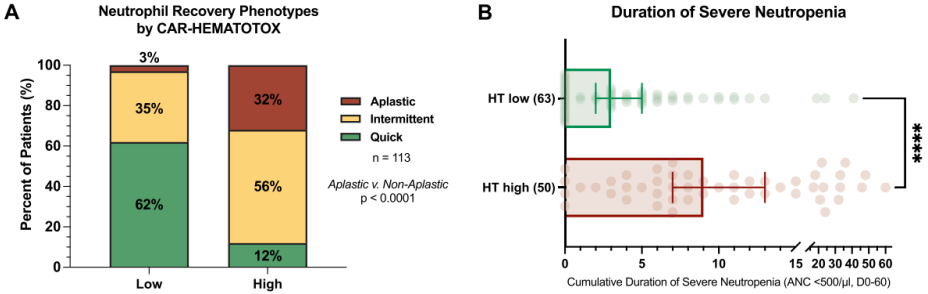
Rejeski et al.
Journal of Hematology & Oncology (2023) 16:88
https://doi.org/10.1186/s13045-023-01465-x

Journal of
Hematology & Oncology

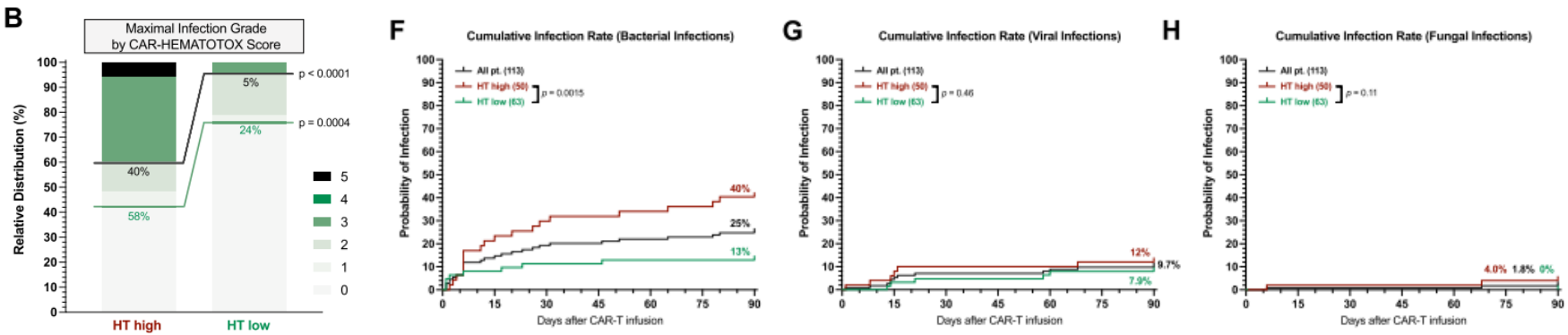
RESEARCH Open Access

The CAR-HEMATOTOX score as a prognostic model of toxicity and response in patients receiving BCMA-directed CAR-T for relapsed/refractory multiple myeloma

Kai Rejeski[1,2,3,4*†], Doris K. Hansen[5†], Radhika Bansal[6], Pierre Sesques[7], Sikander Ailawadhi[8], Jennifer M. Logue[5], Eva Bräunlein[9], David M. Cordas dos Santos[1,3], Ciara L. Freeman[5], Melissa Alsina[5], Sebastian Theurich[1,3], Yucai Wang[6], Angela M. Krackhardt[3,4,9,10], Frederick L. Locke[5], Emmanuel Bachy[7], Michael D. Jain[5], Yi Lin[6†] and Marion Subklewe[1,2,3,4†]



Compared to their HTlow counterparts, HThigh patients displayed prolonged severe neutropenia (median 9 vs. 3 days, p<0.001), an increased severe infection rate (40% vs. 5%, p<0.001), and more severe ICANS (grade≥3: 16% vs. 0%, p<0.001).



Acknowledging Infection Risk in Bispecific Antibody Trials in the Treatment of Multiple Myeloma

Journal of Clinical Oncology®
Volume 41, Issue 10 1949

TABLE 1. Rates of Infection in Bispecific Antibody Trials for Relapsed/Refractory Multiple Myeloma

Drugs	Target	Patients in Trial	ORR, %	≥ VGPRR, %	Incidence of Infections, % (grade ≥ 3, %)	Deaths From Infection, No. (%)	Neutropenia, % (grade ≥ 3, %)	Hypogammaglobulinemia, %
ABBV-383[3]	BCMA	124	57	43	41 (≥ 20)	8 (6.5)	37 (34)	14[a]
Teclistamab[2]	BCMA	165	63	59	76 (45)	≥ 19 (11)	71 (64)	75
Teclistamab + daratumumab[8]	BCMA; CD38	33	78	43	52 (24)	1 (3)	36 (36)	NR
Elranatamab[9]	BCMA	123	61	55	67 (35)	6 (5)	48 (48)	75
Linvoseltamab, REGN5458[10]	BCMA	191	64	45	54 (29)	10 (6)	25 (23)	NR
Pavurutamab (AMG 701)[11]	BCMA	85	26[b]	17	17[c]	2 (2)	25 (NR)	NR
Alnuctamab (CC-93269)[12]	BCMA	30	43	30	57 (30)	1 (3)	47 (43)	NR
Talquetamab[13]	GPRC5D	108	68	53	39 (7)	1 (1)	48 (43)	77
Talquetamab + daratumumab[14]	GPRC5D; CD38	46	77	65	50 (13)	—	NR	NR
Cevostamab[15]	FcRH5	160	45[d]	NR	43 (19)	—	38 (36)	NR

Abbreviations: BCMA, B-cell maturation antigen; FcRH5, Fc receptor-homolog 5; GPRC5D, G protein-coupled receptor family C group 5 member D; NR, not reported; ORR, objective response rate; ≥ VGPRR, rate of very good partial responses or better.

[a]In this trial, although only 14% were documented to be hypogammaglobulinemic, 23% received immunoglobulin.

[b]This is overall ORR; higher response rates were observed with higher dose cohorts.

[c]Rate of serious infections.

[d]ORR 55% among the higher (160 mg) dose level cohort.

Received: 13 July 2023 | Revised: 31 July 2023 | Accepted: 15 August 2023
DOI: 10.1002/ajh.27071

CORRESPONDENCE

AJH WILEY

Increased risk of infection reporting with anti-BCMA bispecific monoclonal antibodies in multiple myeloma: A worldwide pharmacovigilance study

Here, we analyzed the worldwide WHO pharmacovigilance database VigiBase to better evaluate the risk of infections with anti-BCMA BsMAbs, as compared with other MM treatments and especially nonanti-BCMA BsMAbs and anti-BCMA CAR-T cells.

TABLE 1 Characteristics of infection cases in patients receiving anti-BCMA BsMAbs reported in the WHO global safety database.

Reporting characteristics	Teclistamab ($n = 168$)	Elranatamab ($n = 20$)	Overall ($n = 188$)
Type of infection[a]			
COVID-19	32 (19%)	2 (10%)	34 (18%)
Pneumonia NOS	30 (18%)	2 (10%)	32 (17%)
Infection NOS	22 (13%)	3 (15%)	25 (13%)
Bacterial sepsis	20 (12%)	3 (15%)	23 (12%)
Sepsis/Septic shock NOS	18 (11%)	4 (20%)	22 (12%)
Cytomegalovirus reactivation	14 (8%)	2 (10%)	16 (9%)
Other viral infection[b]	15 (9%)	1 (5%)	16 (9%)
Urinary tract infection	6 (4%)	3 (15%)	9 (5%)
Pneumocystis jiroveci pneumonia	5 (3%)	2 (10%)	7 (4%)
Abscess/empyema	5 (3%)	–	5 (3%)
Sinusitis/URTI	4 (2%)	–	4 (2%)
Other opportunistic infection[c]	3 (2%)	–	3 (2%)
Other IFI infection[d]	2 (1%)	–	2 (1%)
Other[e]	6 (4%)	1 (5%)	7 (4%)

TABLE 2 Reporting odds ratio of infection with anti-BCMA BsMAbs as compared with other MM treatments, and teclistamab as compared with elranatamab.

	Cases	Non-cases	ROR [95% CI]
Anti-BCMA BsMAbs as compared with all other myeloma treatments			
Anti-BCMA BsMAbs	188	499	**1.9 [1.6–2.3]**
Other myeloma treatments	44 713	227 368	Ref.
Anti-BCMA BsMAbs as compared with non-anti-BCMA BsMAbs			
Anti-BCMA BsMAbs	188	499	**2.1 [1.1–4.1]**
Non-anti-BCMA BsMAbs	11	62	Ref.
Anti-BCMA BsMAbs as compared with anti-BCMA CAR-T Cells			
Anti-BCMA BsMAbs	188	499	**2.8 [2.1–3.7]**
Anti-BCMA CAR-T Cells	77	568	Ref.
Teclistamab as compared with Elranatamab			
Teclistamab	168	443	1.1 [0.6–1.8]
Elranatamab	20	56	Ref.

We found a disproportionate reporting of infections with anti-BCMA BsMAbs in patients with MM, as compared with other MM treatments including non-anti-BCMA BsMAbs and antiBCMA CAR-T cells. This finding, in line with previous literature, suggests an increased risk of infection with anti-BCMA BsMAbs. The reported infections were early in treatment course and included notably opportunistic, fungal, or viral infections as well as bacterial pneumonia and sepsis with severe outcome. T

OA-51: Preliminary Recommendations for Prevention and Management of Infections, Hypogammaglobulinemia, and Neutropenia During Treatment With Teclistamab Based on Experience From the MajesTEC-1 Study

Location: Trianti

Speaker: Niels van de Donk, MD PhD (he/him/his) – Amsterdam UMC

- **Introduction:** Bispecific antibodies targeting B-cell maturation antigen (BCMA) may contribute to increased infection risk among patients with relapsed/refractory multiple myeloma (RRMM) due to on-target, off-tumor toxicity.. Based on experience from the phase 1/2 MajesTEC-1 study, we provide preliminary recommendations for managing potential infections during teclistamab treatment.
  Methods: Patients (N=165) received subcutaneous teclistamab 1.5 mg/kg weekly following a step-up dosing schedule.
  Results: At median follow-up of 21.7 months, infections occurred in 129 patients (78.2%) overall **(grade 3/4 in 52.1%). 12.1% of patients died** due to infections (most from COVID-19). Median time to first onset of any grade and grade 3–5 infections was **1.7 and 4.2 months**, respectively. Overall, **70.9% of patients had ≥1 immunoglobulin G (IgG) value < 400** mg/dL; 45.5% received IVIG. **Grade 3/4 neutropenia occurred in 65.5%** of patients at a median of 2.3 months; 53.3% of patients received granulocyte colony-stimulating factor (G-CSF).

- **Conclusions:**
- **IVIG** (administered every 3–6 weeks) is indicated for IgG < 400 mg/dL and for serious or recurrent/chronic infections.
- Patients should be **screened for hepatitis B and C** and receive all appropriate **vaccinations** (including COVID-19) before starting teclistamab.
- Prophylaxis for **Pneumocystis jirovecii pneumonia** and **herpes viruses** is recommended;
- other prophylactic antimicrobials should be administered per **institutional guidelines**.
- **G-CSF** should be considered for grade ≥3 neutropenia with infection/fever and/or grade 4 neutropenia.