Sekundäre Immundefizienz bei Multiplen Myelom
Aktuelle Aspekte

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Pathophysiological reasons of Infections in lymphatic neoplasias

- **Hypogammaglobulinemia**
- T-cell-Dysfunction
- NK-cell-Dysfunction
- Neutropenia und Phagocyte deficiency
- Deficiency of complement
- Deficiency of mucosal barrier

Current diagnosis criteria of Mulptiple Myeloma – role recurrent bacterial infections

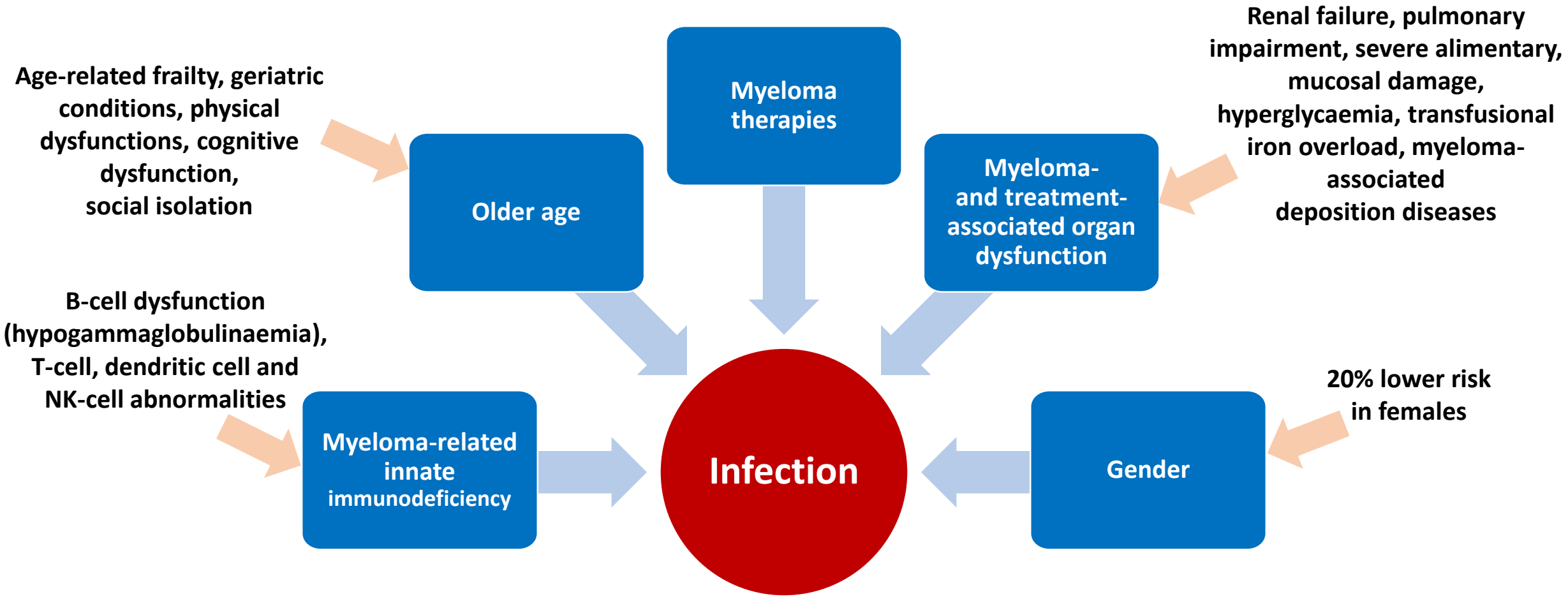
Other related organ or tissue impairment

Although the 2003 IMWG criteria included non-CRAB end-organ damage, specifically hyperviscosity, AL amyloidosis, and recurrent bacterial infections as fulfilling criteria for multiple myeloma, over the years only CRAB features have been regarded as myeloma-defining events.[10,11]

Recurrent infection is a nonspecific criterion, and in view of the prevalence of MGUS in the elderly general population, it is not thought of as a validated or reliable myeloma-defining event in the absence of other CRAB features. Finally, all of these have also become less important with the inclusion of new non-CRAB biomarkers to define the disease. Thus, we do not recommend their use for the initiation of treatment.

Rajkumar SV et al, Lancet Oncology 2014, 15, 538-48

Risk factors for infection in multiple myeloma



1. Nucci M, Anaissie E. Clin Infect Dis 2009;49:1211–25;
2. Blimark C, et al. Haematologica 2015;100:107–13.

Adapted from H.Ludwig, 2016

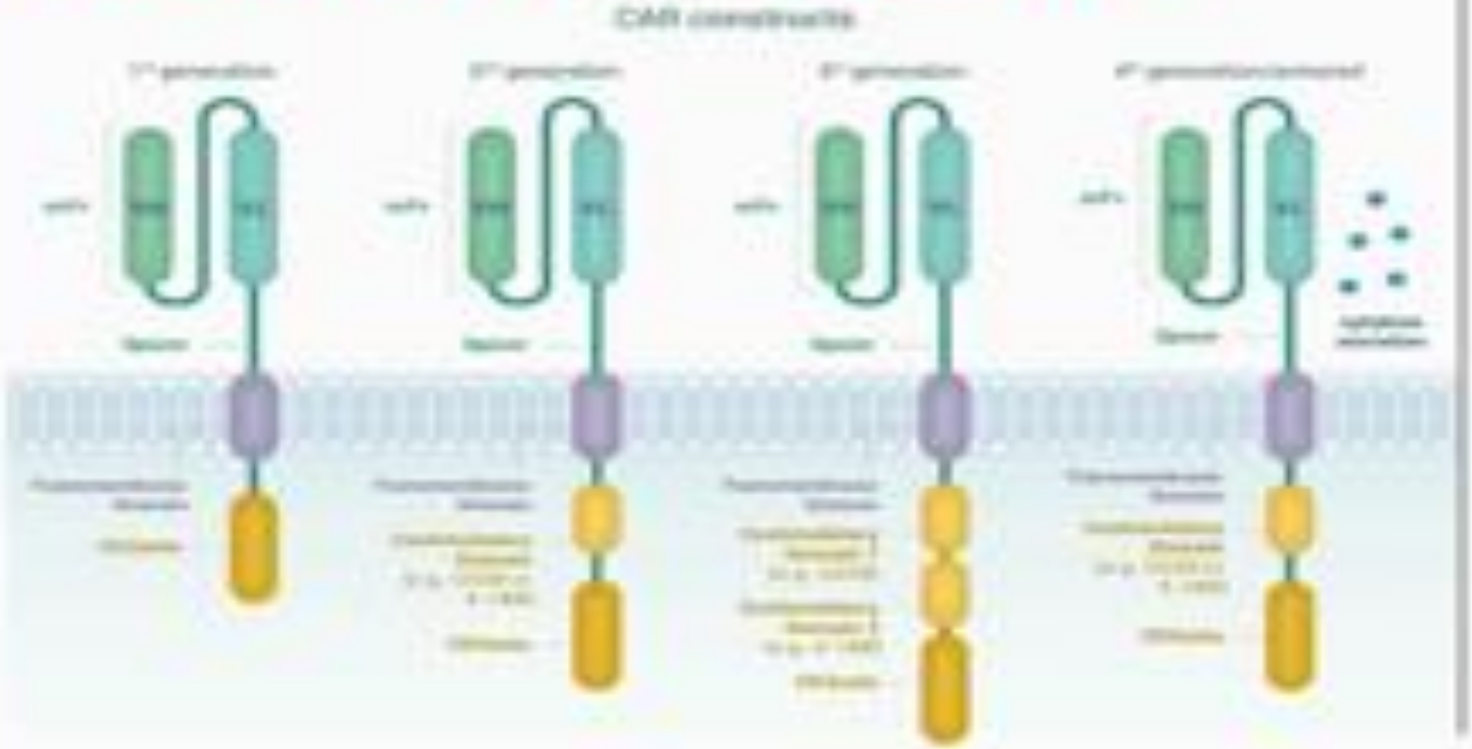
Treatment modality	Effect on immunity	Potential infection
Active disease	Hypogamaglobulinaemia	Bacterial – especially encapsulated
Monoclonal antibodies	Various, lymphocytes depletion	CMV, TBC, various others depending on the type
Corticosteroids	Decreased cellular immunity	Bacterial – especially encapsulated, fungal – *aspergillus*, pneumocystis
SCT – pre engraftment	Serious neutropaenia and mucositis	Bacterial, fungal, *clostridium difficile*
SCT – post engraftment	Decreased cellular immunity	HSV, VZV, CMV, PJP,…

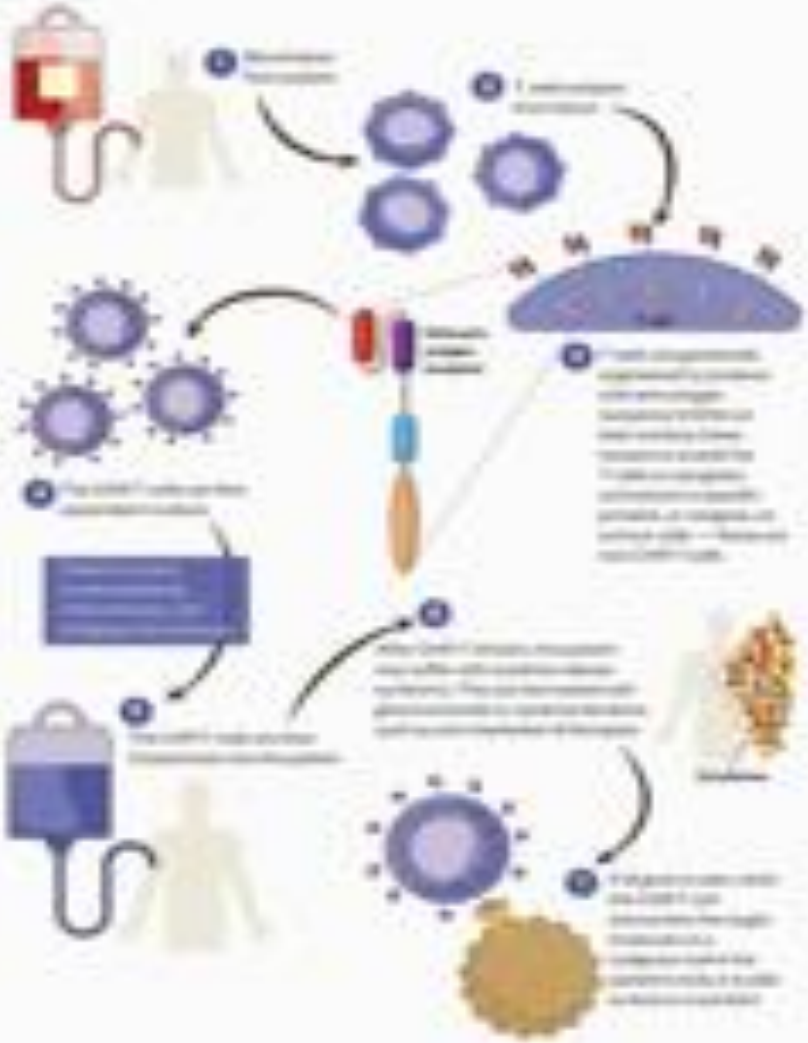
Risk of infection is a HOT TOPIC in the era of modern immunotherapy (CAR-T and bispecific antibodies)

With Courtesy of Hajek et al, EHA 2024

International Myeloma Society

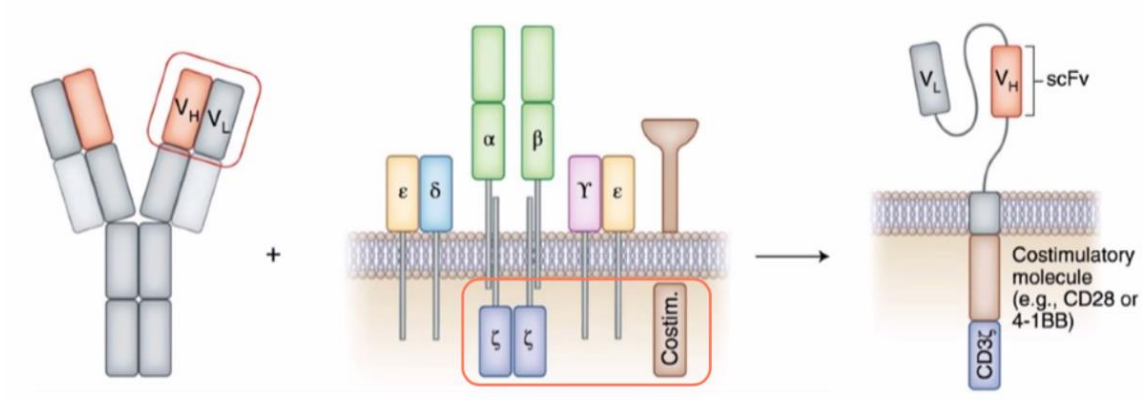
Chimeric Antigen Receptor T Cells



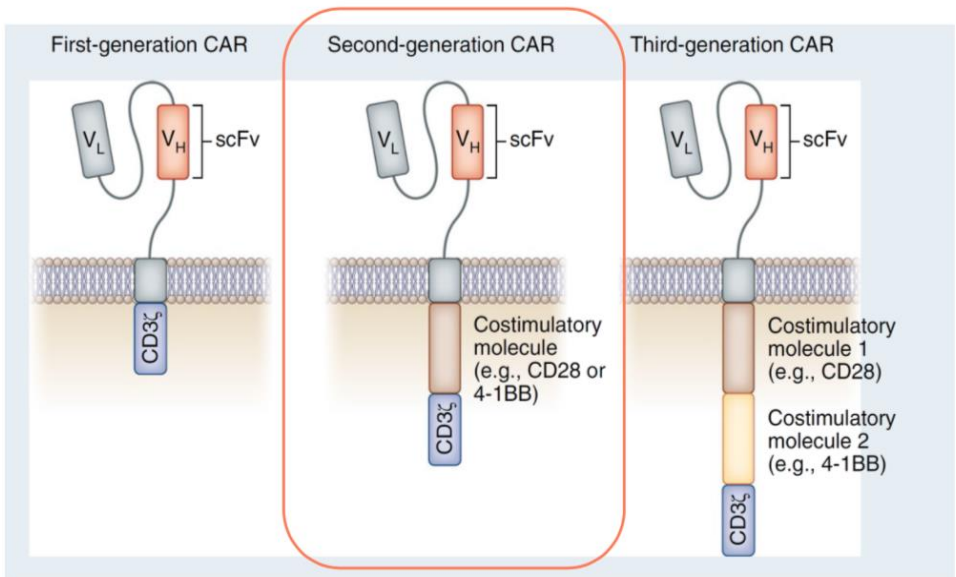


CAR-T-Zell-Therapie

Chimärer Antigen Rezeptor (CAR)

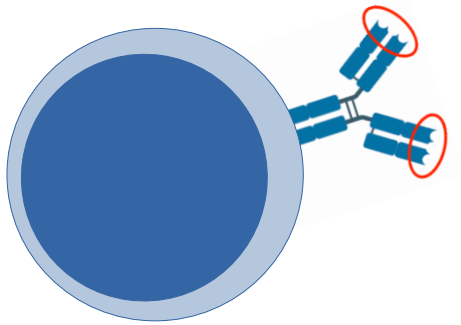


CAR Generationen



Majzner and Mackall, ***Nature Medicine***, 2019

BiTE (bispecific t-cell engagers) and CAR cells in Myeloma



BCMA CAR T-Zelle

BCMAxCD3 -BiTe

GPRC5DxCD3 –BiTe

FcRH5xCD3 BiTe

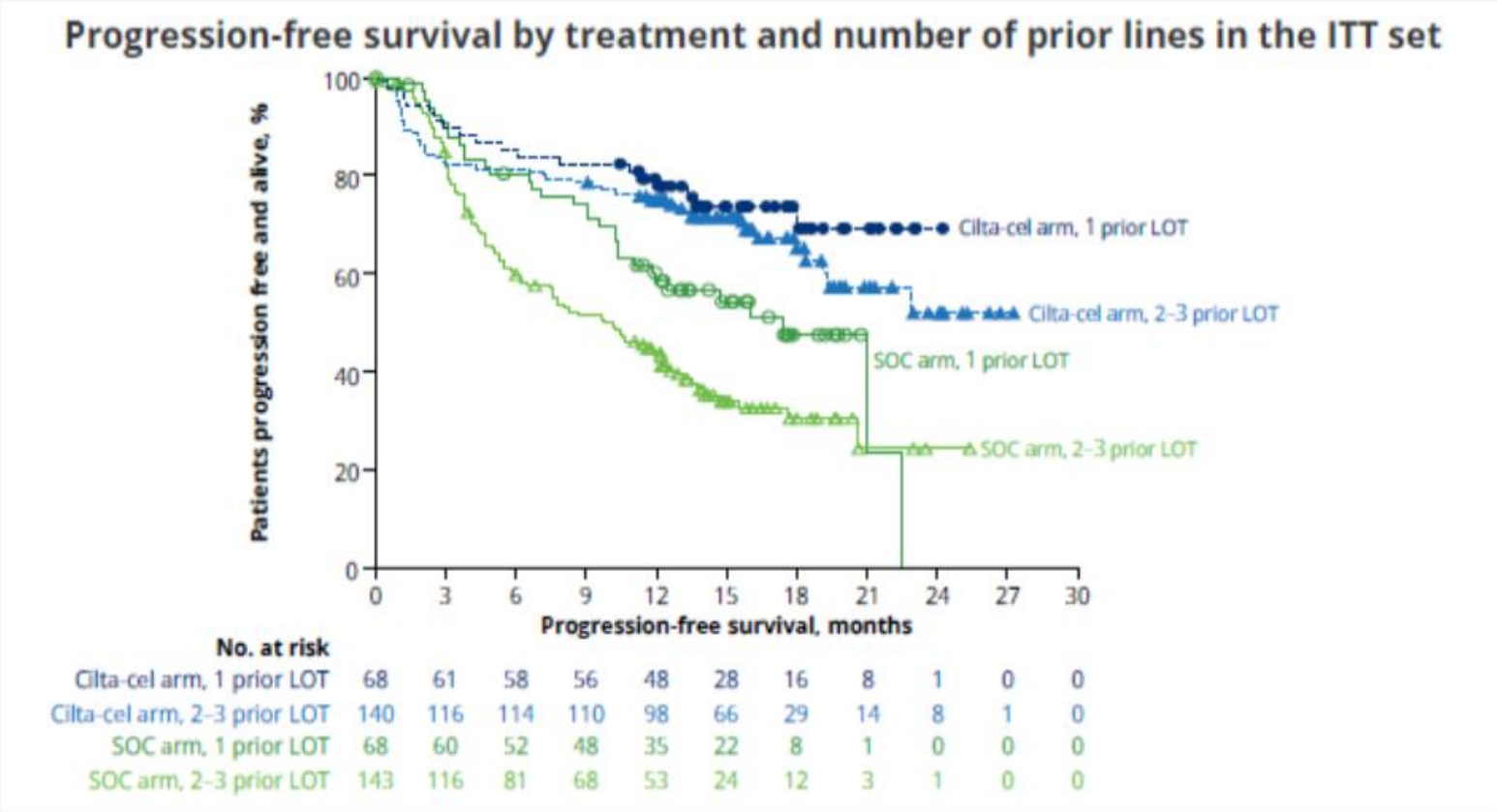
Ide-cel (Abecma)
Cilta-cel (Carvykti)

Teclistamab
Elranatamab

Talquetamab
Linvoseltamab
Cevostamab
Forimtamig

CAR T-cells: randomised trials – Cartitude 4

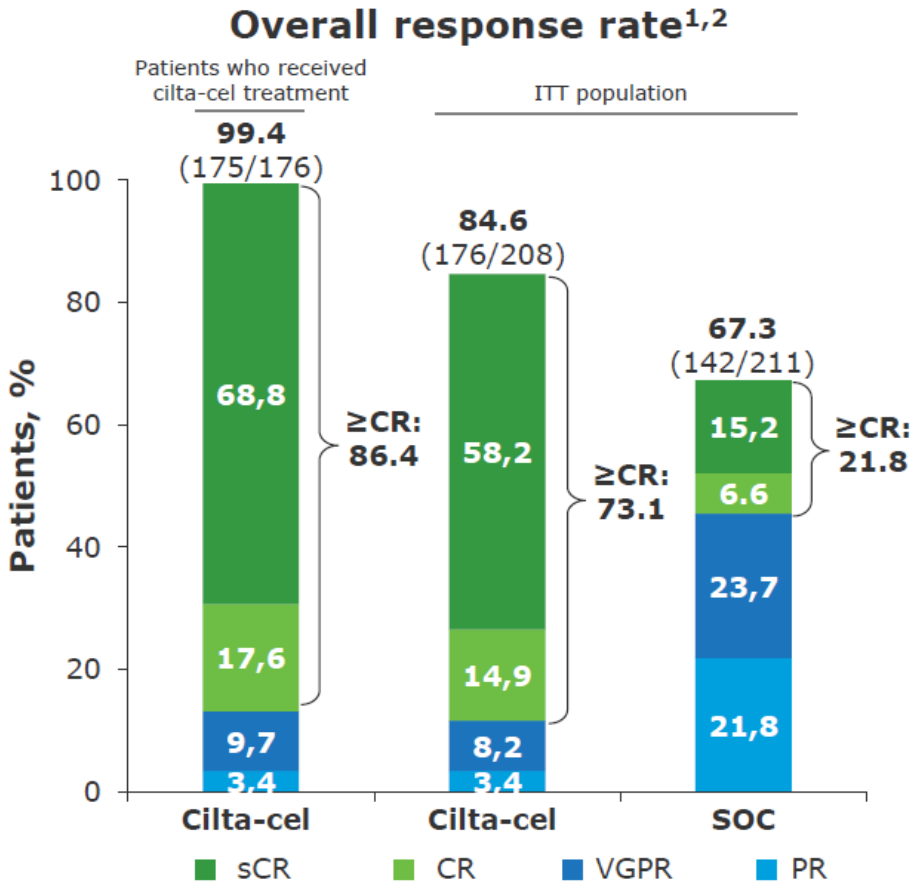
- Cilta-cel improved PFS vs SOC whether patients had 1 or 2–3 prior LOT

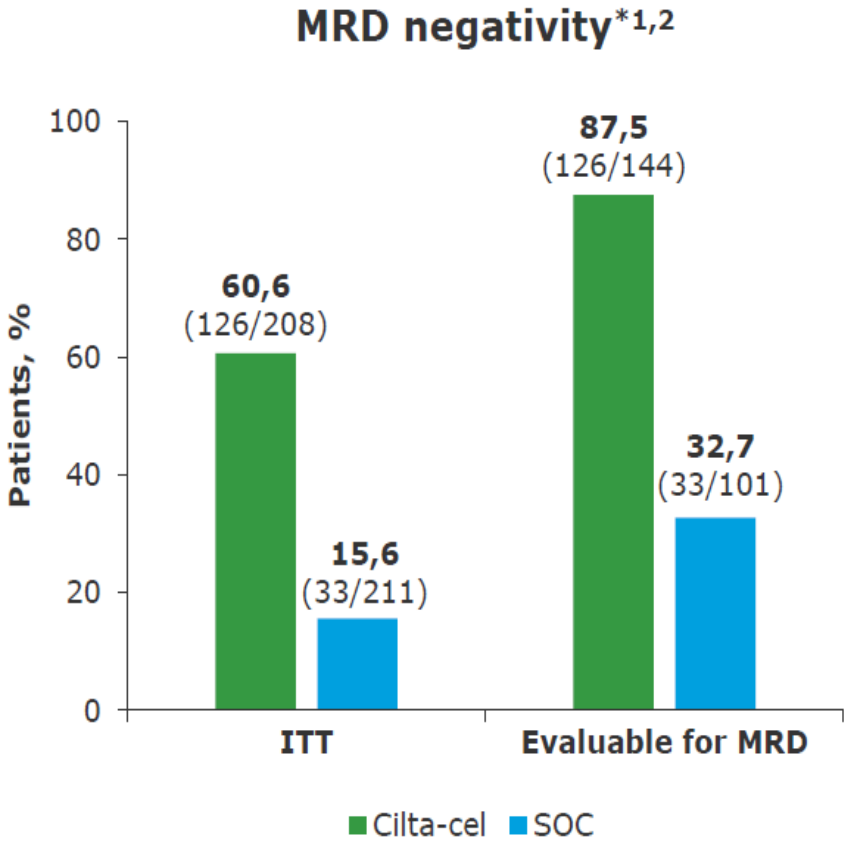


cilta-cel, ciltacabtagene autoleucel; ITT, intent-to-treat; LOT, line of therapy; PFS, progression-free survival; SOC, standard of care.

H.Einsele et al, EHA 2023, Plenary Session

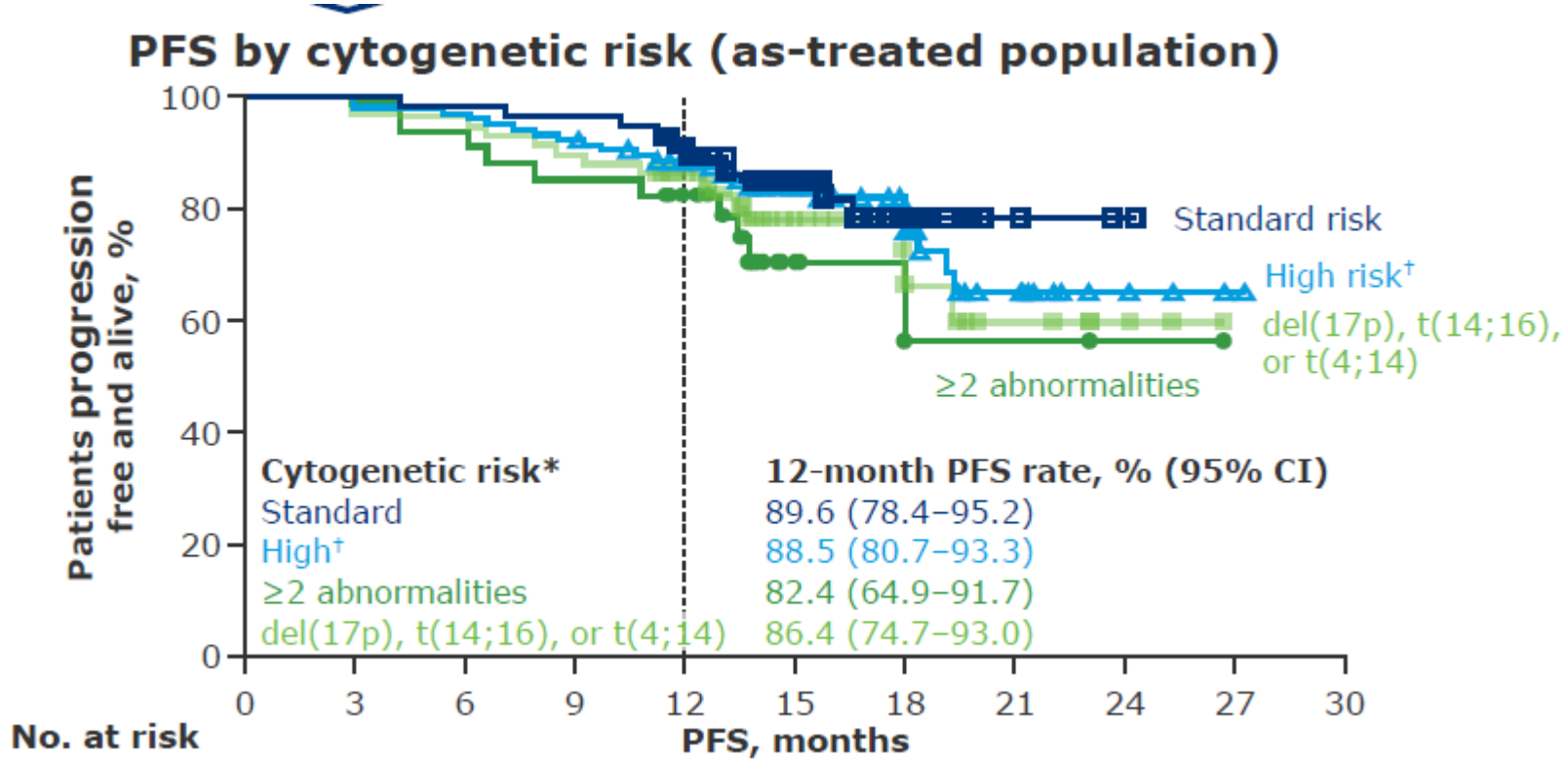
Cartitude – 4: deep response





San-Miguel J, et al. *N Engl J Med* 2023;389:335–347

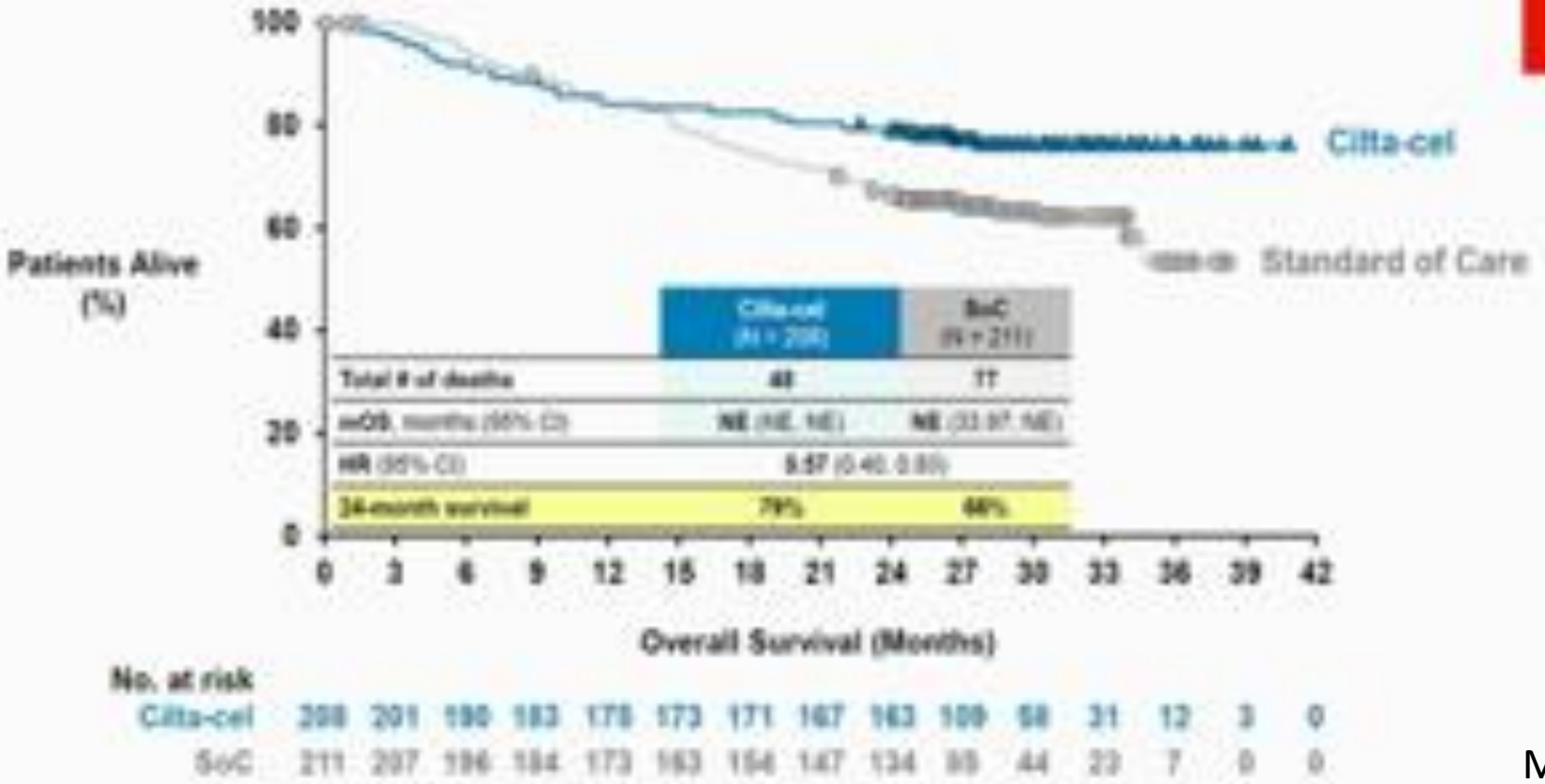
Cartitude – 4
PFS rates were high regardless of cytogenetic risk



Manier S, et al. Presented at IMS, Athens, Greece, 27–30 September 2023. OA-47.

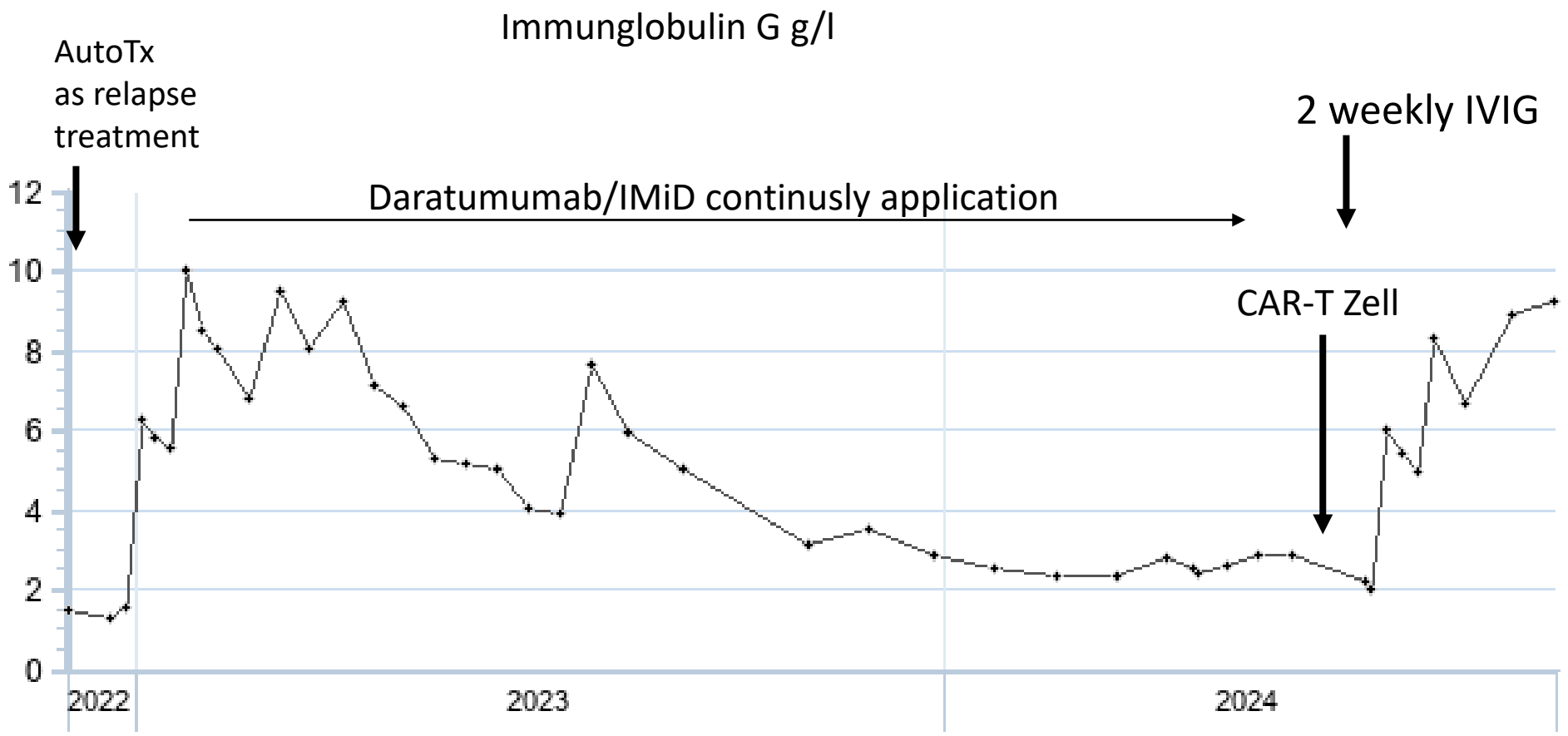
Ciltacabtagene Autoleucel: CARTITUDE-4 Overall Survival

See at IMS 2024
Abstract Session 7
Sept 27th
17:30-18:30



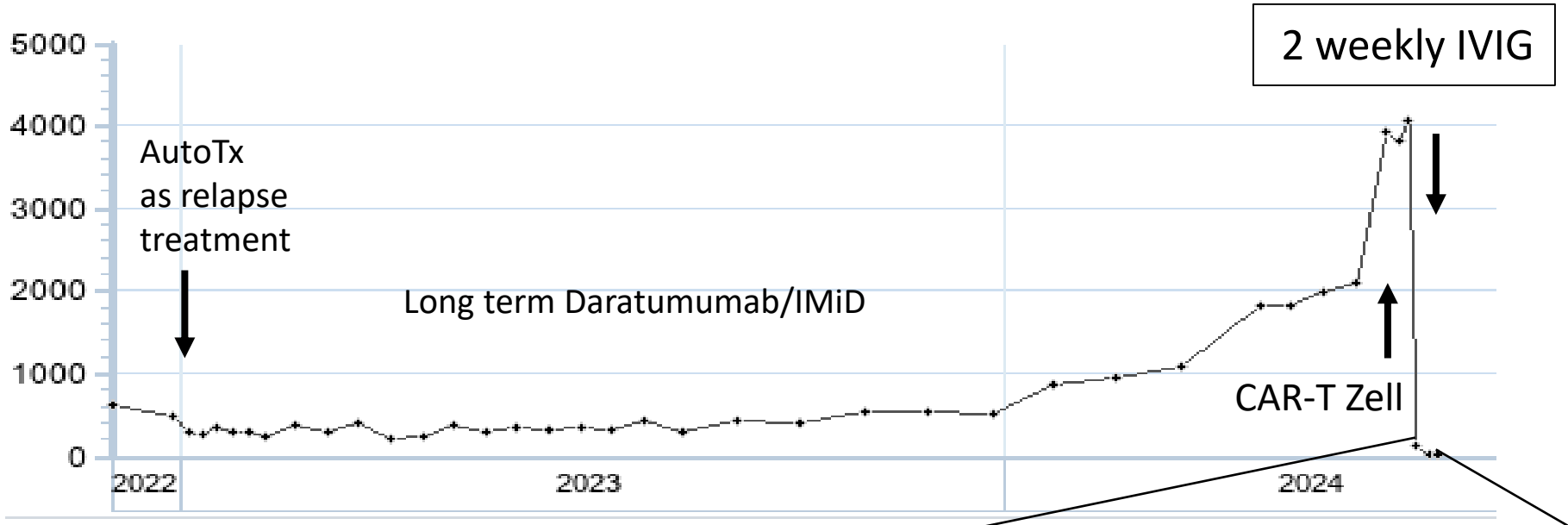
M. Mateus, IMS 2024

Patn. R.A., geb. 1974



Patn. R.A., geb. 1974
Diagnosis: MM LC, 2016, relapse 2021

***Light chain** kappa mg/l*



7.00-16.00	g/l	Immunglobulin		2.21	L	2.02	L	6.03	L	5.40	L
0.70-4.00	g/l	Immunglobulin		<0.02	L	<0.10	L	<0.10	L	0.01	L
0.40-2.30	g/l	Immunglobulin		<0.03	L	<0.05	L	0.07	L	0.01	L
5.70-26.30	mg/l	freie Lambda		<0.70	LK	<0.70	L	<0.70	L	<0.59	L
3.30-19.40	mg/l	freie Kappa L		1.27	L	0.87	L	<0.80	L	<0.41	L
				8.7.		16.7.		23.7.		30.7.2024	

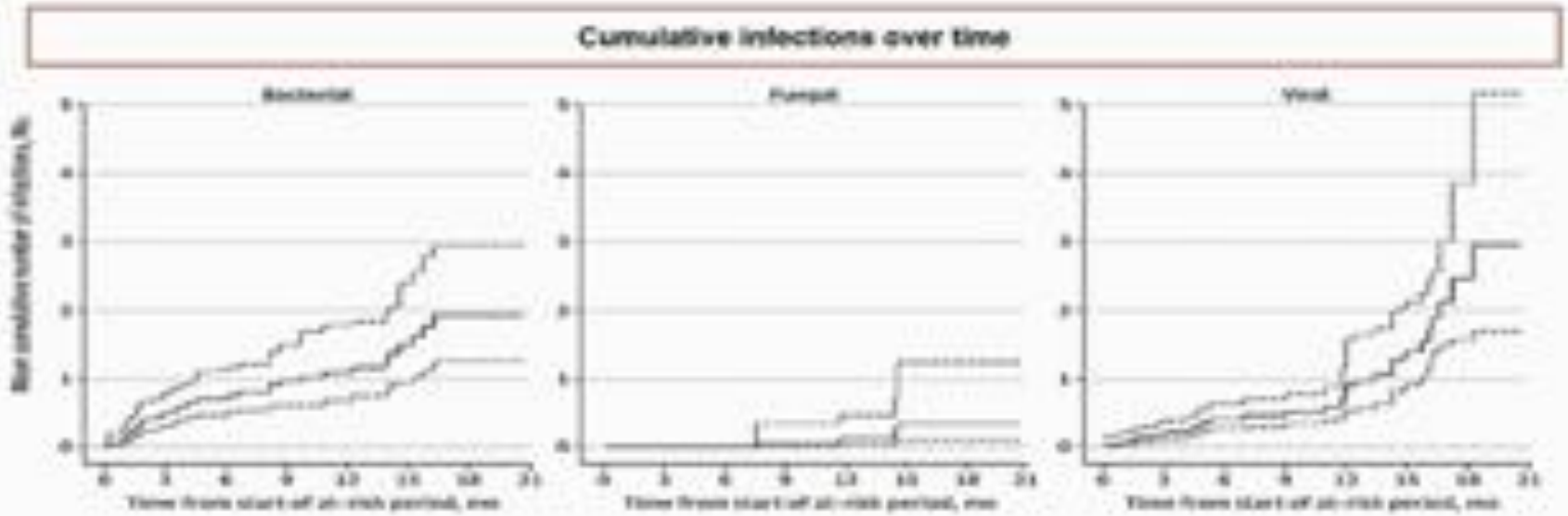
Relative risk of selected infections after diagnosis of myeloma compared to matched controls

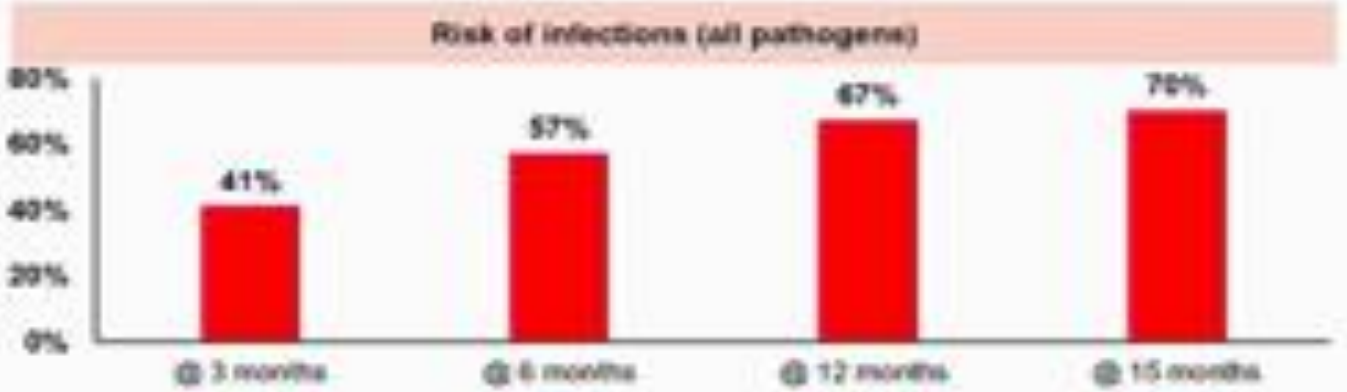
Disease	1-year follow-up		
	Myeloma	Controls	HR (95% CI)
Any infection (combined)	1,626	672	11.6 (10.6–12.7)
Bacterial†	1,388	574	11.5 (10.4–12.7)
Pneumonia	770	279	12.7 (11.1–14.6)
Osteomyelitis	19	12	6.9 (3.4–14.3)
Septicaemia	464	69	29.9 (23.2–38.6)
Pyelonephritis	50	51	4.3 (2.9–6.4)
Cellulitis	47	58	3.7 (2.5–3.4)
Meningitis	12	3	17.3 (4.9–61.3)
Endocarditis	12	6	8.7 (3.3–23.1)
Viral‡	215	54	17.6 (13.1–23.8)
Influenza	52	22	10.5 (6.4–17.3)
Herpes zoster	92	16	25.8 (15.2–43.8)

*Estimated HRs and CIs; †Pneumonia, cellulitis, cystitis, empyema, endocarditis, gonorrhoea, meningitis, osteomyelitis, otitis, pharyngitis/nasopharyngitis, pericarditis, sinusitis, syphilis, tonsillitis, tuberculosis; ‡HIV, herpes simplex virus (HSV), herpes zoster, hepatitis (A–C), cytomegalovirus (CMV), Epstein–Barr virus (EBV), mononucleosis, encephalitis, pericarditis, myocarditis and influenza. CI, confidence interval; HR, hazard ratio.

Blimark C, et al. Haematologica 2015;100:107–13.

Cumulative Incidence of Infections

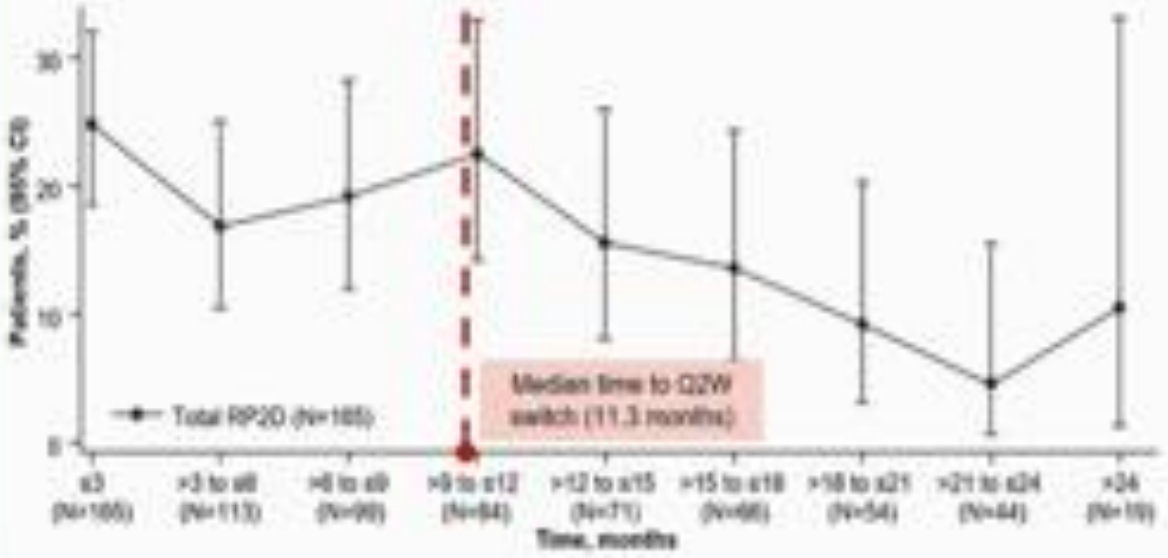




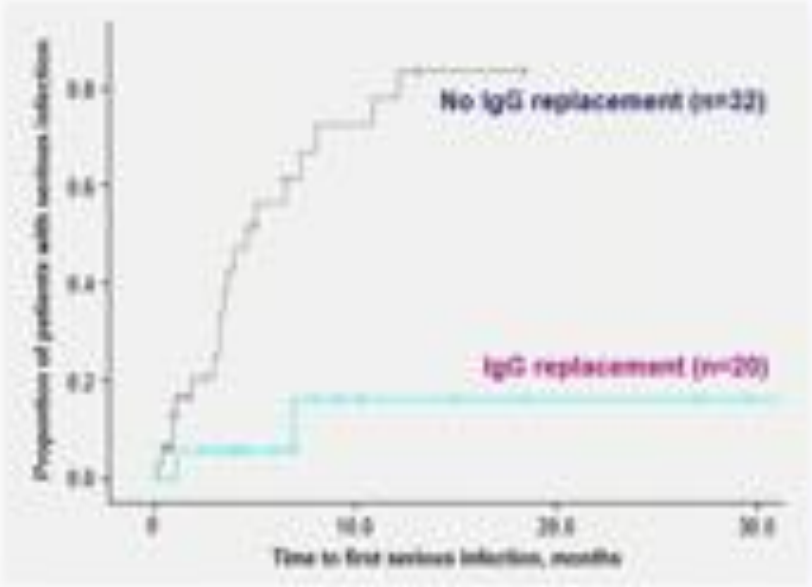
Adapted from: Hammons LR, et al. JAMA 2022; 5(10):e2238981

Mitigating the Incidence of Infections

New-onset grade ≥3 infections in the overall MajesTEC-1 study population



IVIG prophylaxis



Adapted from Frerichs K, et al. HemaSphere 2023; 7(S3), e5193345. Lancman G, et al. Blood 2022;140: 10073-10074. Usmani SZ, et al. J Clin Oncol 2023; 7(14), 3739-3748

Prevention of infections in multiple myeloma

Vaccination[1]

- Influenza A and B, H1N1
- Haemophilus influenza
- Pneumoccoci
- Varicella zoster
- Hepatitis A & B

Prophylactic therapy

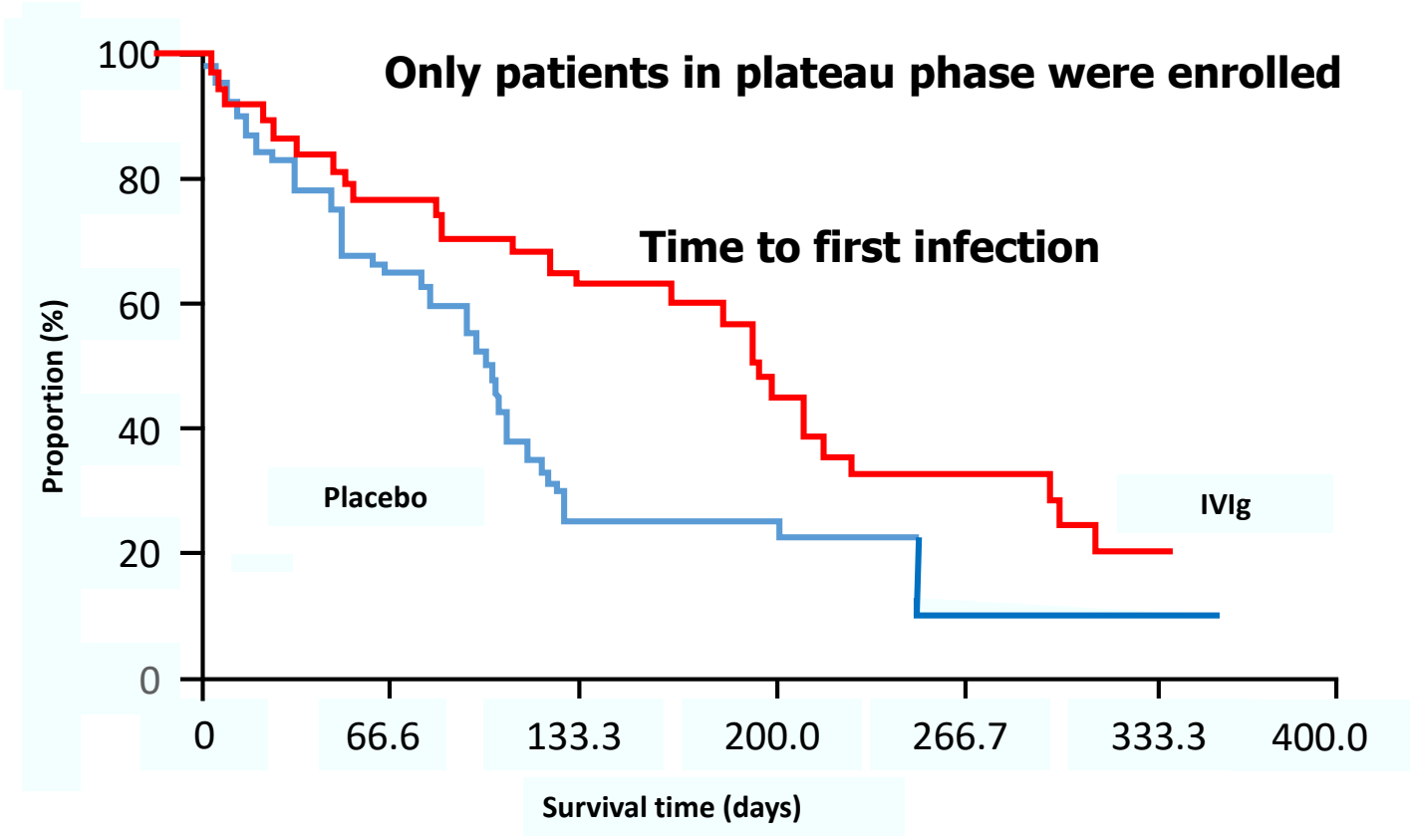
- Antibacterial
- Antiviral
- Antifungal

- Vaccination of relatives and care givers
- Ideally, patients should be vaccinated already during MGUS phase
- Be aware of poor response to vaccination
- Re-vaccinate in case of insufficient response

- **Avoid live vaccines: Yellow fever, BCG, Typhoid fever, MMR**

[1] Anaissie E et al., IMW Paris 2011, Nucci M et al., Clin. Inf. Dis. 2009

Consider IV immunoglobulin prophylaxis in selected patients only



- **Patients with poor antibody response to Pneumovax showed the greatest benefit**
- **0.08 vs. 0.04 infectious episodes per patient months**

Chapel HM, et al. Lancet 1994;343:1059–63.

IV, intravenous; IVIg, intravenous immunoglobulin.

New options for Immunglobuline substitutions

Attribute	IVIg	SCIg	fSCIg
Number of infusion sites	Typically 1	Multiple sites (up to 16/month for 20% SCIg)	Typically 1
Frequency of infusions	Generally once every 3–4 weeks (~2 h/infusion)	Generally weekly (1–2 h/infusion)	Generally once every 3–4 weeks (~2 h/infusion)
Bioavailability	100% of dose administered	~60–70% of IVIg at 1:1 dosing; requires dose adjustment in the United States	PK equivalence to IVIg at 1:1 dosing
Risk of local ADR	Lower risk relative to SCIg	Increased risk relative to IVIg	Increased risk relative to IVIg
Peak-to-trough variation	Large	Low, leads to near constant IgG levels	Similar to SCIg
Risk of systemic ADR	Increased risk relative to SCIg	Lower risk relative to IVIg	Lower risk relative to IVIg; similar to SCIg
Administration options	Requires medical supervision	Self-administration; no medical supervision required after training	Self-administration; no medical supervision required after training
	Requires venous access	No venous access required	No venous access required
	Can be administered in hospital or office setting		Can be administered in hospital or office setting

ADR: Adverse drug reactions; fSCIg: facilitated subcutaneous immunoglobulin; HCP: health-care provider; IVIg: intravenous immunoglobulin; PK: pharmacokinetics; SCIg: subcutaneous immunoglobulin.

Blau IW et al, Expert Review of Clinical Immunology, 2016, 12 (7), 705-11

Key Consensus Recommendations

- Use **anti-viral prophylaxis** against **HSV** and **VZV** in all patients (level III)
- **Screen** for **HBV reactivation risk** in all patients (level III)
- Administer **monthly IVIG** for the duration of **immunoparesis** and in the absence of life threatening infectious manifestations (level IIC)
- Use **colony-stimulating factors** in patients with **Grade ≥3 neutropenia** (level III)
- **Do not use prophylaxis** for **aspergillosis** (level IIC)
- Use **PJP prophylaxis** for all patients (level IIC)

Recommendations were **ranked** on a scale of 1–5, and **average scores** were then calculated to provide a **grading:**

- **Level I:** empirical; however, requires significantly more data to support it (average ranking = 1)
- **Level IIA and IIB:** empirical, with slightly more data available to support the recommendation (average ranking = 2 or 3)
- **Level IIC:** based on routine practice, with sufficient supporting evidence (average ranking = 4)
- **Level III:** considered to be obligatory practice, with strong available evidence (average ranking = 5)

Raje et al., Blood cancer journal, 2023

Conclusions

- Multiple Myeloma leads to an immundeficiency of different reasons
- Treatment of disease increase risk of viral and bacterial infections
- Antiviral and antibacterial prophylaxis is indicated in
  B-cell neoplasia especially Myeloma patients on treatment
- Ig prophylaxis may be helpful in patients suffered from recurrend infections
- Recently, IVIG is indicated very strongly in Immuntherapies
  in MM due to totally depletion of B cells
- In addition, vaccination is helpful for prevention of severe infections,
  but not effective everytime

Thank you!