NUOVE TERAPIE NEI LINFOMI B AGGRESSIVI E NEL MIELOMA MULTIPLO

Terapia di supporto e gestione del rischio infettivo

Norbert Pescosta– Ematologia e Centro TMO Bolzano

CRO Aviano (PN) - 9 ottobre 2024

Convegno Regionale SIE

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

No conflict of interest

RISK FACTORS FOR EARLY AND SEVERE INFECTIONS IN NDMM- DISEASE RELATED

- Immunparesis
- ISS III
- High LDH
- High serum creatinin

Disruption of global T celldiversity

Alteration of functional activity of dentritic cells and natural killer

2557 patients 1981 infections (-30 +180 d)

28% pneumonia; 18% sepsis

Augustson 2005; Sorrig 2018,Schütt 2006; Ratta 2002

IMMUNE PARAMETERS IN MULTIPLE MYELOMA

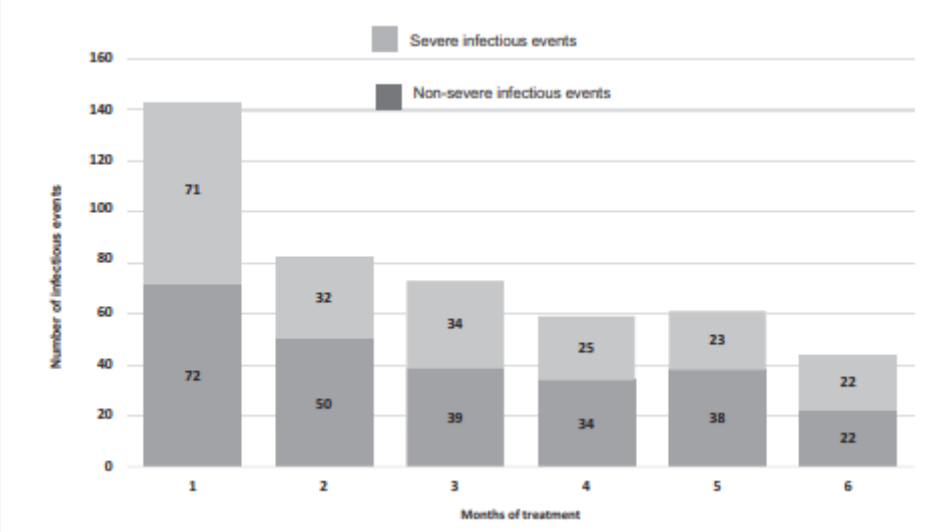
Table I. Immune parameters of multiple myeloma patients.

	Healthy controls ($n=30$)	MM (untreated) ($n=32$)	MM (conv-CTX) ($n=46$)
Cellular parameters			
CD4+ (/μl)	790 (430–1440)	800 (290–1640)	450 (21–1580)*,**
CD4+/CD45RO+ (/μl)	430 (170–940)	340 (130–880)*	250 (21–1020)*,**
CD4+/CD45RO– (/μl)	400 (79–750)	410 (77–890)	140 (1–670)*,**
CD45RO– to CD45RO+ cell ratio	0.85 (0.23–2.74)	1.1 (0.22–3.42)	0.50 (0.01–2.57)*,**
CD8+ (/μl)	400 (110–1250)	406 (81–1250)	380 (16–2180)
CD3+/HLA-DR+ (/μl)	180 (47–440)	88 (7–610)*	180 (24–1920)**
CD4+ to CD8+ cell ratio	1.95 (0.8–7.2)	1.90 (0.8–5.3)	1.3 (0.1–5.3)*,**
CD19+ (/μl)	200 (54–390)	120 (18–740)*	19 (1–170)*,**
NK cells (/μl)	350 (59–1120)	160 (49–560)*	180 (58–730)*
Granulocytes (/μl)	4010 (1760–7890)	3750 (1320–11500)	3890 (1070–19600)
Monocytes (/μl)	519 (280–910)	490 (110–1450)	850 (260–3180)*,**
Nonmyeloma immunoglobulins			
Immunoglobulin G (g/l)†	[6.4–13.5]§	5.4 (1.96–16.1) ($n=15$)	5.7 (1.4–11.9) ($n=38$)
Immunoglobulin A (g/l)†	[0.70–3.1]§	0.58 (0.04–3.04) ($n=26$)	0.70 (0.11–5.9) ($n=41$)
Immunoglobulin M (g/l)	[0.56–3.5]§	0.31 (0.04–3.04) ($n=32$)	0.29 (0.09–1.3) ($n=45$)

Schütt 2006

RISK OF INFECTION IN FIRST MONTHS OF THERAPY IN NDMM

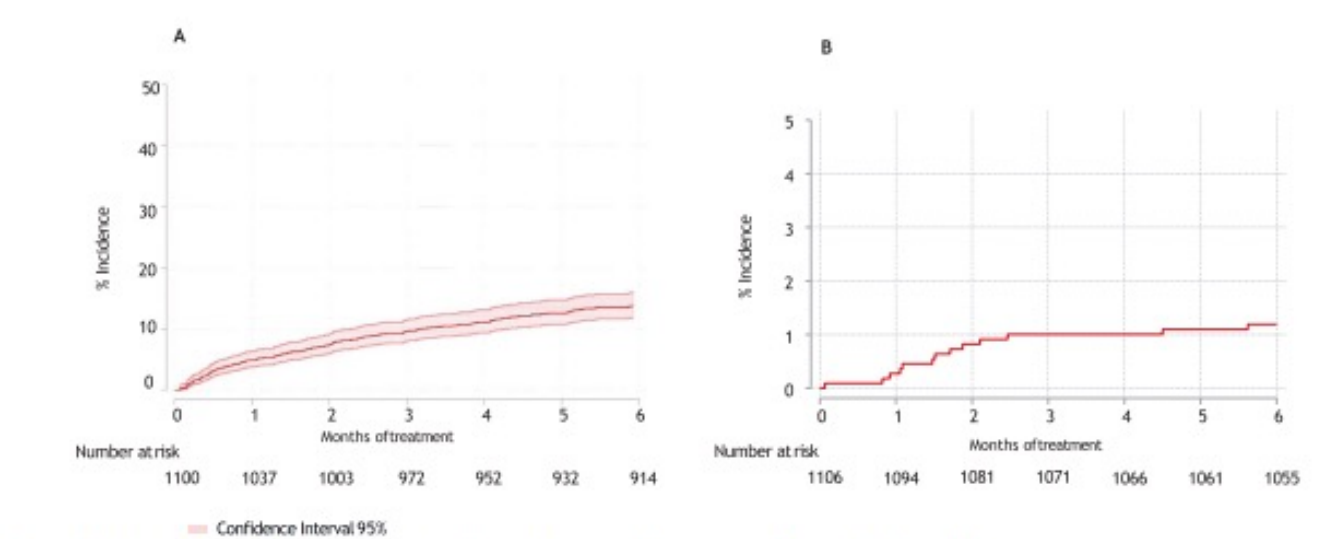
Protocol	*N* Events (%)	Severe (%^)	RTIs/Pneumonia (%^)	UTI (%^)	Febrile syndrome (%^)	BSI (%^)
GEM05 > 65	103 (22.3)	37 (35.9)	57 (55.3)/23 (22.3)	11 (10.7)	14 (13.6)	0 (0)
GEM05 < 65	143 (31.0)	65 (45.5)	106 (74.1)/36 (25.2)	10 (7.0)	3 (2.1)	5 (3.5)
GEM10 > 65*	48 (10.3)	16 (33.3)	18 (37.5)/5 (17.9)	1 (2.1)	6 (12.5)	0 (0)
GEM12 < 65	168 (36.4)	89 (53.2)	92 (54.8)/32 (19)	16 (9.5)	17 (10.1)	19 (11.3)
Total	462 (100)	207 (44.8¶)	273 (59.1¶)/96 (21.7¶)	38 (8.2¶)	40 (8.7¶)	24 (5.2¶)



1347 NDMM age 22-88 Years
(847 transplant candidates)

Risk evaluation in first **6** months

RISK OF INFECTION IN FIRST MONTHS OF THERAPY IN NDMM



Cumulative incidence. A Cumulative incidence of severe infection and **B** mortality by infection.

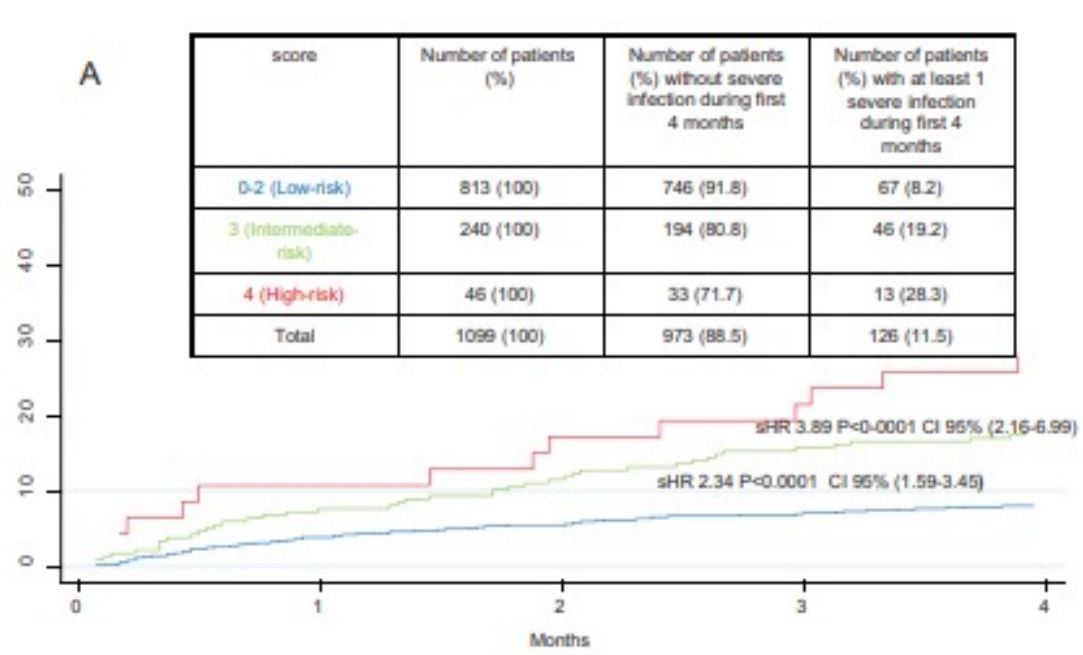
Cumulative incidence of severe infection at 6 months **13,8%** but at **4** months **11,3 %**

Cumulative risk of death at 6 months **1,2 %** but **1%** at **4** months

RISK OF INFECTION IN FIRST MONTHS OF THERAPY IN NDMM

Variables	Odds ratio	*p*-value	95% Confidence interval	Weight (points)
Albumin ≤ 30 g/L	2.12	<0.001	1.40–3.20	1
ECOG PS > 1	1.73	0.005	1.18–2.54	1
Male sex	1.50	0.037	1.02–2.20	1
Non-IgA type MM	1.49	0.091	0.93–2.39	1

Predictive score for early severe infection



BACTERIAL INFECTIONS

- **Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial**
- 977 patients levofloxacin 500mg vs placebo for 12 weeks:

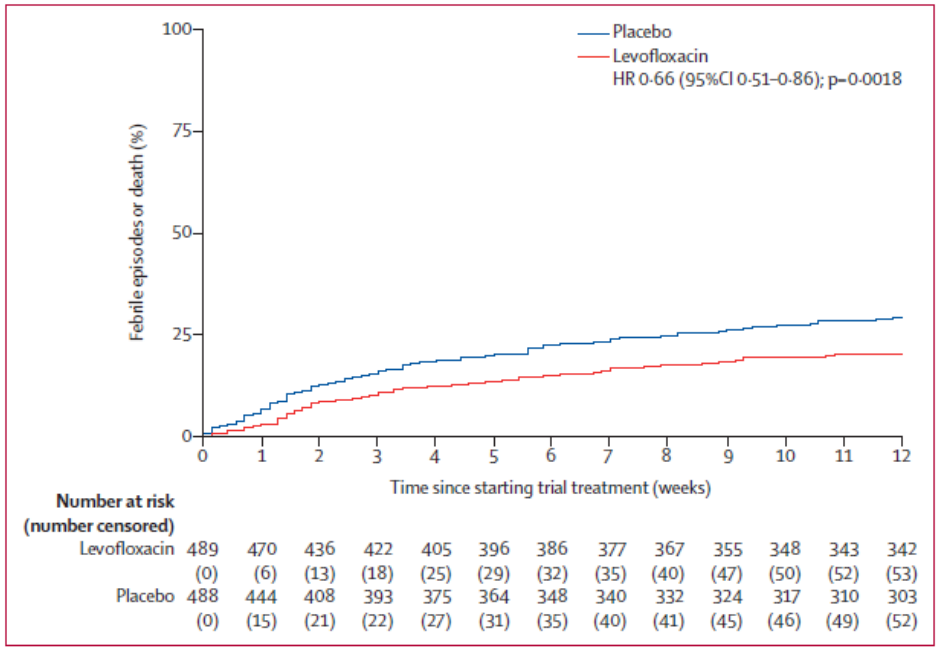


Figure 2: Kaplan-Meier graph of time to febrile episode or death

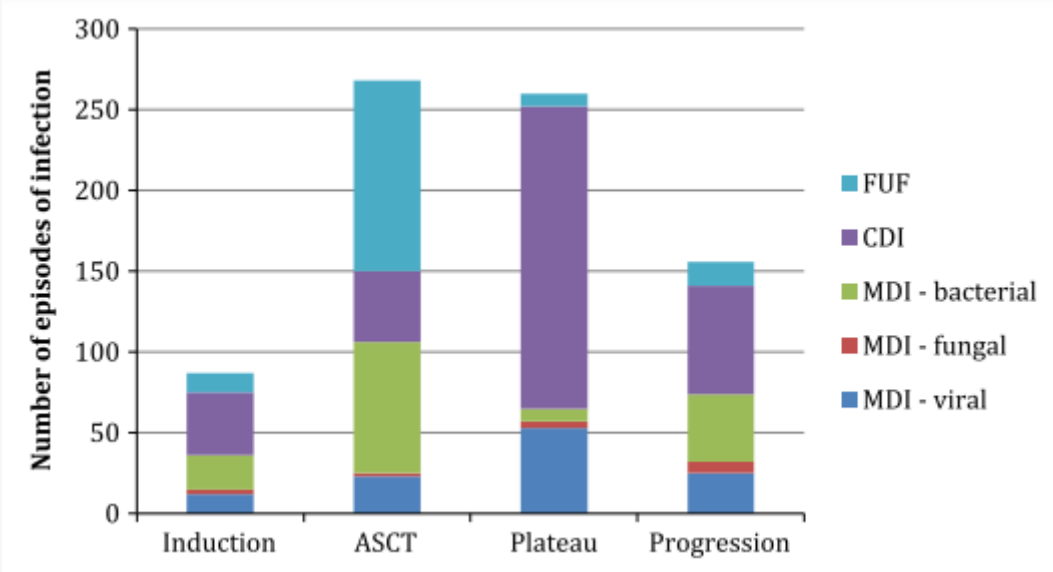
But…
E coli resistance: UK 17.8 % ; Italy 47 % (2017)

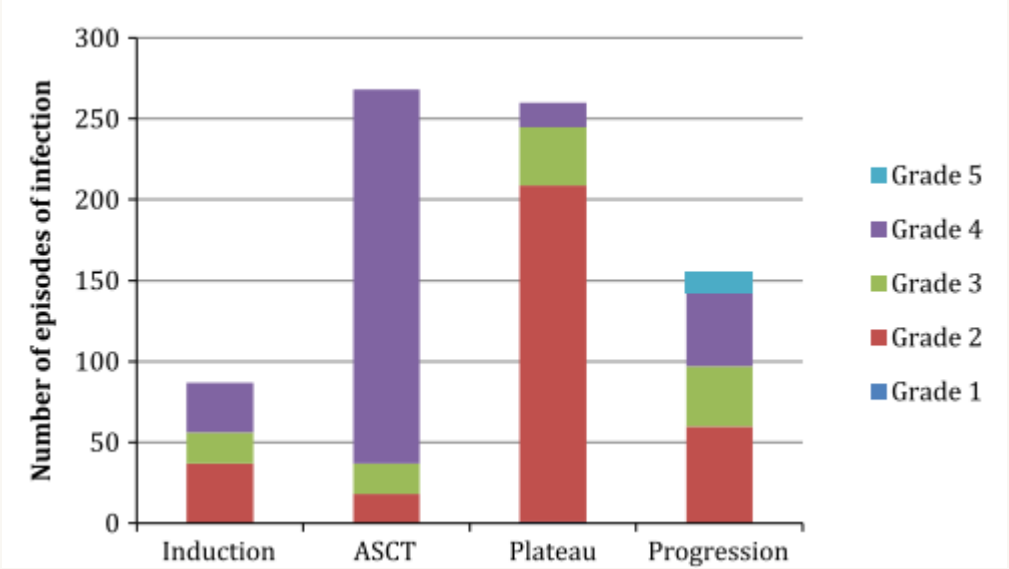
20 %vs 27 % infections (less hospital admissions)

Biggest benefit: older NTE , less fit patients

Drayson 2019

RISK FACTORS FOR INFECTIONS - TREATMENT RELATED-HSCT





RISK FACTORS FOR INFECTIONS - TREATMENT RELATED

Melphalan and prednisone	Bacteremia, pneumonia, UTI	Neutropenia
Glucocorticoids (cumulative doses)	Oral candidiasis, *P jirovecii* pneumonia, other opportunistic infections	T-cell immunodeficiency, hyperglycemia
Proteasome inhibitors	Neutropenia-related infections, *P jirovecii* pneumonia, other opportunistic infections (when combined with glucocorticoids)	Suppression with T-cell immunity, neutropenia
Immunomodulators	Bacteremia, pneumonia	Neutropenia
mAbs	Pneumonia, opportunistic infections	Lymphopenia, neutropenia
Panobinostat	Severe infections and opportunistic infections	Lymphopenia, neutropenia
Selinexor	Neutropenia-related infections	Neutropenia

Standard chemotherapy	Neutropenia-related infections	Neutropenia
Intensive chemotherapy	Bacteremia, pneumonia, colitis, *C difficile* colitis	Severe neutropenia, mucositis
Chemotherapy-based stem cell mobilization	Bacteremia, pneumonia, colitis, *C difficile* colitis	Neutropenia
High-dose therapy with autologous HSCT	Bacteremia, pneumonia, colitis, *C difficile* colitis	Severe neutropenia, mucositis Prolonged humoral and T-cell immunodeficiency following autologous HSCT
Bisphosphonate-induced jaw osteonecrosis	Bacterial infections	Local infections and impaired local host defenses
Vertebroplasty or kyphoplasty	Skin infections	Breach of anatomical barriers

Raje 2022

LENALIDOMIDE MAINTENANCE: RISK OF INFECTION IN MYELOMA XI TRIAL

Adverse events in patients treated with lenalidomide maintenance therapy (n=1097)

	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Haematological				
Neutropenia	419 (38%)	308 (28%)	54 (5%)	0
Anaemia	657 (60%)	40 (4%)	2 (<1%)	0
Thrombocytopenia	489 (45%)	49 (4%)	23 (2%)	0
Infections				
Lower or upper respiratory infection	261 (24%)	89 (8%)	4 (<1%)	4 (<1%)
Sepsis	1 (<1%)	12 (1%)	6 (1%)	2 (<1%)
Other infections and infestations	104 (9%)	23 (2%)	0	0

Overall infections:
45% vs 17 %

Jackson 2019

INFECTIONS POST AUTOLOGOUS SCT

Infectious events after autologous transplantation for multiple myeloma

Characteristics of febrile neutropenia	Number (%)
Clinical sites of infection[1]	
Upper respiratory tract infection[2]	31 (29.8)
Lower respiratory tract infection[3]	27 (26.0)
Combined upper and lower respiratory tract infection	5 (4.8)
Gastroenteritis	5 (4.8)
Catheter-related infection	2 (1.9)
Urinary tract infection	3 (2.9)
Skin and soft tissue infection	3 (2.9)
Herpes zoster	15 (14.4)
Herpes simplex	3 (2.9)
Other[4]	4 (3.8)
Unexplained fever	6 (5.8)
Causative organism[5]	
Respiratory tract infection	
Influenza virus	10
Influenza A (H1N1)/B	9 (3)/1
Pneumococcus	9
Mycoplasma	2
Staphylococcus aureus	2
Haemophilus influenzae	1
Others[6]	3
Gastroenteritis	
Clostridium difficile toxin	3
Catheter-related infection	
Coagulase-negative *Staphylococcus*	1
Urinary tract infection	
Escherichia coli	2

IvIG post ASCT for 6 months:

NO difference in incidence of infections

Park S 2015

INFECTIONS POST AUTOLOGOUS SCT

Immune reconstitution after HD Melphalan:

- IgA : 9 months to pre ASCT levels
- IgM : 3 months to pre ASCT levels
- IgG : 1 month to pre ASCT levels and 9 months to normal levels

but…more time for micromolecolar and IgD MM

→ first 6 months highest incidence

→ incidence strongly negative correlate to IgA and IgG levels

Liu JR 2013

PNEUMOCOCCAL INFECTIONS:

Median incidence of IPD in general population 15/100.000/y

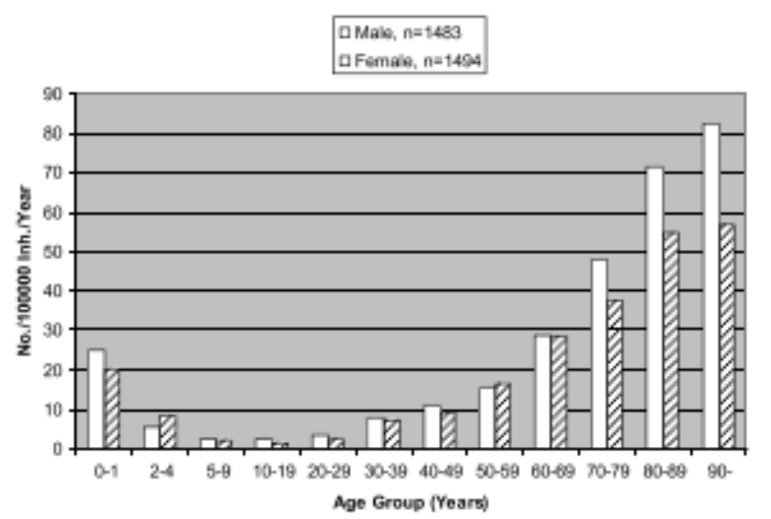


Table 1 Predisposing factors in 2977 patients with invasive pneumococcal disease: proportion, incidence rat

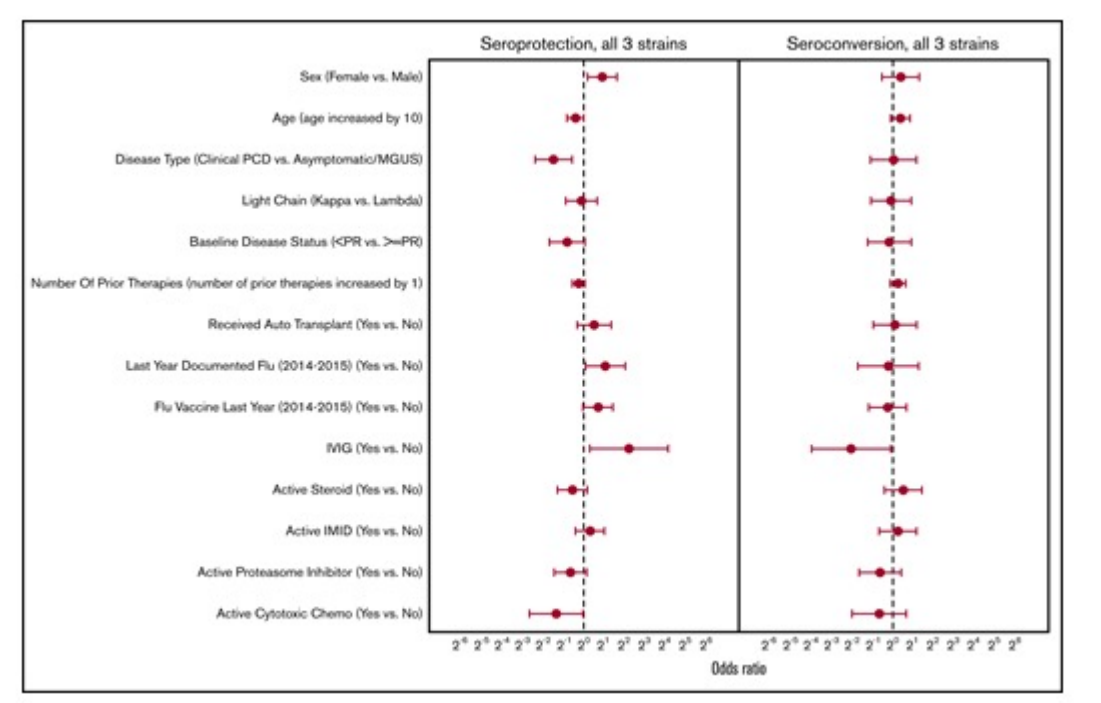
Predisposing Factor	No. of episodes (%)	Died (No.)	CFR (%)	RR of death (95 % CI)	No. of Pat. with Factor[c]	Incidence[d] (No./100,000/y.)
Cardiovascular disease	720 (24)	126	18	2.35 (1.90–2.92)[a]		
Pulmonary disease	531 (18)	51	10	0.97 (0.73–1.29)		
- COPD	307 (10)	38	12	1.29 (0.94–1.78)	49,000	48
- Asthma	145 (5)	4	3	0.27 (0.10–0.71)[b]	130,000	9
Malignancy	485 (16)	87	18	2.16 (1.71–2.72)[a]	72,000	52
- Haematological	257 (9)	35	14	1.43 (1.03–1.99)[a]	4900	403
- - Myeloma	128 (4)	23	18	1.89 (1.28–2.78)[a]	440	2238
- - Chronic Lymphatic Leukemia	53 (2)	4	8	0.76 (0.29–1.96)	950	429
- Solid tumors	158 (5)	50	32	3.66 (2.82–4.73)[a]	67,200	18
- - Lung	52 (2)	21	40	4.33 (3.05–6.13)[a]	1200	333
- - Breast	23 (1)	0	0	n.a.	14,600	12
- - Colon	22 (1)	4	18	1.85 (0.76–4.53)	4600	37
- - Prostate	46 (2)	5	11	1.10 (0.48–2.54)	11,900	30
Diabetes mellitus	336 (11)	36	11	1.10 (0.79–1.52)	60,500	43
Autoimmune Disease	227 (8)	26	11	1.17 (0.80–1.72)		

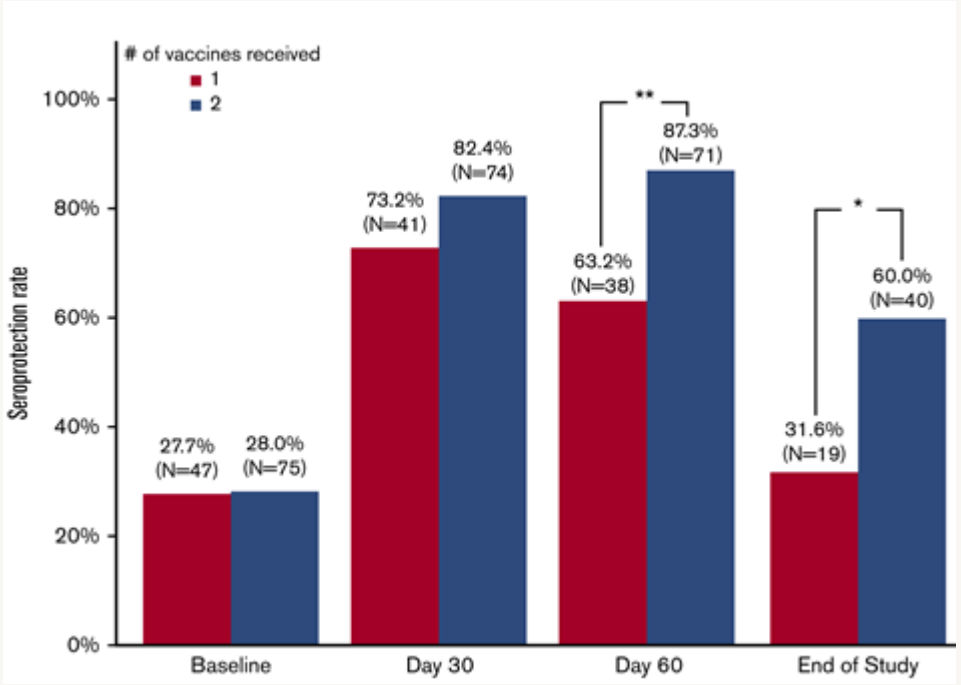
Backhaus 2016

VACCINATION GUIDELINES :INFLUENZA

Vaccination strategy:
standard dose <65Y ; HD >65 Y

1 standard dose vs 2 HD





Branagan AR 2021

VACCINATION GUIDELINES :INFLUENZA

- Serological respose after two standard doses of tetravalent vaccine

- 10-30% seroprotection rates
- (except for A-H3N2 71% but 53 % after daratumumab)

- **Post ASCT** :

2 standard doses at median of **2 months after** ASCT :76% to 97 % seroprotection

Hahn M 2015, Gressens 2024; Teh 2020

VACCINATION GUIDELINES: INFLUENZA

Influenza virus:

- All patients + close contacts , one month prior to influenza season
- 2 doses > 30 days (HD)

(baseline 4% to 49-65% responder)

In first 12 months after ASCT 2 doses starting 2 months after ASCT

Branagan 2017; IMWG Consensus Guidelines 2022; ECIL Guidelines 2019

VACCINATION GUIDELINES : PNEUMOCOCCI

- Colonizing ca 10 % mouth in healthy individuals
- In MM endogenous source more likely
- 98 serotyps identified

<u>Two vaccines</u>:

- polisaccaride vaccine (ppsv 23)

-conjugate vaccine (PCV 13 - valent, now also 20 valent)
T cell dependent

VACCINATION GUIDELINES: PNEUMOCOCCI

- Response to PPSV 23: 33-43%
  - lower in recalls

- Response to PCV 13: 40% 1 month
  - only 10% at 1 Year

BUT

PCV followed by PP23 2 -3 months later: (85% response!) still better under lenalidomide

- All patients with MM,SMM, MGUS :
- preferably14 days **before starting** CTX or **during lenalidomide** maintenance wich enhances responses
- PCV 20 followed by PPSV23 > 8weeks
- PPSV23 to repeat every5 Years

IMWG Consensus Guidelines 2022; ECIL Guidelines 2019; Bahuaud 2017, Renaud 2019

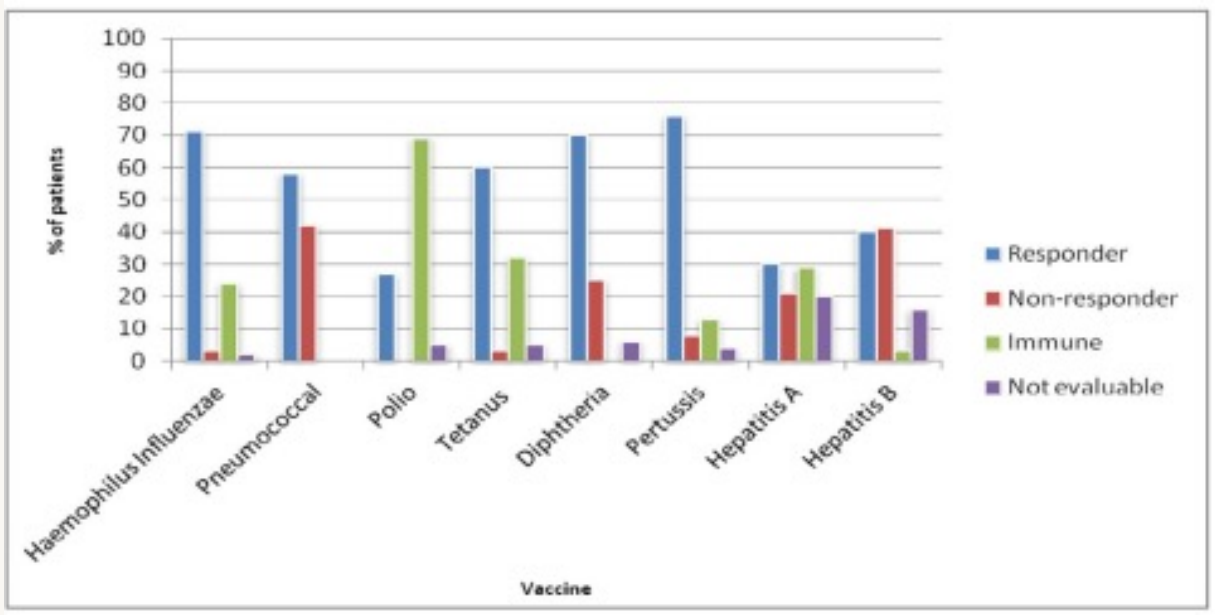
VACCINATION GUIDELINES

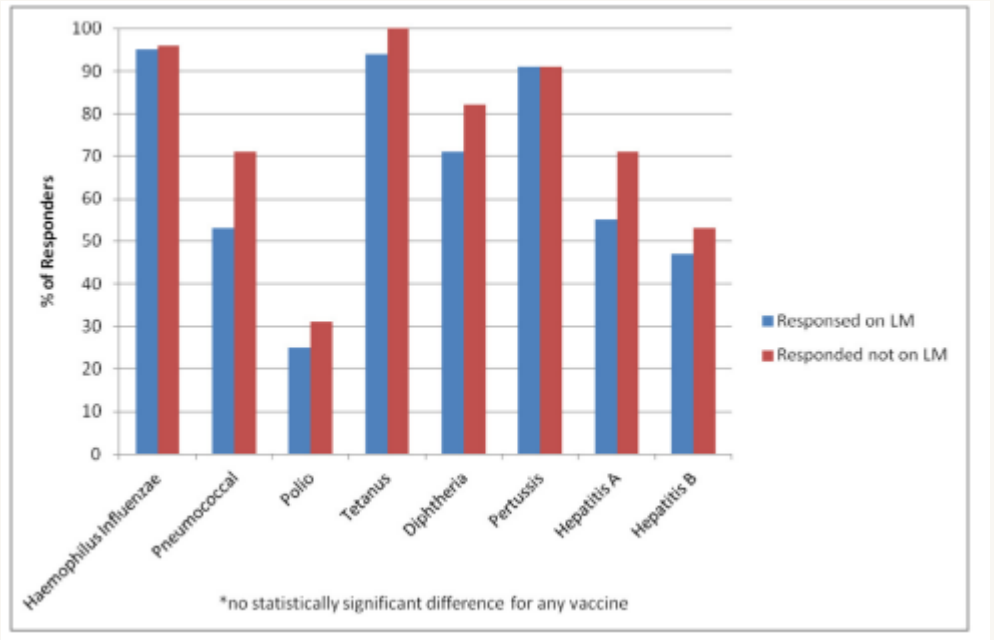
- **Haemophilus influenzae**
  - 55% of MM lack protective ab
  - Frequently colonized nasopharynx
  - Cause: sinusitis pneumonia, meningitis and sepsis
  - Antibody response to **vaccine** 71%
- **Meningococci**
  - Colonize a substantial proportion of general population
  - Hazard ratio of 16,6 of MM patients to develop meningococcal disease (incl sepsis with DIC)
  - **Vaccines**: tetravalent (A,C,Y,W) and recombinant targetting serogroup B

Palazzo 2018; High NJ 2014; Rieger CT 2018

REVACCINATION POST AUTOLOGOUS HSCT

Revaccination time: median 12,6 after AHSCT

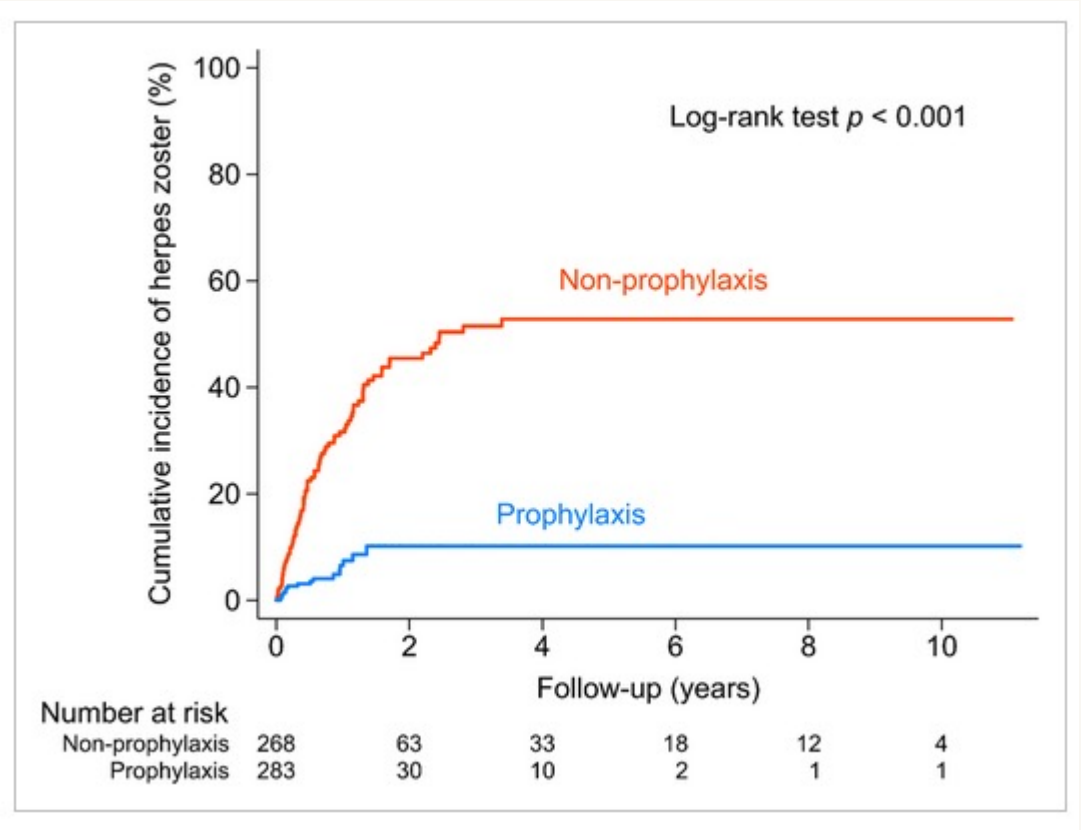




Palazzo M 2018

VARICELLA ZOSTER VIRUS AND MYELOMA

- Hazard ratio for VZV reactivation 14,8%
- **Risk higher** if exposure to PI , Daratumumab, HD melphalan and HSCT, high dose dexamethasone, bispecific Ab and CAR T cells
- Post exposure prophylaxis within 96h (up to 10 days)with VZV Immunoglobulins
- contagiousness 1-2 days before rush, incubation 14 days,



Blimark 2015; Lin 2022

VACCINATION GUIDELINES: VARICELLA ZOSTER

Vaccination after HSCT with Recombinant Vaccine preferable and save :

- **1. after 50-70 days; 2. after 1-2 months (efficacy 72,4%)**

Cumulative incidence after HSCT:

- 10 % vs 20% compared to placebo

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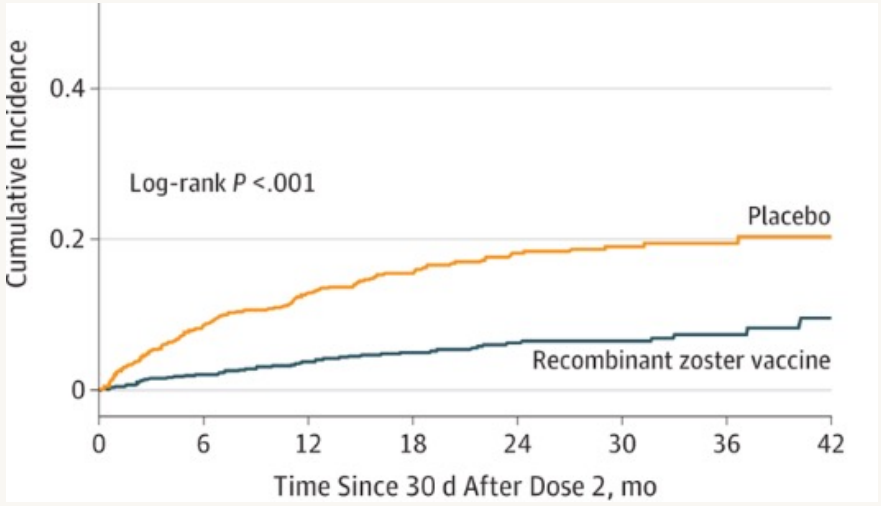


Stadtmauer 2021; Bastidas 2019

VACCINATION GUIDELINES: VARICELLA ZOSTER

Recombinant VZV vaccines reccomended:

But: vaccine <u>Not tested</u> in patients post anti CD 38 Ab, PI, anti SLAM7 Ab

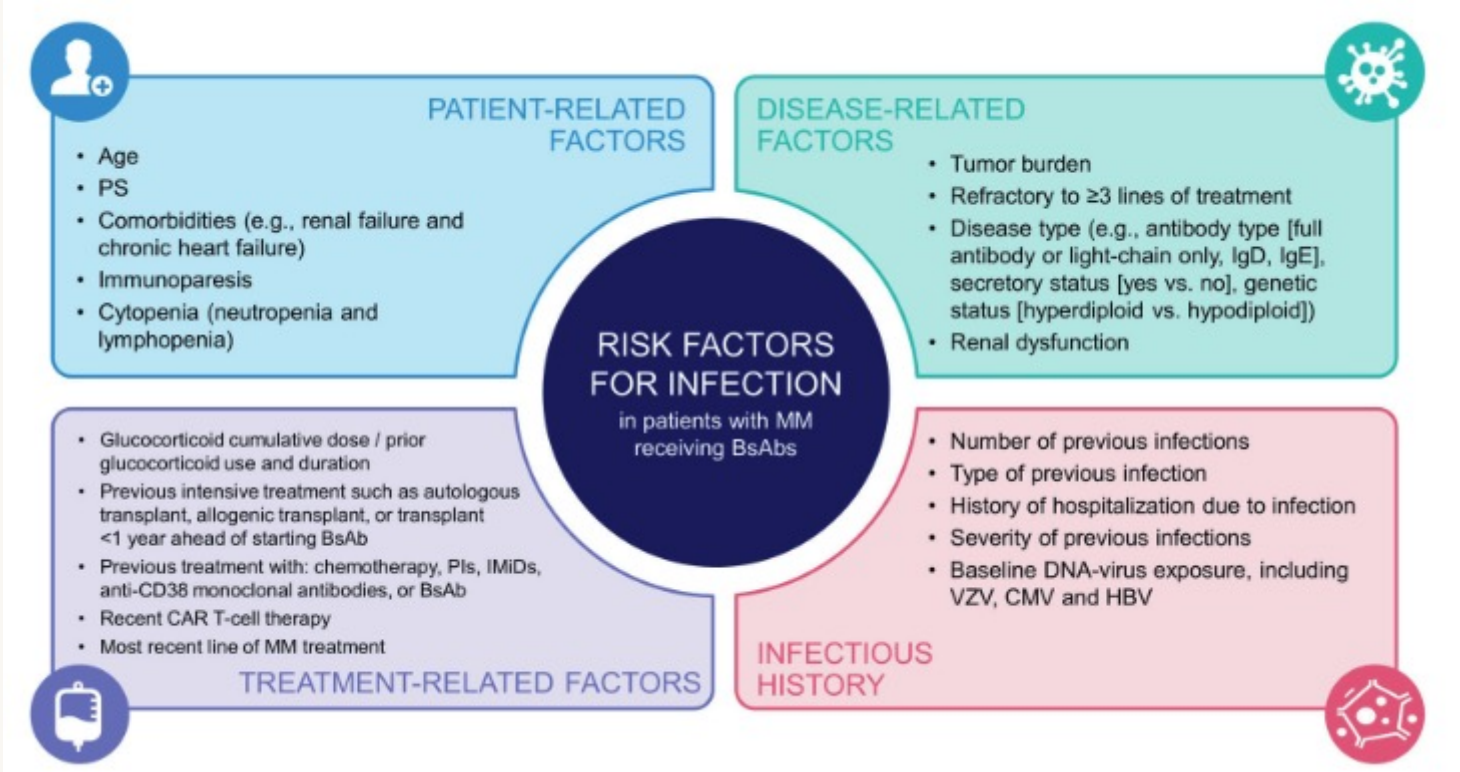
→ prophylaxis recomended despite vaccination if PI, anti CD38 ab and anti SLAM F7 ab

- Aciclovir 400 mg x 2 or Valaciclovir 500 x 1

,

Miceli 2019; Leng 2018

INFECTIONS WITH BISPECIFIC ANTIBODIES



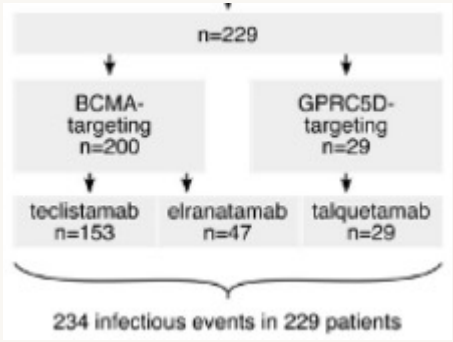
Raje 2023

INFECTIONS WITH BISPECIFIC ANTIBODIES

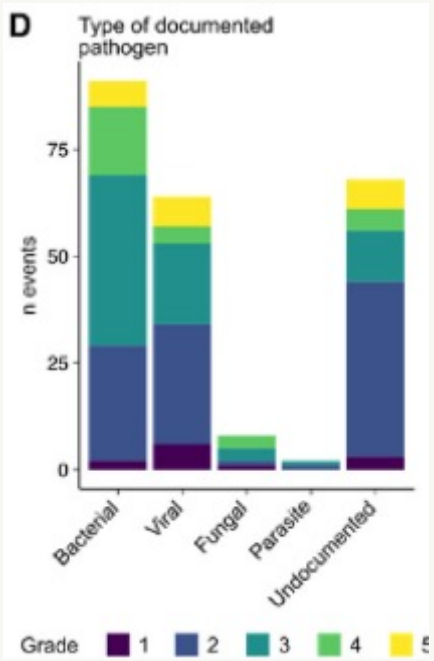
Drugs	Target	Patients in Trial	ORR, %	≥ VGPRR, %	Incidence of Infections, % (grade ≥ 3, %)	Deaths From Infection, No. (%)	Neutropenia, % (grade ≥ 3, %)	Hypogammaglobulinemia, %
ABBV-383[3]	BCMA	124	57	43	41 (≥ 20)	8 (6.5)	37 (34)	14[a]
Teclistamab[2]	BCMA	165	63	59	76 (45)	≥ 19 (11)	71 (64)	75
Teclistamab + 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

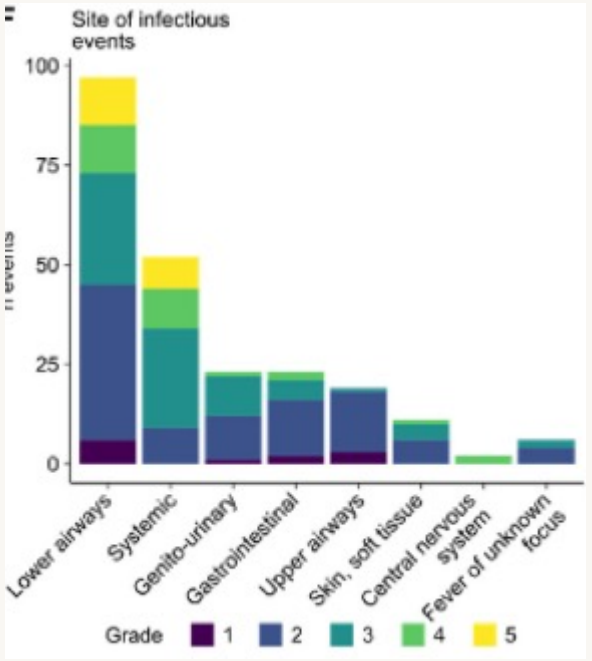
Scheffer 2023

INFECTIONS WITH BISPECIFIC ANTIBODIES



53% Grade 3+;
9% death

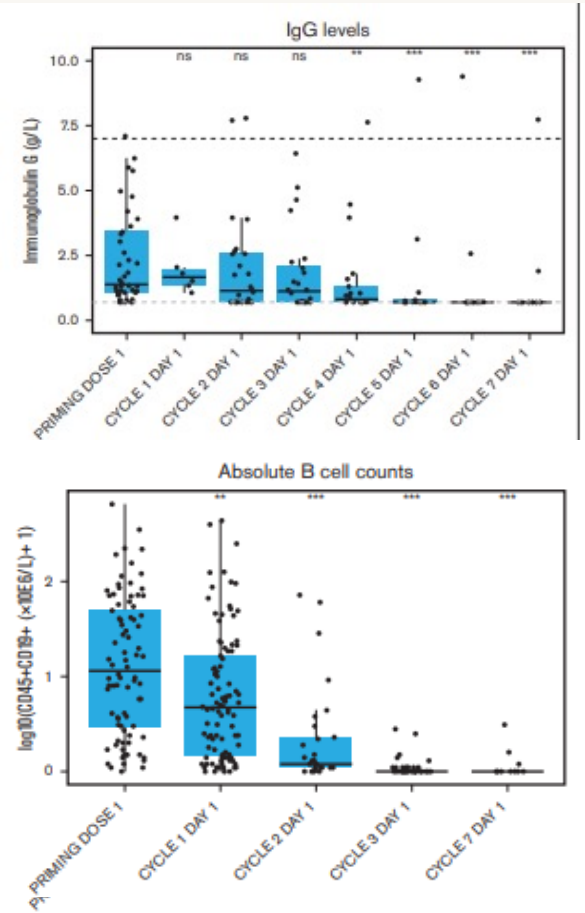


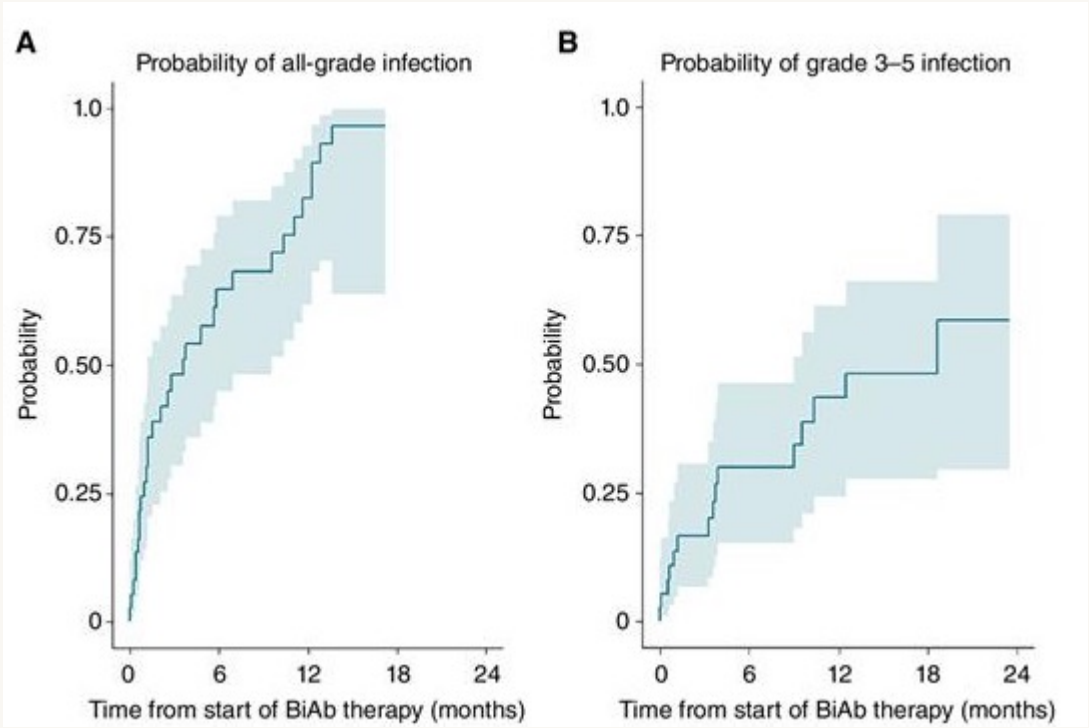


INFECTIONS WITH BISPECIFIC ANTIBODIES:PREVENTION

	Infection prevention before BCMA bispecific	Infection prevention during BCMA bispecific
Bacterial	Vaccinate if appropriate	IVIg q4 weeks
Viral		
Zoster	Vaccinate if appropriate	VZV prophylaxis
Influenza	Vaccinate if due	Hygiene
Hepatitis	Vaccinate if appropriate	Prophylaxis if evidence of Hep B exposure
CMV	N/A	Monitor CMV PCR q monthly
RSV	N/A	Hygiene
COVID-19	Vaccinate/Boost	? Preventative monoclonal antibodies based on viral patterns
		Consider monitoring Ab response and continue boosting
Fungal	N/A	N/A
PCP	N/A	PCP prophylaxis

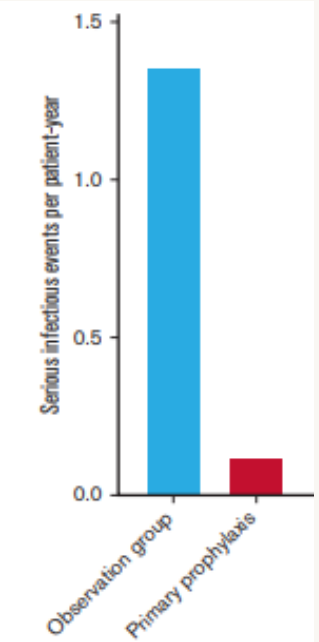
INFECTIONS WITH BISPECIFIC ANTIBODIES:TECLISTAMAB AND HYPOGAMMAGLOBULINEMIA

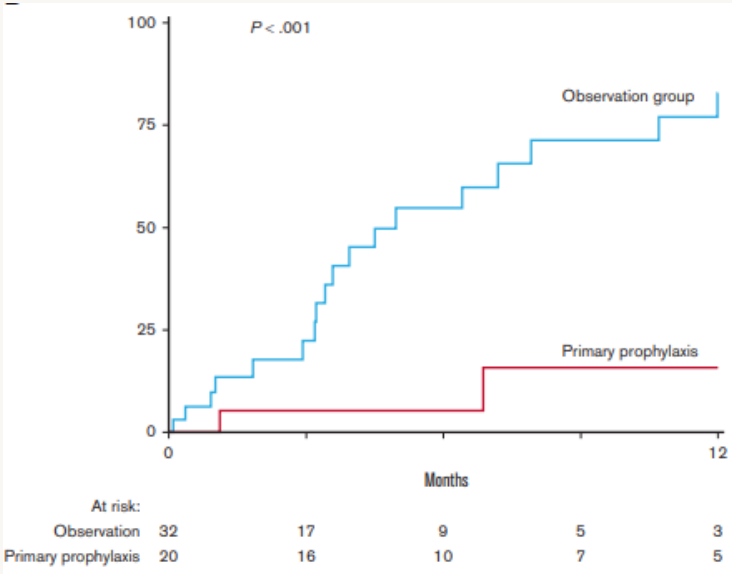




Frerichs 2024; Lancman 2023

INFECTIONS WITH BISPECIFIC ANTIBODIES:TECLISTAMAB AND IMMUNOGLOBULIN SUPPLEMENTATION





	IVIG as primary prophylaxis	No IVIG
Pneumonia/pneumosepsis	1 episode (also with breast abscess) • *P. aeruginosa* (n = 1)	11 episodes • *P. aeruginosa* (n = 5) • *P. aeruginosa* and *Klebsiella pneumoniae* (n = 1 • *Enterobacter cloacae* (n = 1) • Influenza A + *P. aeruginosa* (n = 1) • *Moraxella catarrhalis* (n = 1) • No pathogen (n = 2)
Pneumonia and empyema	0	2 episodes • *P aeruginosa* (n = 1) • *Moraxella catarrhalis* (n = 1)
Urosepsis	1 episode • *E. coli* (n = 1)	3 episodes • *E. coli* (n = 2) • *Citrobacter freundii* (n = 1)

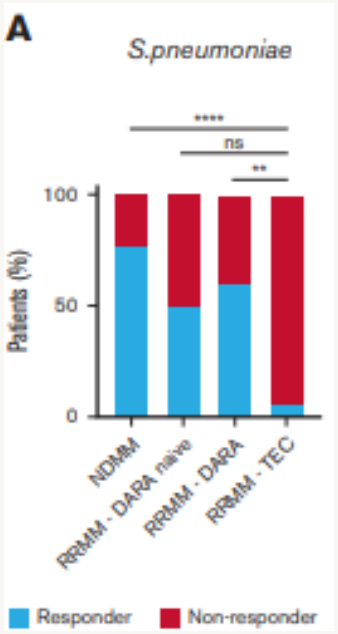
Frerichs 2024

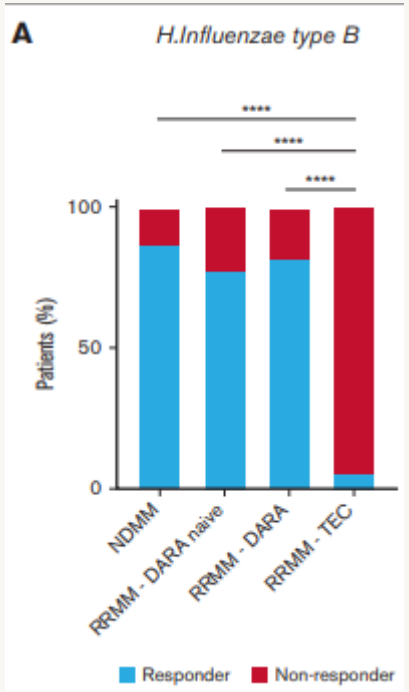
INFECTIONS WITH BISPECIFIC ANTIBODIES: TECLISTAMAB AND VACCINATION

All patients in PR +

-SARS CoV-2 mRNA vaccines:

None developed vaccine induced anti spike IgG after vaccinations





Frerichs 2024

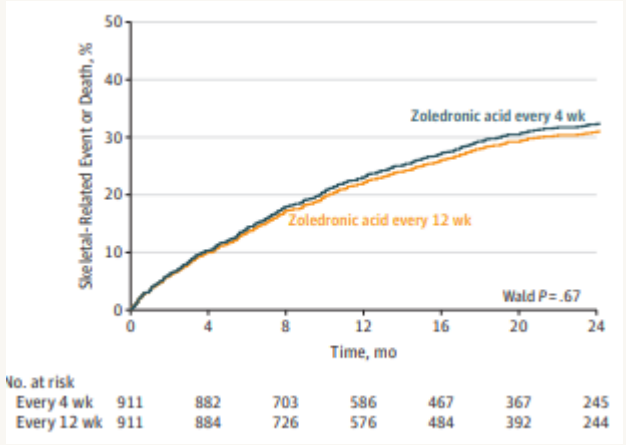
BONE DISEASE:

Bifosfonates:

- **pamidronate or zoledronic acid** in presence of bone disease
- Zoledronic acid also in absence of lesions? (survival benefit? but side effects)
- Pamidronate **30** mg **vs 90** mg no difference (Nordic Myeloma Study)
- Once a month for 1 year than **every 3 months** for another year
- zolendronic acid contraindicated if eGFR < 30 ml/min
- ONJ prevention and managing

BONE DISEASE:

- **Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases**A Randomized Clinical Trial-1822 patients



Zoledronic acid every **4** weeks vs **12** weeks

Secondary End Points	Zoledronic Acid Dose Group	
	Every 4 wk	Every 12 wk
Brief Pain Inventory score[a]		
Worst pain	0.021	0.022
Least pain	0.013	0.007
Average pain	0.011	0.008
Current pain	0.018	0.016
Composite pain	0.022	0.021
Relief from pain	0.016	0.009
Interference	0.019	0.023
ECOG performance status[a]	0.025	0.024
Osteonecrosis of the jaw, No./total available for analysis (%)	18/911 (2.0)	9/911 (1.0)
Kidney dysfunction		
Increased creatinine level, No./total available for analysis (%)[c]	10/852 (1.2)	4/837 (0.5)
Increased creatinine level vs baseline level, No./total available for analysis (%)[d]	174/875 (19.9)	137/882 (15.5)
Skeletal morbidity rate, mean (median) [IQR][e]	0.4 (0) [0-0.5]	0.4 (0) [0-0.5]
Total available for analysis	882	884
Total person-years of follow-up	1397.5	1367.8

Mayo Clinic: monthly in induction or until VGPR than every 3 months for 2 years

Himelstein 2017, Miceli 2021

BONE DISEASE

RANK ligand inhibitors

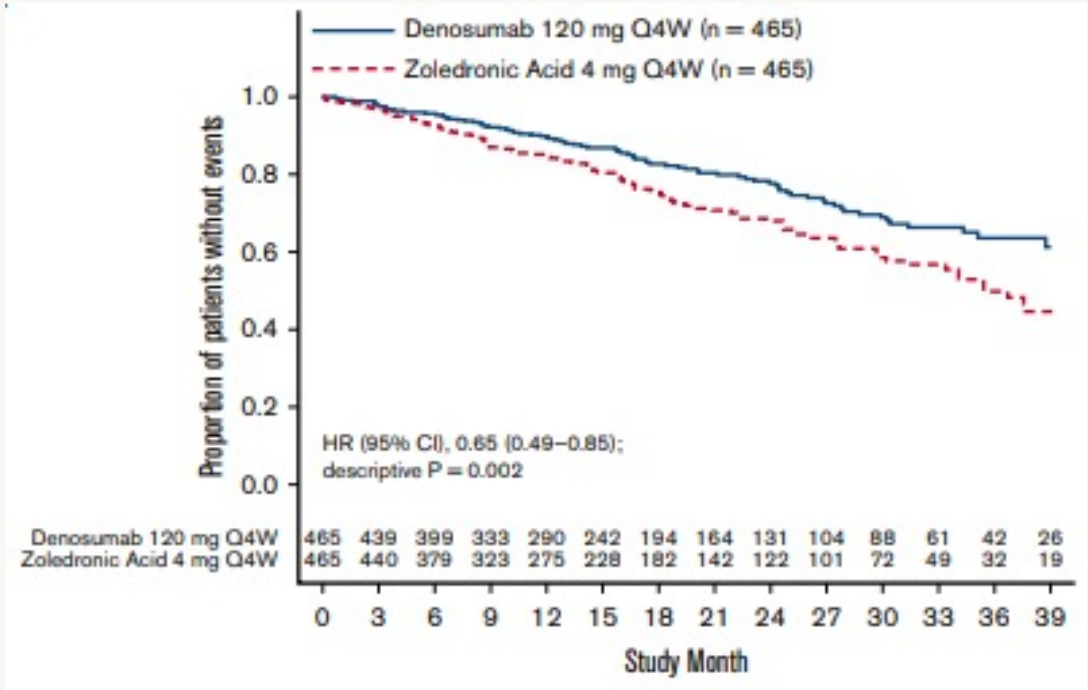
- **Denosumab:** Subcutaneous 120 mg every 4 weeks
- Also if renal insufficiency eGFR < 30 ml/min
- Denosumab increased PFS in bortezomib treated transplant eligible patients
- Rebound effect if stopped : zolendronic acid after 4-6 months

- Vitamin D 800 mg/d + Calcium 1000 mg/d supplementation **to all patients**

BONE DISEASE

Denosumab vs zolendronic acid

PFS : 46,1 vs 35,7 months
OS no difference



Synergistic effect with bortezomib?

VENOUS THROMBOEMBOLISM (VTE)

- >10% in course of disease
  - -Metanalysis 2011 up to 12%
  - Myeloma XI trial UK 2020 (11,8% despite 87,7% of pat. with prophylaxis)
- IMIDS +Dexa : TVP incidence 26%

→ definition of thrombotic risk stratification

→ optimal strategy to prevent VTE

De Stefano 2022

THROMBOTIC RISK ASSESSMENT MODEL IN MYELOMA

-**all patients** candidates for MM treatment need evaluation

- **Patient related factors**
- **Disease related factors**
- **Treatment related factors**

- Bleeding risk to be assessed

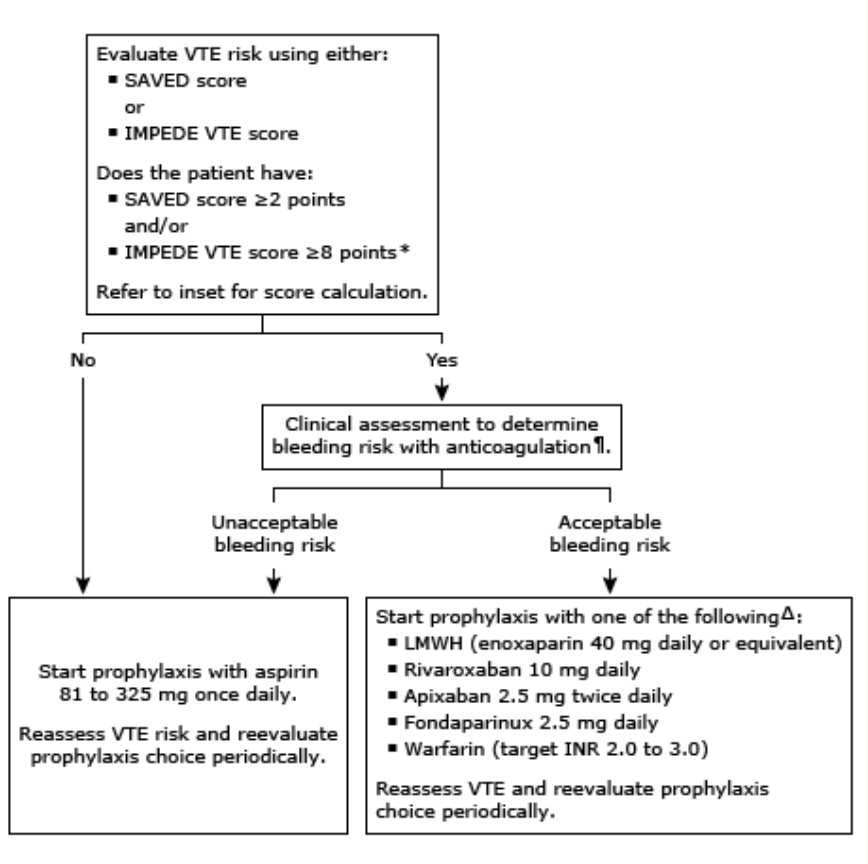
Risk Factors	VTE prophylaxis regimen
Individual • Obesity (BMI >30 kg/m^2) • Prior VTE • CVAD or pacemaker • Co-morbidity (CAD, CKD, DM, acute infection, immobilization) • Surgery (general, any anesthesia, trauma) • Use of erythropoietin • Thrombophilia	0–1 Individual or myeloma-related risk factor • Aspirin 81–325 mg oral daily >1 Individual or myeloma-related risk factors • Enoxaparin 40 mg SQ daily (or LMWH equivalent) • Warfarin (INR 2–3) • DOACs (Apixaban 2.5 mg BID or rivaroxaban 10 mg daily)
Myeloma-related • Diagnosis of myeloma and being treated with and IMiD	

Myeloma therapy
• IMiD in combination with
  • High dose dexamethasone (≥480 mg/month)
  • Doxorubicin
  • Multiagent chemotherapy
  • Carfilzomib*
	• Enoxaparin 40 mg SQ daily (or LMWH equivalent)
	• Warfarin (INR 2–3)
	• DOACs (Apixaban 2.5 mg twice daily or rivaroxaban 10 mg daily)

Miceli 2021;

THROMBOTIC RISK ASSESSMENT MODELS IN MYELOMA

SAVED score calculation (for patients treated with an immunomodulatory drug):		**Point(s)**
S	Surgery within 90 days	+2
A	Asian population	−3
V	VTE history	+3
E	Elders: Age ≥80 years	+1
D	Dexamethasone: ▪ >160 mg/month ▪ 120 to 160 mg/month	 +2 +1
IMPEDE VTE score calculation (for patients treated with or without immunomodulatory drugs):		**Point(s)**
I	Immunomodulatory drug	+4
M	Body mass index ≥25 kg/m^2 (calculator 1)	+1
P	Pelvic, hip, or femur fracture	+4
E	Erythropoiesis stimulating agent	+1
D	Doxorubicin or multiagent chemotherapy	+3
D	Dexamethasone: ▪ >160 mg/month ▪ <160 mg/month	 +4 +2
E	Ethnicity/race is Asian/Pacific Islander	−3
V	History of VTE before diagnosis of MM	+5
T	Tunneled central line or central venous catheter	+2
E	Existing thromboprophylaxis with: ▪ Prophylactic dose low molecular weight heparin or aspirin ▪ Therapeutic dose low molecular weight heparin or warfarin	 −3 −4



Covut 2021; Li 2019

VTE RISK AND PROTEASOME INHIBITORS

Proteasome inhibitors: bortezomib /carfilzomib/ixazomib

- RVD vs KRD: TE events **5% vs 16% (bortezomib vs carfilzomib)**with asa prophylaxis
- RD vs KRD :TE events 6% vs 13% (Aspire)

	Univariate analysis	
Variable	VTE	No VTE
Regimen + prophylaxis		
RVD + ASA	6 (5%)	118 (95%)
KRD + ASA	16 (16%)	83 (84%)
KRD + XA	4 (5%)	78 (95%)

→ KRD + rivaroxaban 10 mg

Piedra K 2021;Steward AK 2015

VTE RISK AND PROPHYLAXIS

Cochrane Collaboration 1042 Pat (2021)

- VTE : 4,5 % asa, 8,2 % fix warfarin dose 1,25 mg, 2,7% LMWH
- but NO significative difference in serious TVE, acute CV-events or sudden death

- If high risk: LMWH first 4 months ,than switch to ASA (IMWG Guidelines)
- Maintenance with lenalidomide: ASA prophylaxis
- **Alternative**: Apixaban 2,5 x 2 or Rivaroxaban 10 mg x 1 (Reg AIFA)

Kahale 2021 De Stefano 2022, Terpos 2015 Cornell 2020, Piedra 2019

VTE TREATMENT IN MM

- Anticoagulant treatment (AC) for minimum 6 months, depending of ongoing therapy and tumor burden
- VTE post ABMT or CVC associated : at least 3 months, if CVC removed 4-6 weeks
- Choice of AC: LMWH or DOAC
- DOAC (apixaban, endoxaban) non inferior to LMWH :
- 2894 cancer patients (10% MM) : recurrence 5,2 % vs 8,2 %
- non major bleeding 10,4 vs 6,4 % (GI tumors)

Kearon 2016, Moik 2020,Raskob 2018, Key 2020,Lyman 2021


GRAZIE!