Infection-related morbidity in a large study of transplant non-eligible newly diagnosed myeloma patients treated with UK standard of care

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Supplementary method, results and tables:

Baseline characteristics:

The following baseline patient characteristics were collected: age, sex, Charlson co-morbidity index (CCI), renal impairment, diabetes, COPD, and smoking status. Disease characteristics were collected as follows: myeloma sub-type, immunoparesis, ISS staging, LDH, hypercalcaemia, neutropenia, lymphopenia and anaemia. Immunoparesis is defined as a reduction (below the lower normal limit) in the levels of 1 or 2 uninvolved immunoglobulins (Ig).

Treatment characteristics data included choice of therapy (IMiD, PI, aklylator), number of treatment cycles, combination (doublet, triplet), dose attenuation, cumulative dexamethasone dose, PCP prophylaxis, antifungal prophylaxis, influenza and pneumococcal vaccinations. The cumulative dexamethasone dose during 1st line therapy was calculated for each patient. Where patients received a prednisolone-containing regimen, cumulative dose was converted to cumulative dexamethasone dose using the following conversion (prednisolone 5mg = dexamethasone 0.75 mg) as per the British National Formulary.

Percentages were used to summarise categorical variables and median values with range and interquartile range (IQR) to summarise continuous variables.

Definition and grading of infections:

An infection in this study is defined as a clinically suspected or microbiologically confirmed episode with an intention to treat with an antimicrobial, antifungal or antiviral drug. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was the method of choice (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)) to grade infection episodes attributed to myeloma or therapy. Time to infection episode was calculated in days from the start date of myeloma therapy to date of diagnosis with infection, within the first 365 days.

Infection outcomes:

Infections data collected for each patient over a 12 month period included: diagnosis (micro-guided or clinical), site, grade, number of episodes, responsible pathogens, time to episode (days), timing category (induction, remission, biochemical progression or during 2nd line therapy), seasonal incidence (Dec-March), duration of inpatient admission, ICU admissions, and mortality.

Response outcomes:

Treatment outcomes data collected included response rate as follows: complete response (CR), very good partial response (VGPR), partial response (PR), minor response or stable disease (MR/SD) and progressive disease (PD).

Survival outcomes:

Survival outcomes included overall survival (OS), progression-free survival (PFS), and cumulative incidence of first any grade or ≥G3 infection episode with death as competing risk. OS was defined as time from initiation of first anti-myeloma treatment to death from any cause. PFS was evaluated as the time between initiation of first anti-myeloma treatment and progressive disease (based on IMWG uniform response criteria) or death. Landmark analysis at 6 months after treatment start was done to assess the effect of infections within the first 6 months on OS and PFS of 6-month survivors. Occurrence of first infection was also examined as time-dependent variable in OS and PFS analysis in univariate testing and in the presence of other significant baseline predictors in multivariate Cox models.

Proportional hazards assumption was checked visually (log-log plot of survival).

Cumulative incidence curves of infections between subgroups:

Cumulative incidence of infections with death as competing risk were compared across the following subgroups using Gray test : age (<75 vs. ≥75), sex (M vs. F), immunoparesis at baseline (N vs. Y), elevated LDH (Y vs. N), ISS (3 vs. <3), CCI co-morbidity (0-2 vs. 3-4 vs. ≥5), diabetes (Y vs. N), COPD (Y vs. N), smoking (Y vs. N), renal impairment (Y vs. N), choice of therapy (IMiD vs. PI vs. Chemo), combination (doublet vs. triplet), dose attenuation (Y vs. N), PCP prophylaxis (N vs. Y) and antifungal prophylaxis (N vs. Y).

Competing risks regression according to the model of Fine and Gray was used to assess sub-hazard ratios in multivariate analysis.

Incidence rate:

Comparison of incidence rates of infections within 3, 6, and 12 months of treatment initiation across groups of patients was made with Poisson regression. Only patients who survived for at least 3, 6 or 12 months were included in the analysis for the corresponding time interval.

Using Poisson regression, univariate (UVA) and multivariate analyses (MVA) were conducted to assess factors associated with increased incidence rates of: all infections, ≥G3 infections, as well as significant inpatient admission (>3 days) within 12 months from treatment start. Factors investigated were the following: age (<75 vs. ≥75), sex (M vs. F), immunoparesis at baseline (N vs. Y), elevated LDH (Y vs. N), ISS (3 vs. <3), CCI co-

morbidity (0-2 vs. 3-4 vs. ≥5), diabetes (Y vs. N), COPD (Y vs. N), smoking (Y vs. N), renal impairment (Y vs. N), neutropenia at baseline (N vs. Y), lymphopenia at baseline (Y vs. N), anaemia at baseline (Y vs. N), hypercalcaemia at baseline (Y vs. N), choice of therapy (IMiD vs. PI vs. Chemo), combination (doublet vs. triplet), dose attenuation (Y vs. N), number of cycles of therapy (≥6 vs. <6), cumulative steroid dose in mg (≥800mg vs. <800mg), PCP prophylaxis (N vs. Y), antifungal prophylaxis (N vs. Y) and response (≥VGPR vs. ≤PR)

Univariate (UVA) and multivariate (MVA) analyses:

Covariates with prognostic significance (p≤0.1) in univariate testing were included in the initial multivariate models of the corresponding outcome. Final models were arrived at by backward selection. Variables were retained in the final model if significant at the 5% level.

No adjustment has been made for multiple testing. We consider all analyses exploratory and descriptive of our dataset.

Analysis was done with STATA version 11.2 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP) and EZR (Bone Marrow Transplantation 2013: 48, 452–458).

Results: influence of immunisation on infections:

There was a large number of patients with unknown vaccination status with either anti-pneumococcal or influenza vaccines.

However, we observed a significant protective effect of anti-pneumococcal vaccination on cumulative incidence of all grade infections (Y: 18.2% (2.5-45.5%), N: 54.2% (32-71.9%), UNK: 30.9% (24-38.1%)), Gray's p=0.0455), reduced 6-month incidence rate of all grade infections (Yes vs No, IRR=0.15 (0.02-1.03), p=0.053, Unknown vs. No, IRR=0.57 (0.3-1.07), p=0.081) and reduced 6-month incidence rate of ≥G3 infections (Yes vs. No IRR=2.28x10-7 (7.39 x 10-8 7.05 x 10-7), p<10-4, unkwnown vs. No IRR=1.06 (0.37-3), p=0.92), and similar results were also obtained for 12-month incidence rates.

Patients who were documented to have received annual influenza vaccination had numerically reduced cumulative incidence of ≥G3 infections at 12 months compared to patients with unknown vaccination status (Y: 11.4% (3.5-24.4%), UNK: 24.2% (18-31%), p=0.102).

Tables (titles and legends):

Table 1 title: Patient, disease and treatment characteristics of subgroups (infection vs. no-infection)

Table 1 legend: MM (multiple myeloma), ISS (International Staging System), LDH (lactate dehydrogenase), PCP (pneumocystis pneumonia). Number of patients with unknown data of the total cohort: 7 (for CCI), 4 (for renal impairment), 4 (for diabetes), 4 (for COPD), 122 (for smoking status), 29 (for ISS), 4 (for immunoparesis), 77 (for LDH), 5 (for neutropenia), 4 (for lymphopenia), 5 (for anaemia), 6 (for hypercalcaemia), 3 (for dose attenuation), 4 for cumulative dexamethasone dose, 5 (for antiviral prophylaxis), 5 (for PCP prophylaxis), 5 (for antifungal prophylaxis), 165 (for pneumococcal vaccine), 165 (for influenza vaccine). First line therapy consisted: cyclophosphamide with thalidomide and dexamethasone (CTD), attenuated CTD (CTDa), thalidomide with dexamethasone (TD), thalidomide with melphalan (MT), melphalan with prednisolone and thalidomide (MPT), lenalidomide with dexamethasone (Rd), lenalidomide with cyclophosphamide and dexamethasone (RCD), bortezomib and dexamethasone (VD), bortezomib with cyclophosphamide and dexamethasone (VCD), bortezomib with thalidomide and dexamethasone (VCD), carfilzomib with melphalan and prednisolone (CarMePred), cyclophosphamide with dexamethasone (CP), and melphalan with prednisolone (MP).

Supplementary Table S1 title: Summary of the total Cohort

Supplementary Table S1 legend: LC (light chains), MM (multiple myeloma), ISS (International Staging System), Cr (creatinine), IMiD (immunomodulatory drug), PI (proteasome inhibitor). Number of patients with unknown data of the total cohort: 29 (for ISS), 4 (for renal impairment), and 7 (for CCI).

Supplementary Table S2 title: Responsible pathogens

Supplementary Table S2 legend: Nil

Supplementary Table S3 title: Characteristics of infection episodes

Supplementary Table S3 legend: ICU (intensive care unit), N/A: not applicable

Supplementary Table S4 title: Diagnoses and sites of infections

Supplementary Table S4 legend: UTI (urinary tract infection), C.Diff (clostridium difficile), PICC (Peripherally inserted central catheter), LRTI (lower respiratory tract infection), URTI (upper respiratory tract infection)

Supplementary Table S5 title: Univariate and multivariate analysis of cumulative incidence of all-grade infections, and ≥G3 infections in 12 months using Gray test.

Supplementary Table S5 legend: Nil

Supplementary Table S6 title: Univariate and multivariate Poisson regression: all grade infections

Supplementary Table S6 legend: Nil

Supplementary Table S7 title: Univariate and multivariate Poisson regression: ≥G3 infections

Supplementary Table S7 legend: Nil

Supplementary Table S8 title: Univariate and multivariate Poisson regression: significant inpatient stay (>3 days)

Supplementary Table S8 legend: Nil

Supplementary Table S9 title: Time-dependent (TD) effect of occurrence of first any grade or G≥3 infectious episode on OS and PFS (multivariate Cox regression)

Supplementary Table S9 legend: Nil

Supplementary Table S1: Summary of the total Cohort

Characteristic		N=200 (100%)
Age at start of therapy (years)	Median (range)	75 (40-94)
	<75	45.5%
	≥75	54.5%
Sex	Male	56%
	Female	44%
Myeloma subtype	LC MM	28%
	IgG	54%
	IgA	15.5%
	IgM	1%
	Non-secretory	1.5%
ISS staging	<3	41.5%
	3	44%
MM renal impairment (Cr≥140)	Y	24%
Charlson Co-morbidity Index (CCI)	0-2	20.5%
	3-4	48%
	≥5	28%
Treatment	IMiD	69%
	PI	20%
	Chemo	11%
Combination	Doublet	31.5%
	Triplet	68.5%
Number of cycles	Median (range)	1-39
	<6	44%
	≥6	56%

Supplementary Table S2: Responsible pathogens

Organism	Infection Diagnosis	Site	Number of infection episodes			
			G1-2	G3	G4	G5
Clostridium Difficile Binary Toxin CDT (1)	C Diff	GI	0	1	0	0
Adenovirus & Enterovirus (1)	LRTI	Respiratory Tract	1	0	0	0
Coagulase Negative Staphylococcous (1)	Urinary Sepsis	GU	1	0	0	0
Coliforms (1)	UTI	GU	1	0	0	0
E.Coli (12)	LRTI	Respiratory Tract	0	1	0	0
	UTI	GU	9	1	0	0
	Urinary sepsis	GU	0	1	0	0
Enterobacter Cloacae (1)	Sepsis	Unknown Origin	0	1	0	0
Enterococcus Faecium (2)	LRTI	Respiratory Tract	0	1	0	0
	Neutropenic sepsis	Unknown Origin	0	0	0	1
Herpes Zoster (1)	Shingles	Skin and Soft Tissue	0	1	0	0
Influenza H1N1 (1)	Influenza H1N1	Respiratory Tract	0	1	0	0
Influenza A (1)	Influenza A	Respiratory Tract	0	1	0	0
Klebsiella (1)	Biliary Sepsis	GI	0	0	1	0
Klebsiella Oxytoca (1)	UTI	GU	1	0	0	0
Klebsiella Pneumoniae (1)	UTI	GU	1	0	0	0
Neisseria Cinerea (1)	LRTI	Respiratory Tract	0	1	0	0
Neisseria Meningitidis (1)	Septic Bacteraemia	Blood stream infections	0	1	0	0
Proteus Mirabillis (2)	UTI	GU	1	0	0	0
	Neutropenic sepsis	GU	0	1	0	0
Pseudomonas Aeroginosa (2)	PICC Line	Peripheral Access	0	1	0	0
	Netropenic sepsis	Unknown origin	0	1	0	0
Staphylococcus Aureus (1)	Finger abscess	Skin and Soft Tissue	1	0	0	0

Supplementary Table S3: Characteristics of infection episodes

Characteristic		Infection episodes	
		All infections=116	≥G3=72
Timing of infection	Induction	57 (49.1%)	34 (47.2%)
	Remission	20 (17.2%)	8 (11.1%)
	Progressive disease	16 (13.8%)	14 (19.4%)
	2nd line therapy	23 (19.8%)	16 (22.2%)
Seasonal infection	N	79 (68.1%)	51 (70.8%)
(December-March)	Y	37 (31.9%)	21 (29.2%)
Significant hospital stay (>3 days)	N	60 (51.7%)	17 (23.6%)
	Y	56 (48.3%)	55 (76.4%)
30 day outcome	survived	107 (92.2%)	64 (88.9%)
	died	9 (7.8%)	8 (11.1%)
ICU admission with infection	N	114 (98.3%)	70(97.4%)
	Y	2 (1.7%)	2 (2.8%)
Outcome of ICU admission	survived	2 (1.7%)	2 (2.8%)
	died	0 (0%)	0 (0%)
	N/A	114 (98.3%)	70(97.4%)

Supplementary Table S4: Diagnoses and sites of infections

Infection site and number of infections	Infection diagnosis	Number of infection episodes (N) = 116			
		G2=43	G3=63	G4=2	G5=8
Eye (2)	Conjunctivitis	2	0	0	0
Ear/Nose/Throat (2)	Sinusitis	0	2	0	0
Genito-urinary tract (22)	UTI	15	4	0	0
	Urinary Sepsis	1	1	0	0
	Neutropenic Sepsis	0	1	0	0
Gastrointestinal (4)	Biliary Sepsis	0	0	1	0
	C. Diff infection	0	1	0	0
	Neutropenic Sepsis	0	0	0	1
	Viral Gastroenteritis	0	1	0	0
Peripheral Access Device (1)	PICC Line	0	1	0	0
Respiratory Tract (61)	Influenza	0	2	0	0
	LRTI	13	34	0	4
	Neutropenic Sepsis	0	1	0	0
	URTI	4	1	0	2
Skin and Soft Tissue (8)	Finger Abscess	1	0	0	0
	Cellulitis	4	0	0	0
	Shingles	1	1	0	0
	Septic Arthritis	0	1	0	0
Blood stream infections (1)	Septic bacteremia	0	1	0	0
Unknown Origin (15)	Neutropenic Sepsis	0	2	0	1
	Pyrexia of Unknown origin	2	6	1	0
	Sepsis of Unknown origin	0	2	0	0
	Unspecified	0	1	0	0

Supplementary Tables S5: Univariate (UVA) and multivariate (MVA) analysis of 12 month cumulative incidence of all grade and ≥G3 infections

Outcome	Characteristic	Univariate analysis		Multivariate analysis	
		Cumulative Incidence at 12 months (95% CI)	Gray test P-value	Subhazard ratio (95% CI)	P-value
		33% (26.6-39.6%)		-	-
Cumulative incidence curves of all grade infections, competing event: death	age (≥75 vs. <75)	≥75 : 35.8% (26.9-44.8%) <75: 29.7% (20.6-39.3%)	0.336	-	-
	Sex (F vs. M)	F: 30.7% (21.3-40.5%) M: 34.8% (26.1-43.7%)	0.59	-	-
	immunoparesis at baseline	N: 28% (12.1-46.4%) Y: 34.7% (27.6-41.9%)	0.283	-	-
	CCI categories	0-2: 34.1% (20.1-48.7%) 3-4: 32.3% (23.2-41.8%) ≥5: 37.6% (24.9-50.1%)	0.302	-	-
	neutropenia at baseline	Y: 40.7% (22-58.7%) N: 32.7% (25.7-39.9%)	0.233	-	-
	lymphopenia at baseline	Y: 38.9% (25.9-51.7%) N: 31.7% (24.2-39.4%)	0.254	-	-
	anaemia at baseline	Y: 35.6% (27.9-43.3%) N: 28.3% (16.1-41.7%)	0.216	-	-
	ISS at baseline	<3: 36.1% (25.9-46.5%) 3: 35.2% (25.4-45.2%) UNK: 17.2% (6.1-33.1%)	0.215	-	-
	Renal impairment at baseline	Y: 25% (13.7-38%) N: 36.5% (28.8-44.2%)	0.122	-	-
	elevated LDH at baseline	Y: 63% (41.2-78.5%) N: 32.3% (23.2-41.8%) UNK: 23.4% (14.6-33.4%)	0.0005	Y vs. N: 2.2 (1.2-4.03) UNK vs. N: 0.7 (0.39-1.26)	0.01 0.234 0.0045
	COPD at baseline	Y: 90.9% (29.1-99.3%) N: 30.3% (23.8-37%)	1.71×10^{-8}	6.28 (3.04-13)	$<10^{-3}$
	Smoking	Y: 71.4% (45.5-86.6%) N: 31.6% (20-43.9%) UNK: 27% (19.5-35.2%)	7.32e-05	-	-
	diabetes at baseline	Y: 50% (27.2-69.7%) N: 31.6% (24.8-38.6%)	0.156	-	-
	1st line triplet vs. doublet	Doublet: 25.4% (15.4-36.7%) Triplet: 36.5% (28.5-44.5%)	0.162	-	-
	1st line agent	IMID: 32.8% (25.1-40.8%) PI: 34.1% (20-48.8%) Chemo: 31.8% (13.7-51.7%)	0.984	-	-
	Treatment dose attenuation	Y: 36.5% (26.9-46.1%) N: 30.7% (22-39.8%)	0.361	-	-
	PJP prophylaxis	Y: 33.3% (23.8-43.2%) N: 33.3% (24.5-42.4%)	0.845	-	-
	antifungal prophylaxis	Y: 37.9% (27.7-48%) N: 29.6% (21.3-38.4%)	0.405	-	-

Outcome	Characteristic	Univariate analysis		Multivariate analysis	
		Cumulative Incidence at 12 months (95% CI)	Gray test P-value	Subhazard ratio (95% CI)	P-value
		22% (16.5-28%)		-	-
Cumulative incidence curves of ≥G3 infections, competing event: death	**age (≥75 vs. <75)**	≥75 : 22.9% (15.5-31.2%) <75: 20.9% (13.2-29.8%)	0.742	-	-
	Sex (F vs. M)	F: 19.3% (11.8-28.2%) M: 24.1% (16.6-32.4%)	0.478	-	-
	immunoparesis at baseline	N: 24% (9.5-42.1%) Y: 22.4% (16.4-28.9%)	0.475	-	-
	CCI categories	0-2: 24.4% (12.5-38.4%) 3-4: 21.9% (14.2-30.6%) ≥5: 23.2% (13.1-35%)	0.56	-	-
	neutropenia at baseline	Y: 18.5% (6.7-35.2%) N: 23.2% (17.1-29.9%)	0.435	-	-
	lymphopenia at baseline	Y: 25.9% (15.1-38.2%) N: 21.1% (14.8-28.2%)	0.459	-	-
	anaemia at baseline	Y: 24.8% (18.2-32%) N: 15.2% (6.6-27.1%)	0.216	-	-
	ISS at baseline	<3: 22.9% (14.5-32.4%) 3: 23.9% (15.5-33.2%) UNK: 13.8% (4.2-28.9%)	0.572	-	-
	Renal impairment at baseline	Y: 12.5% (5-23.6%) N: 25.7% (18.9-32.9%)	0.0925	Y: 0.23 (0.09-0.59) N: Ref	0.002
	elevated LDH at baseline	Y: 44.4% (25-62.2%) N: 20.8% (13.3-29.5%) UNK: 15.6% (8.5-24.6%)	0.0074	Y: 3.78 (1.76-8.11) N: Ref UNK: 0.79 (0.38-1.65)	0.001 0.531 0.0003
	hypercalcaemia at baseline	Y: 22.2% (8.8-39.4%) N: 22.2% (16.2-28.7%)	0.96	-	-
	COPD at baseline	Y: 72.7% (31.5-91.6%) N: 19.5% (14.1-25.5%)	1.79×10^{-5}	-	-
	Smoking	Y: 52.4% (28.8-71.5%) N: 14% (6.5-24.4%) UNK: 20.5% (13.8-28.1%)	6×10^{-5}	Y: 7.7 (3.15-18.8) N: Ref UNK: 2.12 (0.98-4.57)	$<10^{-3}$ 0.056 $<10^{-4}$
	diabetes at baseline	Y: 40.9% (20.1-60.8%) N: 20.1% (14.5-26.4%)	0.081	-	-
	1st line triplet vs. doublet	Doublet: 17.5% (9.2-27.8%) Triplet: 24.1% (17.3-31.5%)	0.277	-	-
	1st line agent	IMID: 22.6% (16-30%) PI: 17.1% (7.4-30.1%) Chemo: 27.3% (10.7-47%)	0.61	-	-
	Treatment dose attenuation	Y: 24% (15.9-32.9%) N: 20.8% (13.5-29.2%)	0.556	-	-
	PJP prophylaxis	Y: 23.3% (15.2-32.5%) N: 21% (13.7-29.2%)	0.911	-	-
	antifungal prophylaxis	Y: 28.7% (19.6-38.5%) N: 16.7% (10.3-24.3%)	0.125	-	-

Supplementary Table S6: Univariate and multivariate Poisson regression: all grade infections

Outcome	Characteristic	Univariate analysis		Multivariate analysis	
		Incidence Rate Ratio (95% CI)	P-value	Incidence Rate Ratio (95% CI)	P-value
All infections in 12 months from Tx start (N=145) Poisson regression	age (≥75 vs. <75)	1.24 (0.64-2.39)	0.526	-	-
	Sex (F vs. M)	0.87 (0.47-1.6)	0.657	-	-
	immunoparesis at baseline (N vs. Y)	0.77 (0.33-1.79)	0.543	-	-
	CCI categories			-	-
	3-4 vs. 0-2	0.82 (0.32-2.13)	0.688		
	≥5 vs. 0-2	1.34 (0.48-2.73)	0.571		
	neutropenia at baseline (N vs. Y)	0.9 (0.5-1.64)	0.734	-	-
	lymphopenia at baseline (Y vs. N)	1.25 (0.68-2.29)	0.473	-	-
	anaemia at baseline (Y vs. N)	1.13 (0.55-2.33)	0.747	-	-
	ISS at baseline			-	-
	3 vs. <3	0.95 (0.5-1.79)	0.868		
	UNK vs. <3	0.57 (0.18-1.85)	0.35		
	Renal impairment at baseline (Y vs. N)	0.47 (0.19-1.15)	0.1	-	-
	elevated LDH at baseline		0.004		0.0037
	Y vs. N	2.7 (1.41-5.02)	0.002	2.43 (1.39-4.26)	0.002
	UNK vs. N	0.91 (0.41-2.01)	0.817	0.93 (0.44-1.96)	0.839
	hypercalcaemia at baseline (Y vs. N)	0.67 (0.26-1.72)	0.402	-	-
	COPD at baseline (Y vs. N)	3.44 (1.85-6.41)	$<10^{-3}$	-	-
	Smoking		0.006		0.002
	Y vs. N	2.07 (1.03-4.17)	0.042	2.11 (1.12-3.98)	0.021
	UNK vs. N	0.69 (0.33-1.42)	0.312	0.73 (0.37-1.44)	0.361
	diabetes at baseline (Y vs. N)	1.39 (0.75-2.58)	0.298	-	-
	1st line triplet vs. doublet	1.38 (0.67-2.82)	0.38	-	-
	1st line			-	-
	PI vs. IMID	1.13 (0.58-2.22)	0.72		
	Chemo vs. IMID	1.03 (0.34-3.1)	0.959		
	number of cycles of therapy (≥6 vs. <6)	0.45 (0.25-0.81)	0.008	0.49 (0.28-0.88)	0.017
	cumulative dexamethasone dose (≥800 vs. <800mg)	0.7 (0.38-1.27)	0.237	-	-
	Treatment dose attenuation (Y vs. N)	1 (0.54-1.87)	0.977	-	-
	PCP prophylaxis (Y vs. N)	1.1 (0.6-2.05)	0.761	-	-
	antifungal prophylaxis (Y vs. N)	1.73 (0.96-3.11)	0.07	-	-
	response (≥VGPR vs. ≤PR)	0.58 (0.31-1.09)	0.09	-	-

Supplementary Table S7: Univariate and multivariate Poisson regression ≥G3 infections

Outcome	Characteristic	Univariate analysis		Multivariate analysis	
		Incidence Rate Ratio (95% CI)	P-value	Incidence Rate Ratio (95% CI)	P-value
≥G3 infections in 12 months from Tx start (N= 154) Poisson regression	age (≥75 vs. <75)	0.95 (0.43-2.08)	0.892	-	-
	Sex (F vs. M)	0.73 (0.33-1.59)	0.424	-	-
	immunoparesis at baseline (N vs. Y)	0.54 (0.22-1.34)	0.182	-	-
	CCI categories			-	-
	3-4 vs. 0-2	0.69 (0.24-1.96)	0.490		
	≥5 vs. 0-2	0.88 (0.28-2.83)	0.835		
	neutropenia at baseline (N vs. Y)	0.69 (0.23-1.96)	0.488	-	-
	lymphopenia at baseline (Y vs. N)	1.07 (0.5-2.3)	0.863	-	-
	anaemia at baseline (Y vs. N)	1.77 (0.64-4.93)	0.272	-	-
	ISS at baseline			-	-
	3 vs. <3	0.95 (0.42-2.15)	0.910		
	UNK vs. <3	0.49 (0.14-1.78)	0.279		
	Renal impairment at baseline (Y vs. N)	0.56 (0.16-1.94)	0.363	-	-
	elevated LDH at baseline				0.0014
	Y vs. N	3.8 (1.74-8.3)	0.001	3.57 (1.78-7.15)	$<10^{-3}$
	UNK vs. N	1.33 (0.51-3.45)	0.560	1.4 (0.58-3.37)	0.456
	hypercalcaemia at baseline (Y vs. N)	0.91 (0.32-2.58)	0.865	-	-
	COPD at baseline (Y vs. N)	4.93 (2.34-10.41)	$<10^{-3}$	-	-
	Smoking				0.0005
	Y vs. N	5.46 (2-14.86)	0.001	5.41 (2.26-12.93)	$<10^{-3}$
	UNK vs. N	1.99 (0.76-5.2)	0.155	2.19 (0.91-5.28)	0.080
	diabetes at baseline (Y vs. N)	1.75 (0.79-3.86)	0.165	-	-
	1st line triplet vs. doublet	1.13 (0.47-2.7)	0.783	-	-
	1st line			-	-
	PI vs. IMID	0.92 (0.37-2.27)	0.856		
	Chemo vs. IMID	1.33 (0.4-4.48)	0.642		
	number of cycles of therapy (≥6 vs. <6)	0.39 (0.18-0.83)	0.015	0.46 (0.23-0.95)	0.035
	cumulative dexamethasone dose (≥800 vs. <800mg)	0.71 (0.33-1.53)	0.380	-	-
	Treatment dose attenuation (Y vs. N)	0.92 (0.43-1.98)	0.833	-	-
	PCP prophylaxis (Y vs. N)	1.76 (0.83-3.71)	0.141	-	-
	antifungal prophylaxis (Y vs. N)	1.93 (0.9-4.13)	0.093	-	-
	response (≥VGPR vs. ≤PR)	0.35 (0.17-0.75)	0.007	0.35 (0.17-0.69)	0.003

Supplementary Table S8: Univariate and multivariate Poisson regression: inpatient stay (>3days)

Outcome	Characteristic	Univariate analysis		Multivariate analysis	
		Incidence Rate Ratio (95% CI)	P-value	Incidence Rate Ratio (95% CI)	P-value
Hospital stay >3 days in 12 months from Tx start (N=154) among 12-month survivors, Poisson regression	age (≥75 vs. <75)	1.01 (0.37-2.76)	0.982	-	-
	Sex (F vs. M)	0.84 (0.33-2.18)	0.727	-	-
	immunoparesis at baseline (N vs. Y)	0.6 (0.17-2.12)	0.432	-	-
	CCI categories			-	-
	3-4 vs. 0-2	0.61 (0.15-2.45)	0.489		
	≥5 vs. 0-2	1.02 (0.23-4.44)	0.979		
	neutropenia at baseline (N vs. Y)	0.4 (0.1-1.65)	0.207	-	-
	lymphopenia at baseline (Y vs. N)	0.93 (0.38-2.31)	0.882	-	-
	anaemia at baseline (Y vs. N)	1.52 (0.45-5.1)	0.502	-	-
	ISS at baseline			-	-
	3 vs. <3	0.75 (0.28-2.01)	0.568		
	UNK vs. <3	0.51 (0.14-1.89)	0.313		
	Renal impairment at baseline (Y vs. N)	0.57 (0.13-2.4)	0.442	-	-
	elevated LDH at baseline				0.0001
	Y vs. N	5.72 (2.1-14.83)	0.001	6.05 (2.59-14.15)	$<10^{-3}$
	UNK vs. N	1.99 (0.61-6.5)	0.254	2.12 (0.66-6.76)	0.206
	hypercalcaemia at baseline (Y vs. N)	1.22 (0.41-3.66)	0.724	-	-
	COPD at baseline (Y vs. N)	5.32 (2.12-13.39)	$<10^{-3}$	-	-
	Smoking				0.0014
	Y vs. N	6.61 (1.98-22.07)	0.002	6.47 (2.22-18.86)	0.001
	UNK vs. N	2.32 (0.73-7.41)	0.154	2.41 (0.77-7.52)	0.130
	diabetes at baseline (Y vs. N)	1.48 (0.44-4.94)	0.522	-	-
	1st line triplet vs. doublet	0.95 (0.34-2.64)	0.917	-	-
	1st line			-	-
	PI vs. IMID	0.95 (0.3-2.99)	0.928		
	Chemo vs. IMID	2.2 (0.62-7.85)	0.224		
	number of cycles of therapy (≥6 vs. <6)	0.36 (0.19-0.89)	0.028	-	-
	cumulative dexamethasone dose (≥800 vs. <800mg)	0.58 (0.23-1.45)	0.247	-	-
	Treatment dose attenuation (Y vs. N)	0.9 (0.35-2.31)	0.828	-	-
	PCP prophylaxis (Y vs. N)	2.05 (0.84-5)	0.114	-	-
	antifungal prophylaxis (Y vs. N)	1.56 (0.63-3.89)	0.338	-	-
	response (≥VGPR vs. ≤PR)	0.44 (0.18-1.08)	0.072	0.38 (0.17-0.87)	0.022

Supplementary Table S9: Time-dependent (TD) effect of occurrence of first any grade or G≥3 infectious episode on OS and PFS (multivariate Cox regression)

Outcome	Covariate 1	Covariate 2	Covariate 3	Covariate 4	Covariate 5
PFS	TD any grade: HR 1.44, 95%CI 1.02-2.04	CCI≥5 vs CCI≤4 HR 1.41, 95%CI 1.02-1,96	triplet vs doublet 1st line HR 0.71, 95% CI 0.52-0.99		
PFS	TD G≥3: HR 2.11, 95%CI 1.41-3.18	CCI≥5 vs CCI≤4 HR 1.42, 95%CI 1.02-1,97	triplet vs doublet 1st line HR 0.71, 95% CI 0.52-0.98		
OS	TD any grade: HR 1.4, 95%CI 0.94-2.09	CCI≥5 vs CCI≤4 HR 1.44, 95%CI 0.97-2.15	immunoparesis HR 2.66, 95%CI 1.41-5.03	smoking HR 2.15, 95%CI 1.35-3.43	diabetes HR 2.25, 95%CI 1.28-3.97
OS	TD G≥3: HR 1.84, 95%CI 1.2-2.82	CCI≥5 vs CCI≤4 HR 1.49, 95%CI 1-2.22	immunoparesis HR 2.75, 95%CI 1.46-5.18	smoking HR 2, 95%CI 1.25-3.21	diabetes HR 2.15, 95%CI 1.22-3.77

Supplementary Figure 1 (1S) title: Cumulative incidence curves of infections within 12 months from diagnosis:

Supplementary Figure 1 (1S) legend: A) Cumulative incidence of all grade infections: at 3 months 21.5% (95% CI 16.1-27.4%), at 6 months 26.5% (95% CI 20.6-32.8%) and at 12 months 33% (95% CI 26.6-39.6%). B) Cumulative incidence of ≥G3 infections: at 3 months 13% (95% CI 8.8-18.1%), at 6 months 16% (95% CI 11.3-21.4%), and at 12 months 22% (95% CI 16.5-28%)

Supplementary Figure 1 (1S)