Case Discussion
PMCID meeting

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Case Discussion

Dec'18

Mr T

61y Chinese Male
Biohazard waste plant operator
Married with 1 son
Smoker
No known drug allergies

PMHx

1. Hypertension
2. Hyperlipidaemia
3. Impaired fasting glucose
4. Diverticular disease
5. RUL mild bronchiectasis

Presented with 6-month history of non-vertiginous giddiness, lethargy, decreased effort tolerance. Hb 10 → 8

Workup

Dec'18

- Hb 8g/dL, Tw 5.7 x 10^9/L, Plt 204 x 10^9/L
- Prt 70g/L, Alb 55g/L, Cr 88umol/L

Jan'19

- Hb 7.5g/dL, Tw 7.1 x 10^9/L, Plt 210 x 10^9/L
- 24H UTP: 5.47g/day
- M-panel
  - Anti-lambda M-band
  - Lambda 2576mg/L, Kappa 1.8mg/L
  - FLC ratio: <0.01

BMA/T

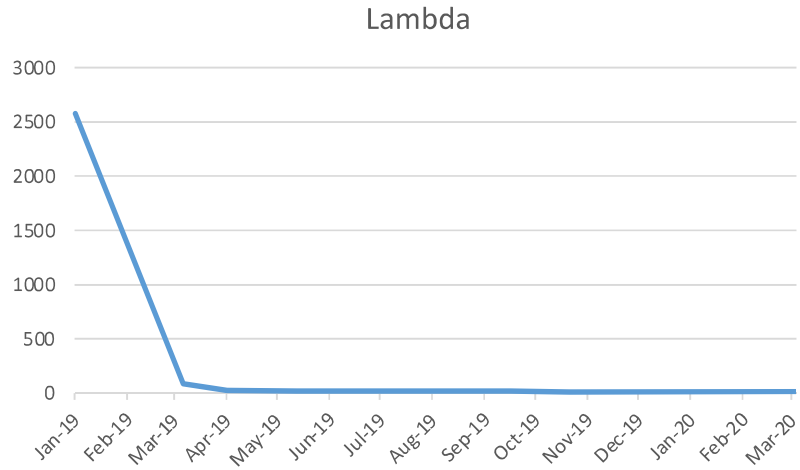
- Aspirate: 50% plasma cells
- Flow: 7.8% clonal plasma cells with light chain restriction
- Trephine: 60-70% plasma cells
- FISH: Trisomies 7,9,15,18,21; 1q21 amplification

Renal biopsy

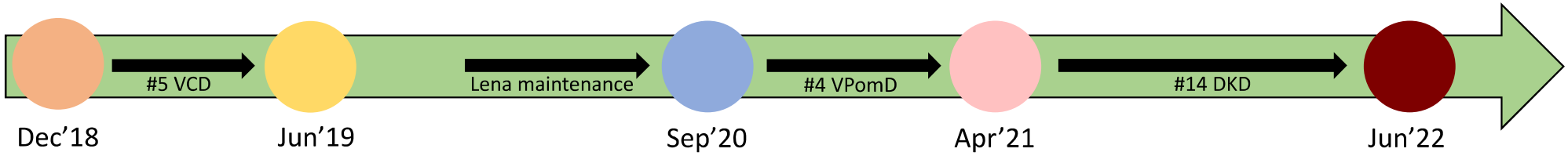
- FSGS (1+ to 2+ lambda light chain staining)

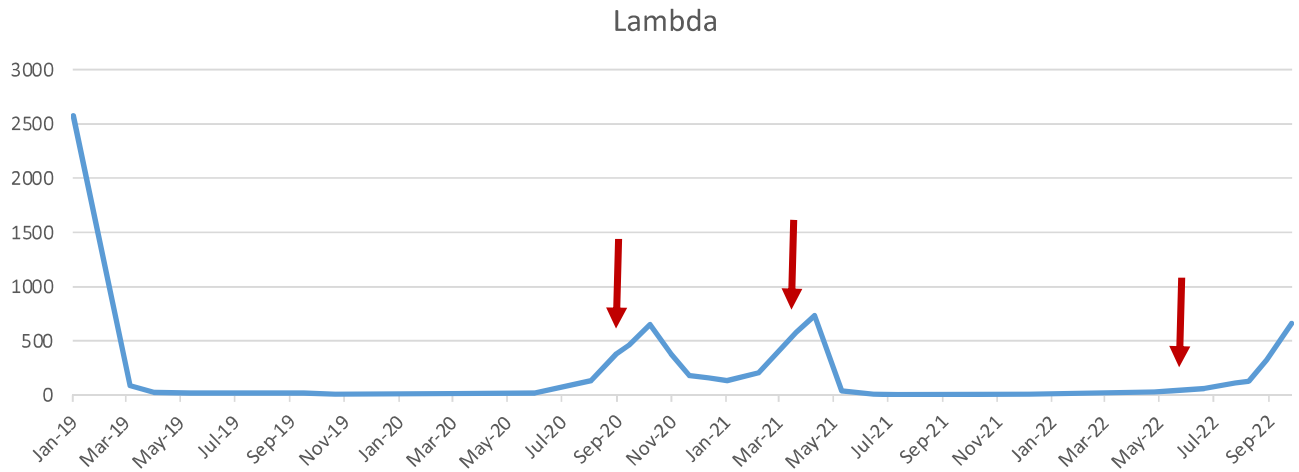
Case Discussion

- #5 VCD → CR
- Cyclophosphamide/vinorelbine mobilization
  - Harvested 11million/kg cells
- Underwent HDM(200)-AutoHSCT on 28/6/19
  - Post-transplant MRDneg
  - CMV viraemia post transplant (3,238 IU/ml) > treated with Valganciclovir
  - Len maintenance since Oct'19



Case Discussion

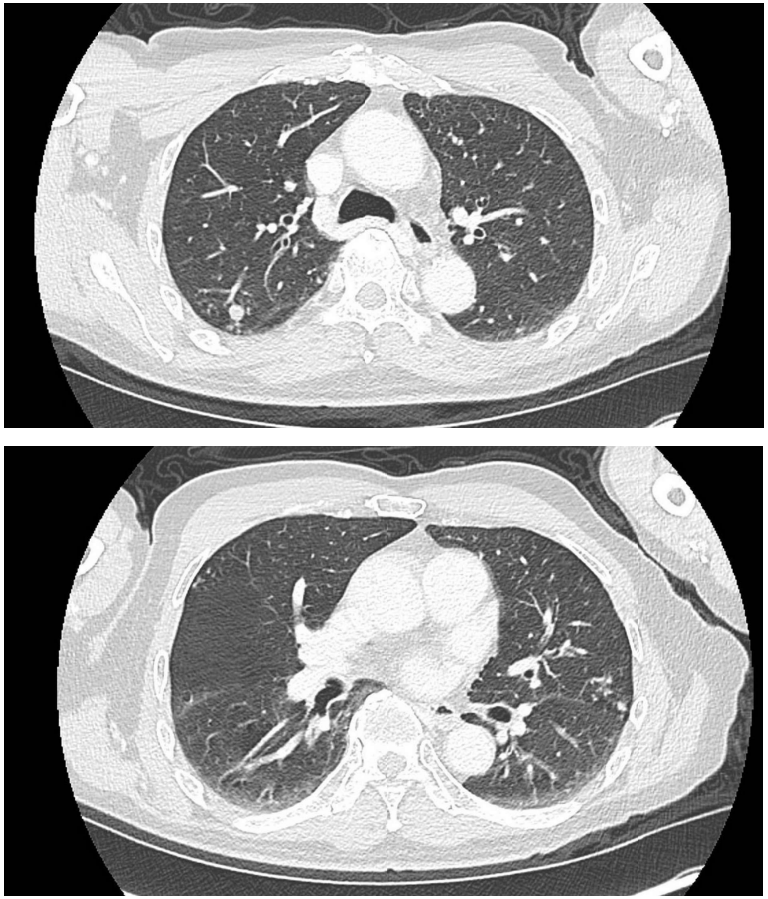




- Relapsed in Sep'20 while on Len maintenance
- #4 VPomD → PR then relapsed
- #14 DKD → relapsed in Jun'22 → considered for BCMA-directed CAR-T clinical trial

Pre-CAR-T workup/screening

Labs	Microbiology	
Hb 9.4 g/dL	HIV Screen	Negative
TW 7.07 x10^9/L	Hepatitis B	Negative (non-immune)
Plt 216x10^9/L	Hepatitis C	Negative
Cr 93 umol/L	CMV IgG	Positive
	EBV IgG	Positive
	Varicella IgG	Negative
	HTLV I/II IgG	Non-reactive



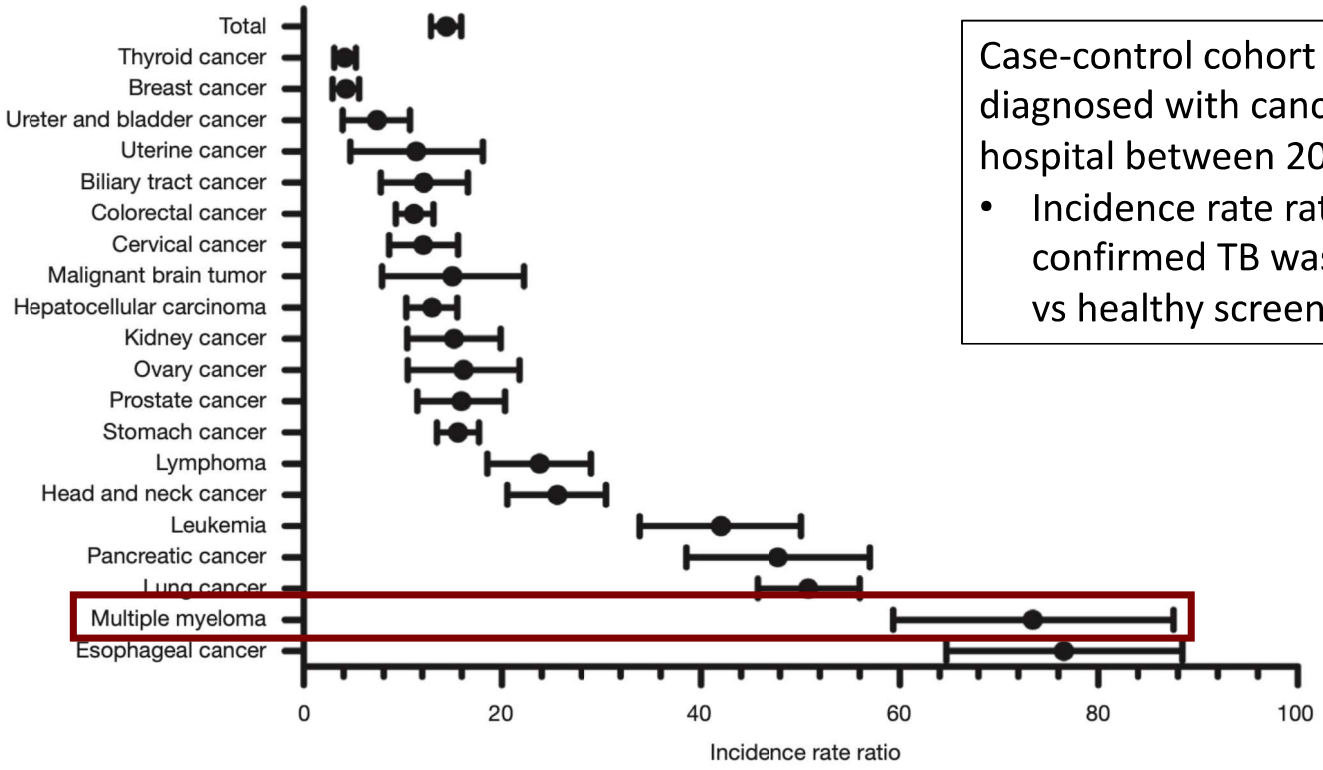
Bronchoscopy/BAL

Labs		BAL	
Serum Cryptococcal Ag	Negative	GS	Negative
Serum GM Ag	0.03	Bacterial c/s	Negative
		Respiratory virus PCR	**Rhinovirus, hMPV, Coronavirus OC43**
		COVID PCR	Negative
		Pneumonia multiplex PCR	Negative
		CMV virus	Negative
		HSV Ag	Not isolated
		Fungal c/s	***C. tropicalis***
		GM Ag	**0.62**
		AFB smear	Negative
		AFB c/s	**MTB, TB PCR positive**
		Cytology	Inflammatory yield, no malignant cells

TB in MM

Considerations in management

TB in MM – what's the risk?



Case-control cohort study of adults diagnosed with cancer at a Korea university hospital between 2000-2014

- Incidence rate ratio of bacteriologically-confirmed TB was **70.76** for MM patients vs healthy screening subjects

Cheon et al. J Thorac Dis. 2020 Sep;12(9):4950-4959.

TB in MM – what's the risk?

Table 2. Incidence of TB in patients with MM and the matched cohort.

	Patients with MM		Matched cohort					
	TB no.	Per 10,000 person-years	TB no.	Per 10,000 person-years	Crude HR (95% CI)	*p* Value	Adjusted HR[a] (95% CI)	*p* Value
Total	83	95.5	241	32.9	2.78 (2.16–3.59)	<.001	3.11 (2.41–4.02)	<.001
Age								
≥65	53	130.6	186	47.5	2.64 (1.93–3.61)	<.001	2.75 (2.01–3.76)	<.001
<65	30	64.7	55	16.1	4.03 (2.56–6.34)	<.001	4.14 (2.62–6.53)	<.001
Sex								
Male	57	114.4	196	46.2	2.40 (1.78–3.25)	<.001	2.70 (2.00–3.66)	<.001
Female	26	70.0	45	14.6	4.41 (2.69–7.23)	<.001	4.81 (2.92–7.93)	<.001
Type								
Pulmonary TB	76	87.4	218	29.8	2.82 (2.16–3.68)	<.001	3.14 (2.40–4.11)	<.001
Extrapulmonary TB	7	8.1	23	3.1	2.44 (1.03–5.75)	.042	2.74 (1.15–6.50)	.023

Table 4. Relationship between steroid dose and risk of TB in patients with MM.

	Univariate analysis		Multivariate analysis[a]	
Exposure	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Steroid daily dose[b]				
No use	reference		reference	
0–5 mg	1.71 (0.95–3.08)	.075	1.46 (0.80–2.66)	.221
5–10 mg	2.19 (1.08–4.48)	.031	2.00 (0.97–4.11)	.060
≥ 10 mg	3.07 (1.76–5.35)	<.001	3.23 (1.84–5.69)	<.001

- Those with MM had increased incidence of **extrapulmonary TB** than those without MM (adjusted HR 2.74)
- Presence of dose-response relationship between steroid dose and risk of TB
- MM patients with TB had nearly 2x mortality rate than those without TB

Tsai et al. Leuk Lymphoma. 2017 Nov;58(11):2598-2606.

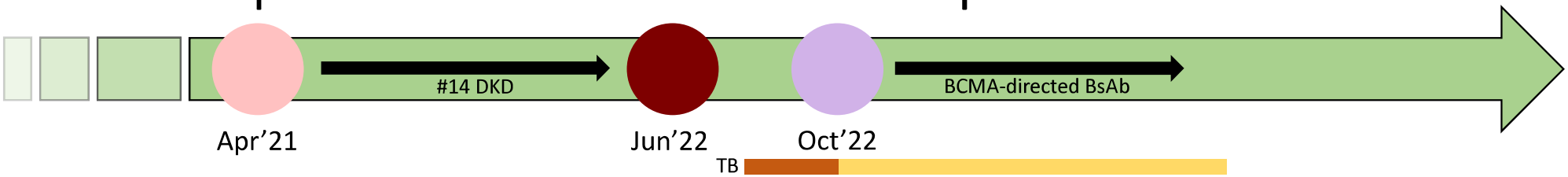
TB in MM – challenges

X	Velcade (Bortezomib) Rifampicin, Isoniazid, and Pyrazinamide (INT) (CYP3A4 Inducers (Strong))
D	DexAMETHasone (Systemic) Rifampicin, Isoniazid, and Pyrazinamide (INT) (CYP3A4 Inducers (Strong))
C	CycloPHOSphamide Rifampicin, Isoniazid, and Pyrazinamide (INT) (CYP2B6 Inducers (Moderate))

- Interruption in MM treatment because of drug-drug interactions
  - A single-centre Korean experience showed that interruption of bortezomib-containing regimen in TB patients led to significantly lower response rates to bortezomib-containing therapy, and significantly shorter overall survival vs non-TB MM patients
- In Mr T's situation, the diagnosis of TB precluded him from CAR-T therapy trial (which may have been life-saving)

Ahn et al. Blood Res. 2013 Mar;48(1):35-9.

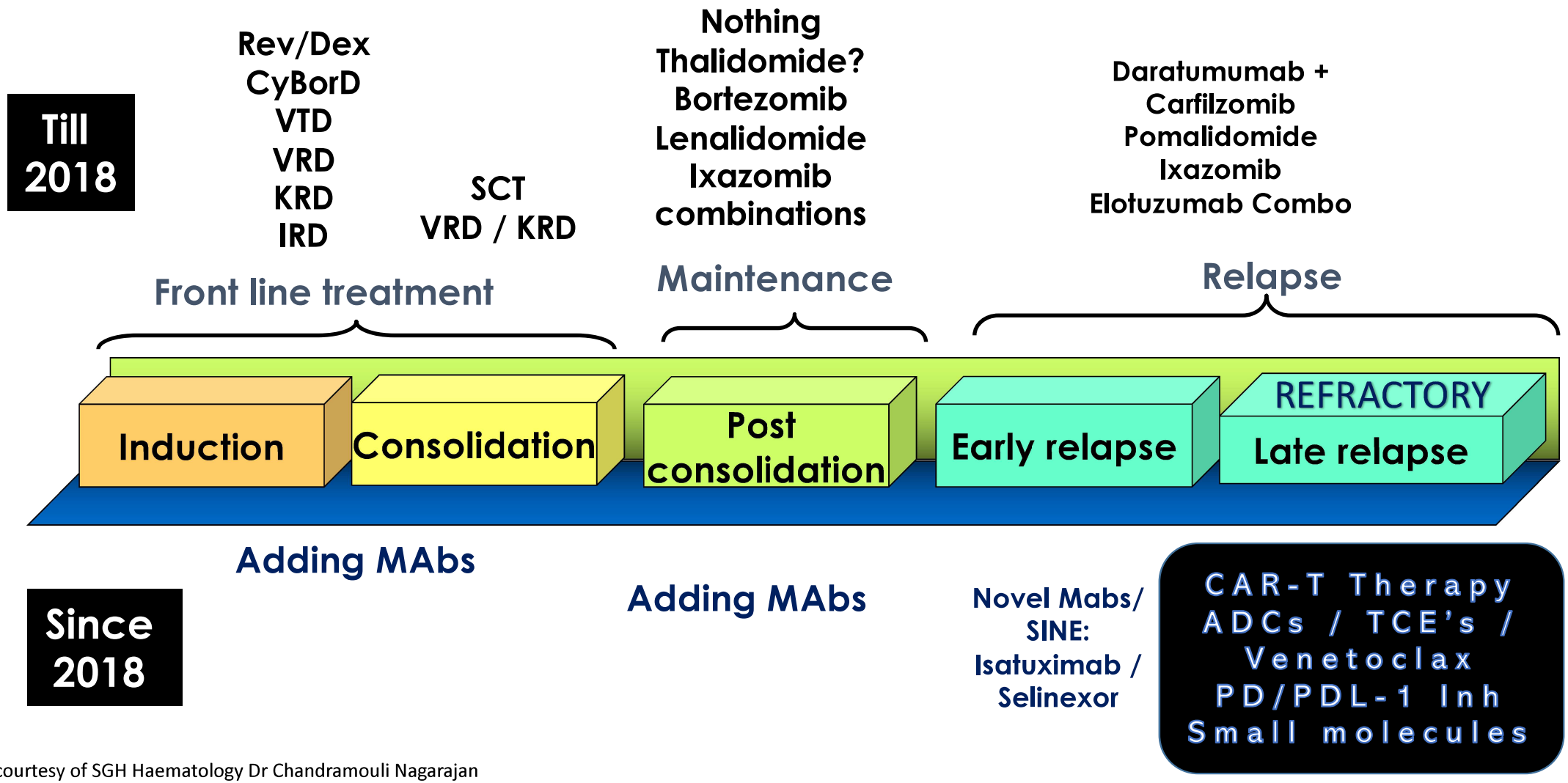
4th relapse and infective complications



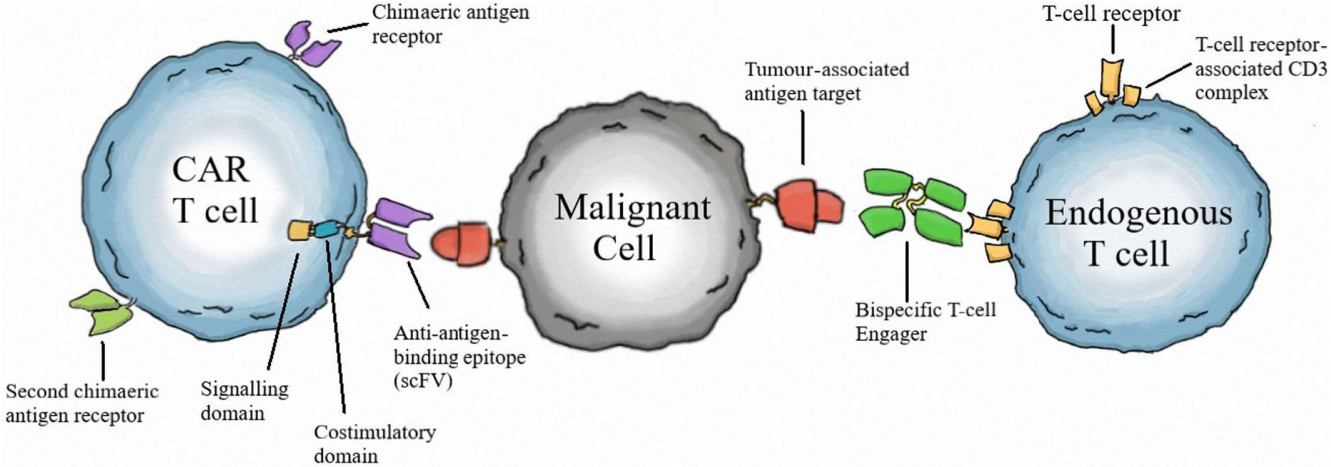
- Viral URTI expectantly managed.
- Not treated for fungal pneumonia. Did not fulfill criteria.
- **Treated for pTB**
  - RHEL 17/8/22 – 21/9/22
    - **Developed skin rash, N&V → TB meds stopped then re-challenged sequentially**
    - L → H → R (pan-sensitive TB)
  - Completed TB induction. Non-infectious. No clinically significant active infection
- **Proceeded with BCMA-directed BsAb 12/10/22**
- Ongoing TB treatment
  - Levo + INH + pyridoxine: 12/10/22 – 19/10/22
  - Levo + INH + pyridoxine + RIF: 20/10/22 onwards
  - **Gastric symptoms ++**

Treatment landscape in MM

Myeloma – changing treatment paradigm

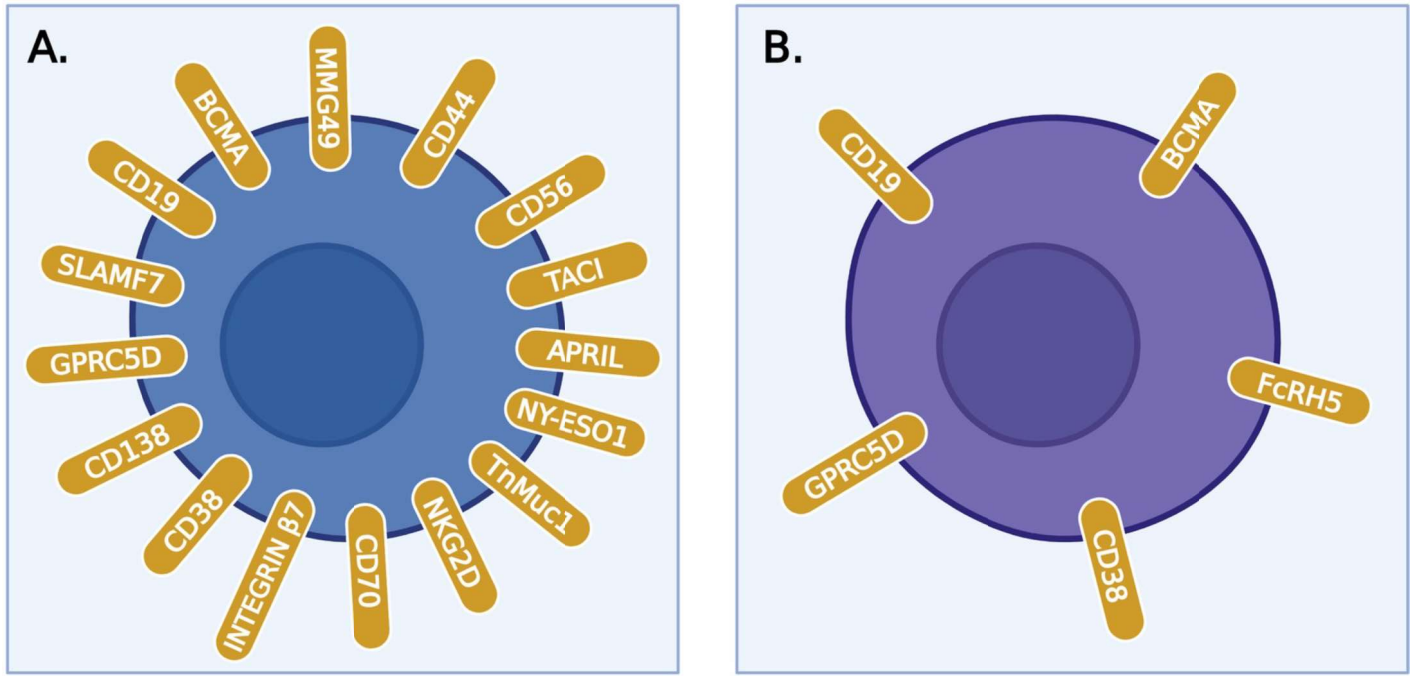


Slide courtesy of SGH Haematology Dr Chandramouli Nagarajan



	CAR-T	BiAb/BiTE
Structure	**Synthetic receptor** composed of a target antigen-binding domain (scFv), a hinge region, a transmembrane domain, and intracellular signaling domains.	BiAb: **Engineered artificial antibodies** to recognize two epitopes of an antigen or two antigens. BiTE: **Recombinant protein** composed of two linked scFvs, with one targeting CD3 and the other one targeting MM antigen
Effector cells	CD4 and CD8	CD4 and CD8
Availability	>2 weeks to manufacture 10% manufacturing failure	Off the shelf
Administration	Conditioning treatment Pre-treatment: anti-histamine, paracetamol One-time infusion.	No conditioning treatment Pre-treatment with steroids Repeat dosing
Response rate in RRMM	Generally higher	Generally lower, although may be similar to CAR-T therapy in patients treated with top doses or at recommended phase 2 doses.
Target antigen loss	Higher risk	Lower risk
CRS risk (≥G3)	Higher risk	Lower risk
Neurotoxicity risk (≥G3)	Higher risk	Lower risk

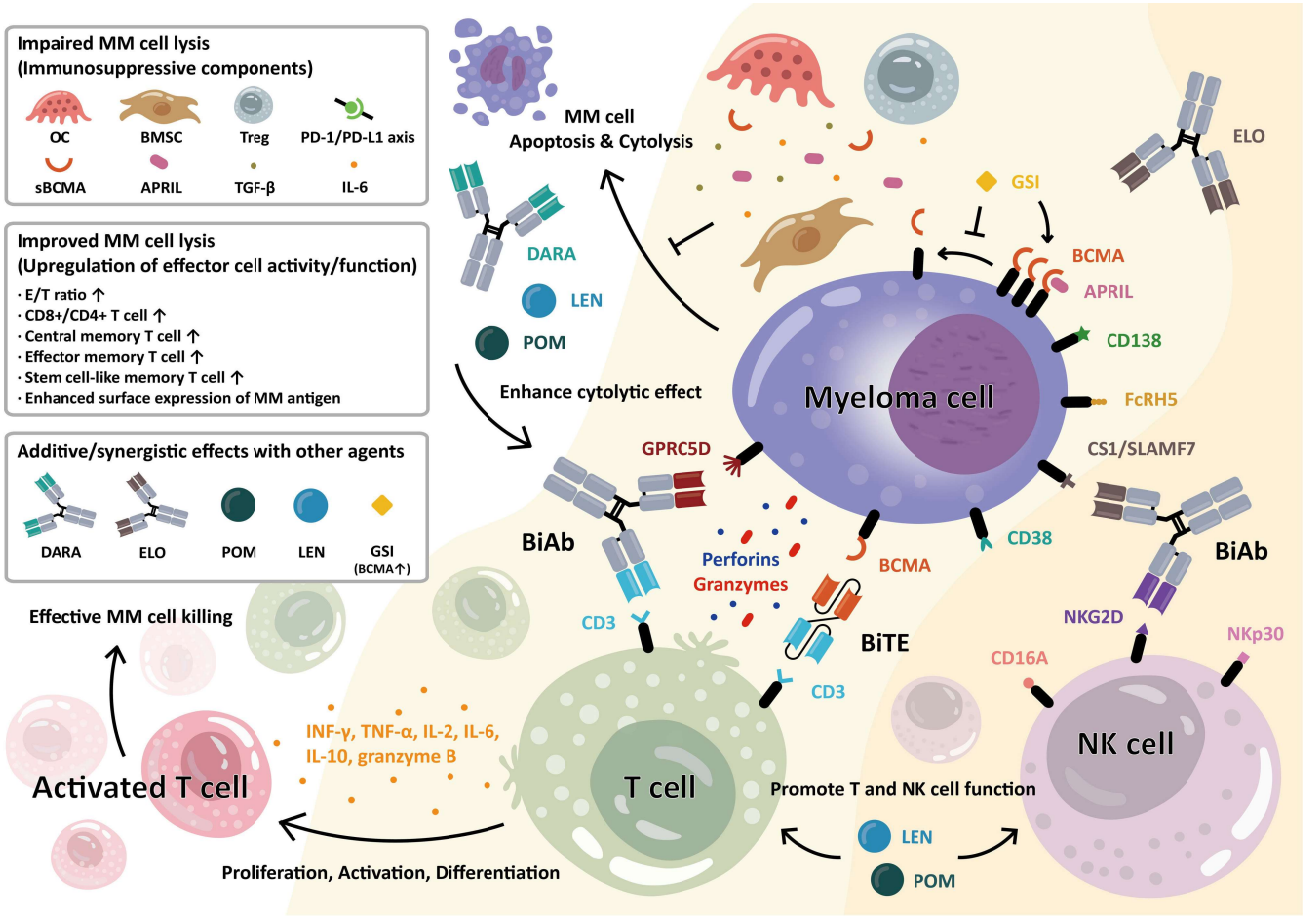
CAR-T vs BsAb/BiTE



Surface antigens found on MM cells, studied in clinical trials
A: CAR clinical trials; **B:** BsAb/BiTE clinical trials

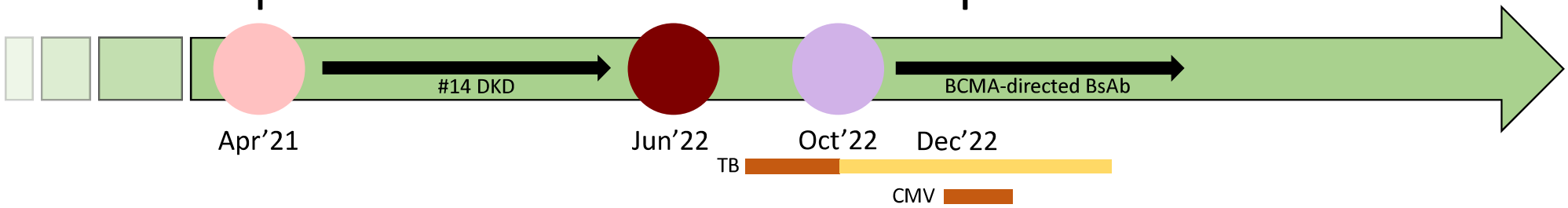
Kegyes et al. J Hematol Oncol 15, 78 (2022),

BsAb/BiTE therapy



Cho et al. Front Oncol. 2022 Oct 18;12:1032775.

4th relapse and infective complications

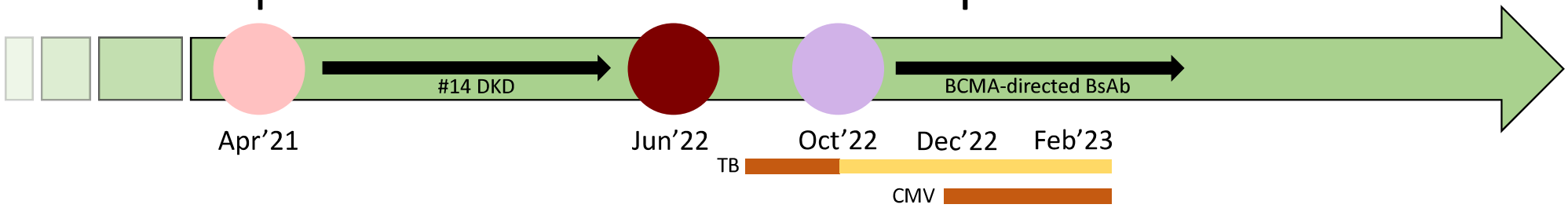


- TB
- Dec'22 – CMV DNAemia with gastritis
  - Screened for CMV in view of persistent N/V, despite completing
  - CMV PCR 15,500 IU/ml
  - OGD: Active chronic gastritis with CMV cells present. Non-specific duodenitis.

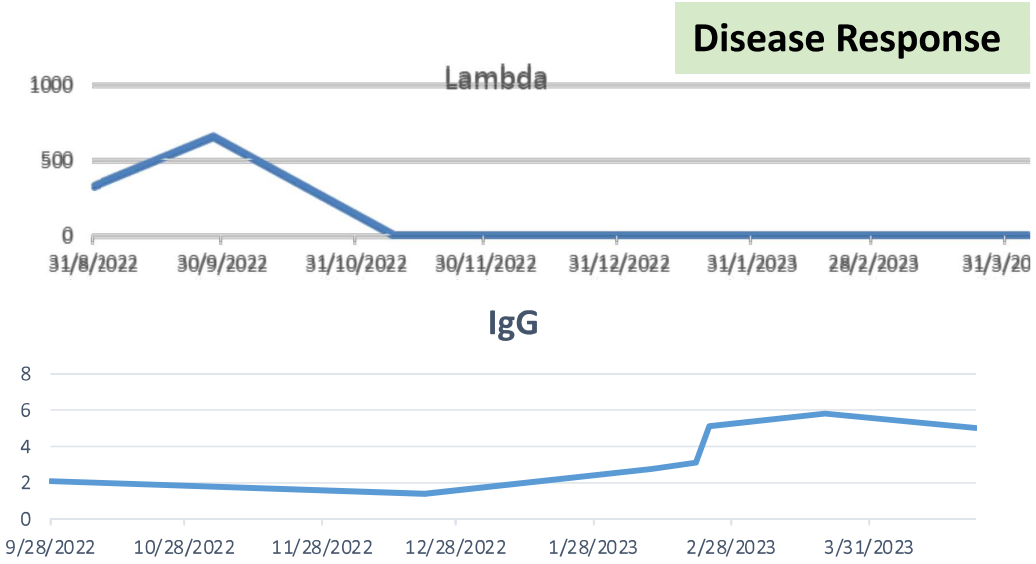
Completed 4/52 of anti-CMV therapy
- Ganciclovir had to be switched to Foscarnet at later stage of treatment in view of leukopenia

Date	CMV (IU/ml)	Labs
29/12/22	15, 500	Hb 11.2, WBC 2.45, Plt 98 Cr 64 µmol/L, LFTS WNL, Ig G 1.39 g/L
3/1/23	7, 150	Hb 12.6, WBC 3.51, Plt 112 Cr 67 µmol/L, LFTS WNL
9/1/23	1, 660	Hb 10.8, WBC 2.26, Plt 106 Cr 62 µmol/L, LFTS WNL
16/1/23	62	Hb 11.7, WBC 2.48, Plt 116 Cr 63 µmol/L, LFTS WNL
25/1/23	< 34.5	Hb 10.5, WBC 1.84, Plt 119 Cr 75 µmol/L, LFTS WNL

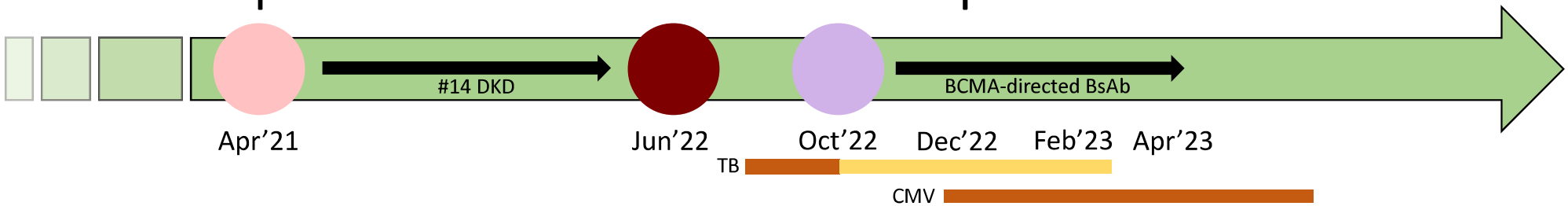
4th relapse and infective complications



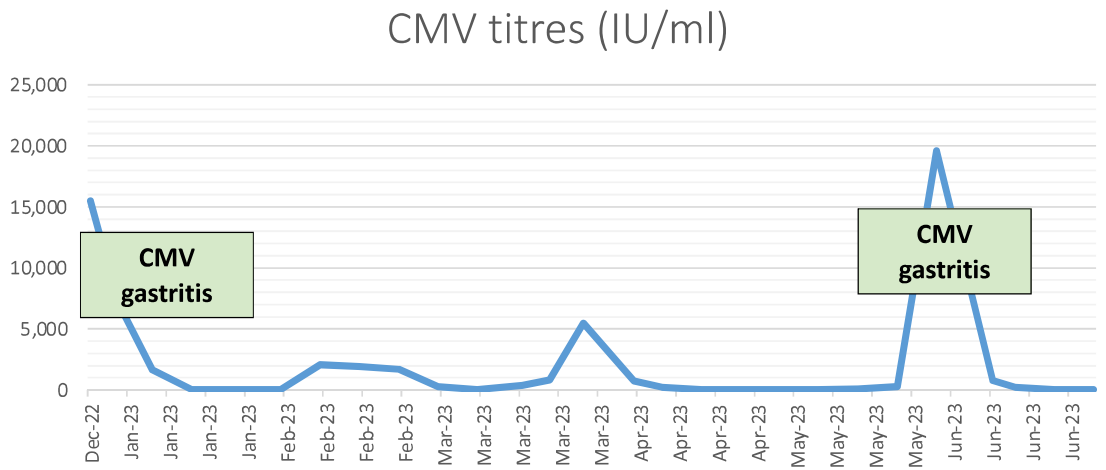
- TB
- Dec'22 – CMV DNAemia with gastritis
- Feb'23 – CMV DNAemia, Astrovirus GE, Rhinovirus URTI
  - Colonoscopy: mild patchy active ileitis, focal active colitis
- Apr'23 – Salmonella GE
- Aug'23 – Parainfluenza URTI



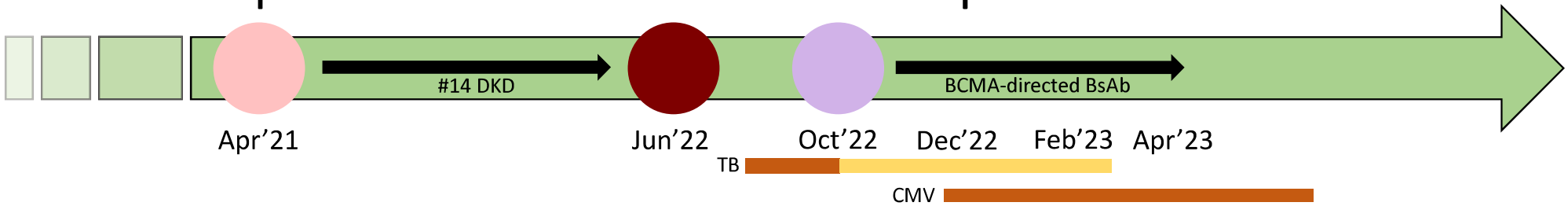
4th relapse and infective complications



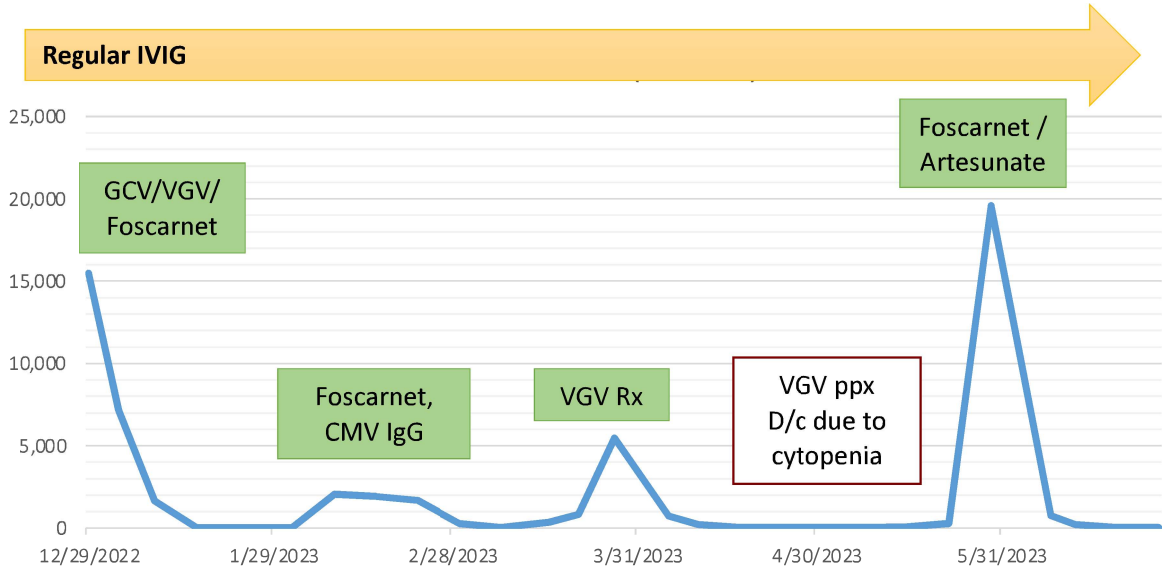
- Dec'22 – CMV DNAemia with gastritis
- Feb'23 – CMV DNAemia, Astrovirus GE, Rhinovirus URTI
- Mar'23 – CMV DNAemia
- Jun'23 – CMV DNAemia
  - Presented with intermittent epigastric pain and chronic diarrhea x few months
  - Scopes: Friable mucosa above Z line. CMV stains negative. No inclusion bodies
  - Treated as for CMV gut due to inflammation seen, chronicity of symptoms and high VL (18,500IU/ml)



4th relapse and infective complications



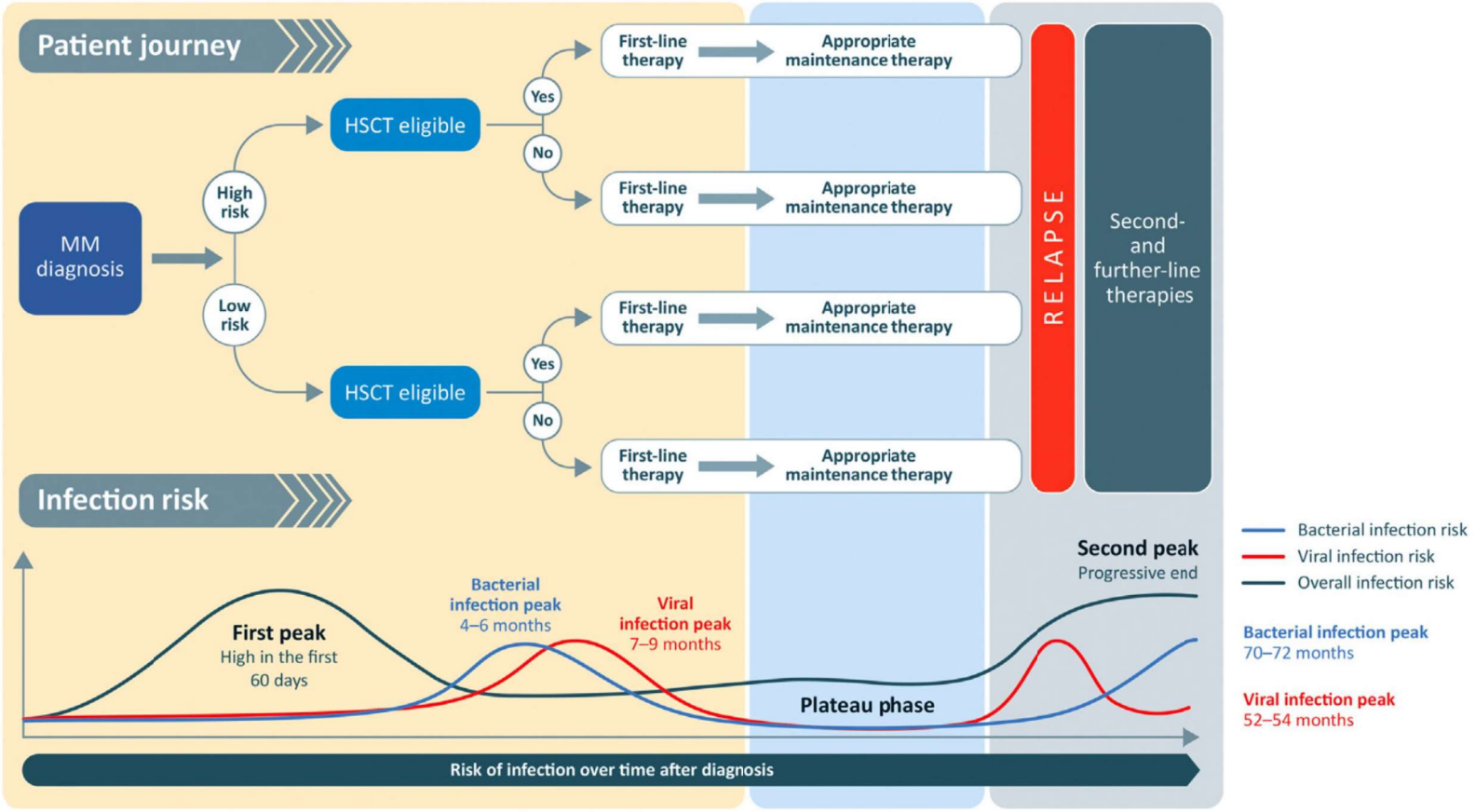
- Dec'22 – CMV DNAemia with gastritis
- Feb'23 – CMV DNAemia
- Mar'23 – CMV DNAemia
- Jun'23 – CMV DNAemia with presumptive CMV gastritis



Some questions we had…

- Which patients are the ones at highest risk?
- Are there strategies to prevent CMV reactivation in BsAb?
- If so, what are some strategies that may be implemented?
- For how long?
- If we can’t prevent reactivation in the first place, is there any role for secondary prophylaxis in patients on BsAb therapy?

Review of BsAb related infections



- Elevated risk of infections in MM: estimated 7-fold and 10-fold increase in bacterial and viral infections respectively[1]
- Immunoparesis found to occur in >90% of newly diagnosed MM cases, and 75% of plateau phase MM[2]
  - Patient factors (age, comorbidities, prior infections)
  - Disease-related (stage, disease status)
  - Treatment related factors (no. of prior treatment lines, BsAb/CAR-T therapies, severity of hypogammaglobulinemia)

1. Blimark et al. Haematologica. 2015 Jan;100(1):107-13.
2. Giralt et al. Clin Lymphoma Myeloma Leuk. 2023 Oct;23(10):719-732.

BsAb related infections

- BsAB/BiTE therapy with on-target off-tumour toxicities contribute to infection risks
  - Neutropenia
  - Elimination of normal (non-MM) plasma cells resulting in hypogammaglobulinemia
  - Persistence of B cell aplasia
  - Disruption of plasma cell survival and T cell exhaustion
- Treatment of CRS/ICANS can alter infection risks as well

Nooka et al. Cancer. 2023 Nov 14.

SYSTEMATIC REVIEW

blood advances

Infections following bispecific antibodies in myeloma: a systematic review and meta-analysis

Gemma Reynolds,[1,2,*] Edward R. Scheffer Cliff,[3,*] Ghulam Rehman Mohyuddin,[4] Rakesh Popat,[5] Shonali Midha,[6] Melissa Ng Liet Hing,[7] Simon J. Harrison,[7,8] Aaron S. Kesselheim,[3] and Benjamin W. Teh[1,8]

- 20 studies; 16 clinical trials (1666 patients)
  - 12 trials – bispecific or trispecific monotherapy (1477 patients)
  - 4 trials – combination therapy that included BsAb (189 patients)
- Median age 64.7 years old
- 78% had triple-class refractory disease. 38% had penta drug-refractory disease
- Median follow-up was 7.6 months

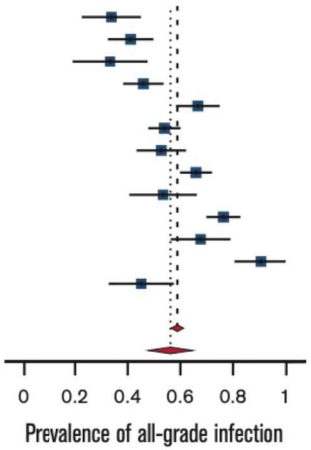
Reynolds et al. Blood Adv. 2023 Oct 10;7(19):5898-5903.

BsAb related infections

A

Study	Cases	Total	Proportion	95% C.I.
Wong et al., 2022	23	68	0.34	[0.23; 0.45]
D'Souza et al., 2022	51	124	0.41	[0.32; 0.50]
Topp et al., 2020	14	42	0.33	[0.19; 0.48]
Trudel et al., 2021	74	161	0.46	[0.38; 0.54]
Bahlis 2022	82	123	0.67	[0.58; 0.75]
Bumma et al., 2022	136	252	0.54	[0.48; 0.60]
Carlos–Stella et al., 2022	57	108	0.53	[0.43; 0.62]
Chari et al., 2022	153	232	0.66	[0.60; 0.72]
van de Donk et al., 2022	31	58	0.53	[0.41; 0.66]
Moreau et al., 2022	126	165	0.76	[0.70; 0.83]
Rodriguez–Otero et al., 2022	44	65	0.68	[0.56; 0.79]
Searle et al 2022	29	32	0.91	[0.81; 1.00]
Abdallah et al., 2022	28	62	0.45	[0.33; 0.58]
Common effect model			0.59	[0.56; 0.61]
Random effects model			0.56	[0.48; 0.65]

Heterogeneity: $I^2 = 92\%$, $\tau^2 = 0.0218$, $\chi^2_{12} = 144.55$ ($P < .01$)

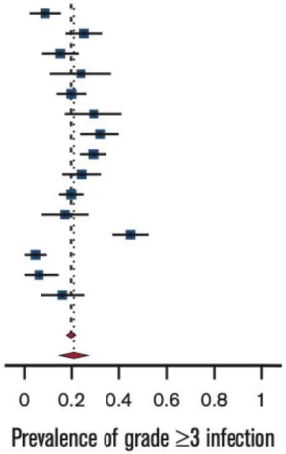


(A) Rates of all-grade infections among patients with multiple myeloma treated with bispecific antibodies in clinical trials.

B

Study	Cases	Total	Proportion	95% C.I.
Wong et al., 2022	6	68	0.09	[0.02; 0.16]
D'Souza et al., 2022	31	124	0.25	[0.17; 0.33]
Harrison et al., 2020	13	85	0.15	[0.08; 0.23]
Topp et al., 2020	10	42	0.24	[0.11; 0.37]
Trudel et al., 2021	32	161	0.20	[0.14; 0.26]
Raje 2022	16	55	0.29	[0.17; 0.41]
Bahlis 2022	39	123	0.32	[0.23; 0.40]
Bumma et al., 2022	73	252	0.29	[0.23; 0.35]
Carlos–Stella et al., 2022	26	108	0.24	[0.16; 0.32]
Chari et al., 2022	46	232	0.20	[0.15; 0.25]
van de Donk et al., 2022	10	58	0.17	[0.08; 0.27]
Moreau et al., 2022	74	165	0.45	[0.37; 0.52]
Rodriguez–Otero et al., 2022	3	65	0.05	[0.00; 0.10]
Searle et al 2022	2	32	0.06	[0.00; 0.15]
Abdallah et al., 2022	10	62	0.16	[0.07; 0.25]
Common effect model			0.20	[0.18; 0.22]
Random effects model			0.21	[0.15; 0.27]

Heterogeneity: $I^2 = 89\%$, $\tau^2 = 0.0107$, $\chi^2_{14} = 122.21$ ($P < .01$)



(B) Rates of Grade ≥3 infections among patients with multiple myeloma treated with bispecific antibodies in clinical trials.

BsAb related infections

- Trials generally did not provide sufficient granularity in terms of microbiological causes of infection-related deaths.
  - Most were abstracts, only 3 were full publications.
  - Steroids use ranged from 2-38% and Tocilizumab use ranged from 2-45%.
- Total 65 reported deaths attributed to infection (3%)
  - Viral infection-associated mortality was as common as bacterial sepsis-associated mortality
  - 12 deaths from COVID-19, 2 deaths due to adenovirus (hepatitis and pneumonia), 1 death from PML

BsAb related infections

- COVID-19 infections were the commonest
- Other common viral infections including adenovirus (fulminant hepatitis, pneumonitis) and CMV infections (1 case of CMV pneumonia)
- URTI, pneumonia (PsA, pneumococcal reported), and sinusitis were common sites of infection
- Small numbers of VZV (disseminated, HZO), PCP, rarely PML and invasive aspergillosis

BsAb related infections

- 4 observational studies (141 patients) provided greater details in terms of pathogens, infection onset and outcomes
- 293 infection events – 68% microbiologically confirmed
  - **Viral (49%), bacterial (45%) and fungal (6%)**
    - COVID-19, CMV reactivation (including oesophagitis), adenovirus
  - Gram negatives predominant cause of bacterial infections (64%) when reported
  - Respiratory infections were commonest (URTI, LRTI), followed by GI infections
- Median onset of all-grade infection typically earlier (49-79 days) than that of severe infection (≥3 months)

What we have gleaned from current data…

- Elevated risk of infections/higher grade infections
  - Heavily pre-treated prior to BsAb
  - Combination therapy (BsAb + daratumumab)
- Certain patterns of infections are emerging
  - **Viral infections** – sinopulmonary, COVID-19, adenovirus, CMV
  - Bacterial infections always a consideration
  - Handful of PCP and VZV, rarely PML
  - Fungal infections are uncommon

Pre-BsAb considerations

Pre-treatment screen

	US-based (CAR-T/BsAb) COMMIT 2023[1]	Europe and US-based (BsAb) Raje et al 2023[2]	Aus-based (MM) Teh et al 2023[3]
EBV	Yes	No PCR if clinical syndrome	-
CMV	Yes PCR if clinical syndrome	Yes, baseline serology PCR if clinical syndrome	Yes prior to planned HCT or treatment of RRMM
HBV	Yes	Yes	Yes
HCV	Yes	-	Yes
HIV	Yes	-	Yes
VZV	-	-	Yes prior to planned HCT
Others			Consider LTBI screen with IGRA Consider endemic tropical pathogens (eg. strongyloidiasis)

1. Mohan et al. Br J Haematol. 2023 Jun 7
2. Raje et al. Blood Cancer J. 2023 Aug 1;13(1):116
3. Teh et al. Intern Med J. 2023 Aug;53(8):1469-1477.

Prophylaxis

	US-based (CAR-T/BsAb) COMMIT 2023	Europe and US-based (BsAb) Raje et al 2023	Aus-based (MM) Teh et al 2023
IgG	Start at 2nd month of therapy and continue until end of therapy or serum IgG >4g/L (whichever is longer)	Replace if IgG<4g/L, ≥2 severe recurrent infections by encapsulated bacteria, regardless of IgG level, life-threatening illness, documented bacterial infection with no/insufficient response to ABx	Replace if IgG <4g/L, IgG<normal + ≥1 life-threatening in a 12-month period or recurrent severe infections requiring more than a standard course of ABx (≥2 in 6 months)
Neutropenia	Start LEV with onset of therapy and administer during the 1st month (when neutropenia is more commonly unpredictable)	Offer ppx if at risk for prolonged neutropenia, high risk of infections, recurrent bacterial infections	During Rx of RRMM – assess risk

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Prophylaxis

	US-based (CAR-T/BsAb) COMMIT 2023	Europe and US-based (BsAb) Raje et al 2023	Aus-based (MM) Teh et al 2023
HSV/VZV	Offer ppx	Offer ppx	Offer ppx in HCT
CMV	No ppx Routine monitoring not recommended	No ppx	-
HBV	Offer ppx if HBsAg+ or HBsAg-/HBc IgG+	Offer ppx if HBsAg+	Offer ppx if chronic HBV, or resolved HBV in HCT
Fungal	FLC when ANC <500 and continue until neutrophil recovery Consider anti-mould azole ppx high-risk patients	No ppx unless prior Hx of IFI, prolonged neutropenia, or Hx of prolonged steroids FLC recommended if for ppx	FLC during autoHCT Consider anti-mould if prolonged and severe neutropenia and other concurrent IFI risk factors
PCP	Offer ppx	Offer ppx	Offer ppx in HCT
Vaccinations	Influenza SARS-CoV-2 Pneumococcal	Influenza SARS-CoV-2 Pneumococcal VZV (if no Hx of Tx)	Influenza SARS-CoV-2 Pneumococcal Routine post-HCT vaccinations

1. Mohan et al. Br J Haematol. 2023 Jun 7
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CMV with BsAb in MM

CMV with BsAb in MM

- Incidence of CMV infection in MM patients vary widely in the literature
- Ranges from 0.7% to 20%[1-5] - **heterogenous**
  - Definitions may vary (antigenemia vs DNAemia)
  - Denominator – ALL MM patients vs MM patients who had a CMV PCR done
  - Thresholds for treatment
  - Date of publication
  - Non-HSCT vs autoHSCT vs alloHSCT

1. Han. J Clin Microbiol. 2007 Apr;45(4):1126-32.
2. Marchesi et al. Transpl Infect Dis. 2014 Dec;16(6):1032-8.
3. Hasegawa et al. Eur J Haematol. 2016 Jan;96(1):78-82.
4. Massoud et al. J Clin Virol. 2017 Oct;95:36-41.
5. Tay et al. Intern Med J. 2022 Oct;52(10):1759-1767.

CMV with BsAb in MM

- Limited data from current BsAb experience

RCTs	Retrospective cohorts
MagnestisMM-1 (Phase 1 Elranatanab): • 5.5% (3/55) CMV infections (1 was pneumonia)	Lancman (Mt Sinai cohort): • **22%** had CMV infections (37 patient in study; 2 cases of CMV oesophagitis)
MagnetisMM-3 (Phase 2 Elranatanb): • 5.7% (7/123) CMV infections	Mohan (Medical College of Wisconsin cohort): • 8 cases of viral infections in 36 BiTE patients (including rhinovirus, CMV DNAemia, norovirus, parvovirus B19 and SARS-CoV-2 but no detailed breakdown of numbers)
MajesTEC-1 (Phase 1/2 Teclistamab) • 1.2% (2/165) CMV infections	Sim (Peter Mac cohort): • 39 patients with 111 infective episodes. 4 of which were CMV.
MonumenTAL-1 (Talquetamab): • **No** CMV infections (0/165)	

1. Bahlis et al. Nat Med. 2023 Oct;29(10):2570-2576.
2. Lesokhin et al. Nat Med. 2023 Sep;29(9):2259-2267.
3. Nooka et al. Cancer. 2023 Nov 14.
4. Chari et al. N Engl J Med. 2022 Dec 15;387(24):2232-2244.
5. Lancman et al. Blood 2022; 140 (Supplement 1): 10073–10074.
6. Mohan et al. Blood Adv. 2022 Apr 26;6(8):2466-2470.
7. Sim et al. Blood Cancer J. 2023 Mar 10;13(1):34

CMV with BsAb in MM: questions

- Infectious diseases screening – variance in practice
- Is there a role for CMV PET vs primary prophylaxis, or should we only test when the right clinical syndrome arises?
- Thresholds for treatment remains undefined
- Role of secondary prophylaxis in recurrent CMV

CMV treatment

Adjuncts

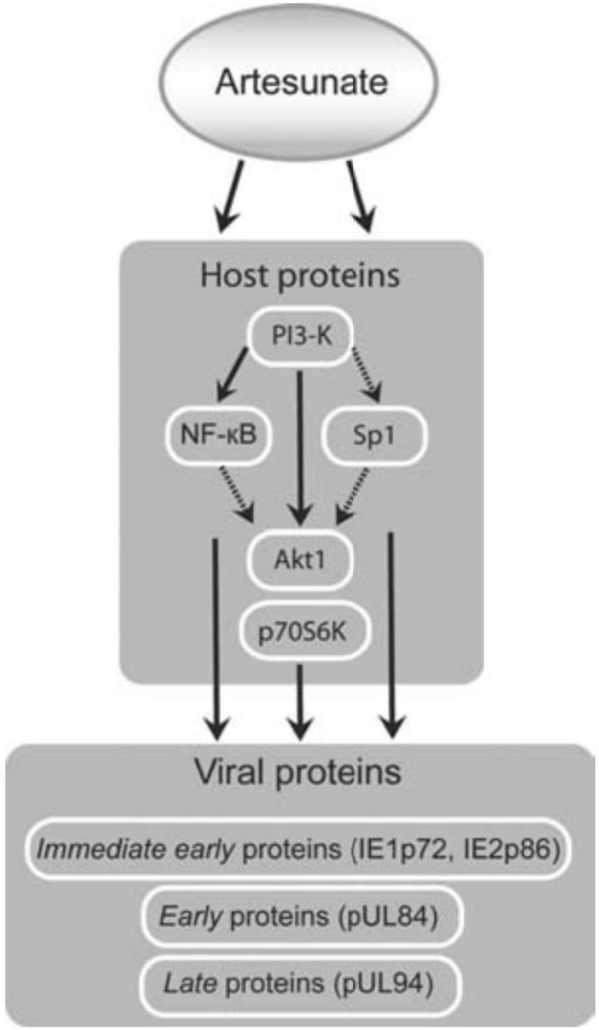
Artesunate

- First found as a natural product derived from a Chinese herb *Artemisia annua* that contained anti-malarial properties (artemisinin being the active compound)
- Generally well-tolerated
  - Mild and reversible haematological toxicities (neutropenia, haemolysis)
  - First degree AVB
  - Rarely neurotoxicity (ataxia, slurred speech, hearing loss)

Efferth et al. Clin Infect Dis. 2008 Sep 15;47(6):804-11.

Artesunate

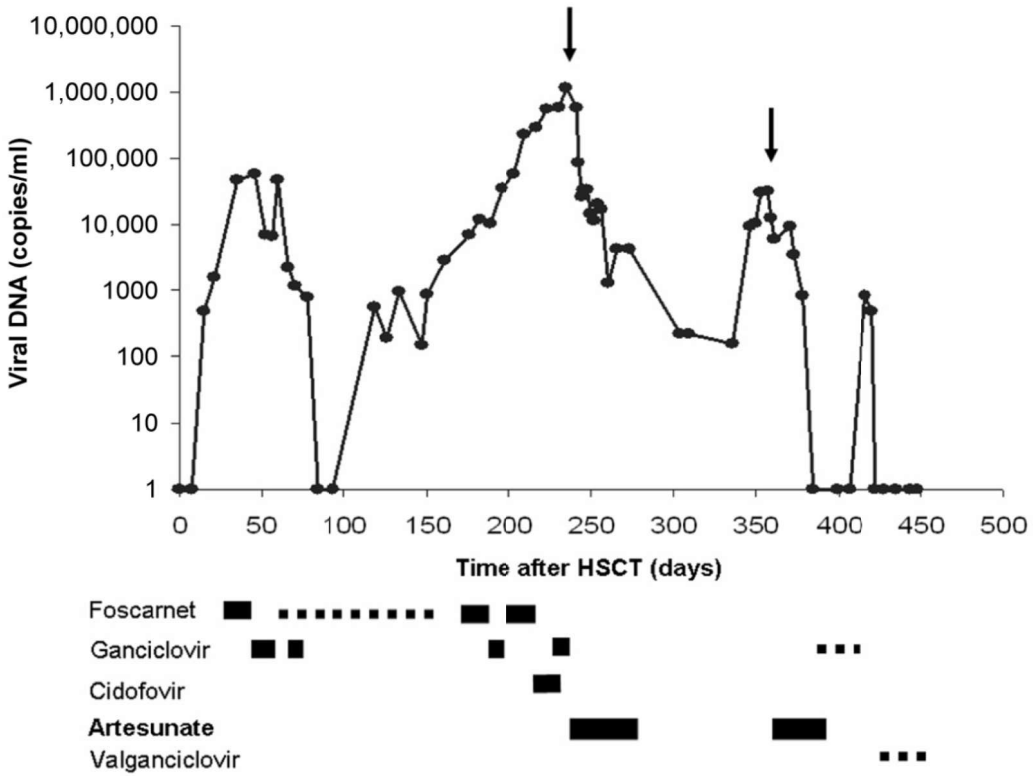
- Inhibits in vitro replication of human CMV (HCMV) – postulated to inhibit central regulatory processes of HCMV-infected cells
- Has activity against drug-resistant strains of HCMV as mechanism of action independent of DNA-polymerase



Efferth et al. Clin Infect Dis. 2008 Sep 15;47(6):804-11.

Artesunate in resistant CMV

- Shapira 2008 reported the first case of artesunate use in a 12y boy with X-linked adrenoleukodystrophy who had recurrent and resistant CMV infection post-haploHSCT despite FOS > GCV > CDV + IVIG.
- Germi 2014 reported 5 cases (2 HSCT, 3 SOTr) with resistant CMV infection



Shapira et al. Clin Infect Dis. 2008 May 1;46(9):1455-7.

Shapira et al. Clin Infect Dis. 2008 May 1;46(9):1455-7.
Germi et al. Antiviral Res. 2014 Jan;101:57-61.

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721.CLINICAL ALLOGENEIC TRANSPLANTATION: CONDITIONING REGIMENS, ENGRAFTMENT, AND ACUTE TRANSPLANT TOXICITIES | NOVEMBER 13, 2019

Efficacy of Artesunate for Treatment of Cytomegalovirus Reactivations in Allogeneic Haematopoietic Stem Cell Transplant Recipients Who Are Intolerant/Unsuitable for Ganciclovir Therapy

- Largest single-centre retrospective cohort study in an Indian hospital consisting of 117 alloHSCT patients
  - 78 episodes of CMV reactivation in 67 patients (58%)
- Artesunate used in 25 patients for 27/78 episodes (34%) of the total 78 episodes
  - Median duration of use 14 days

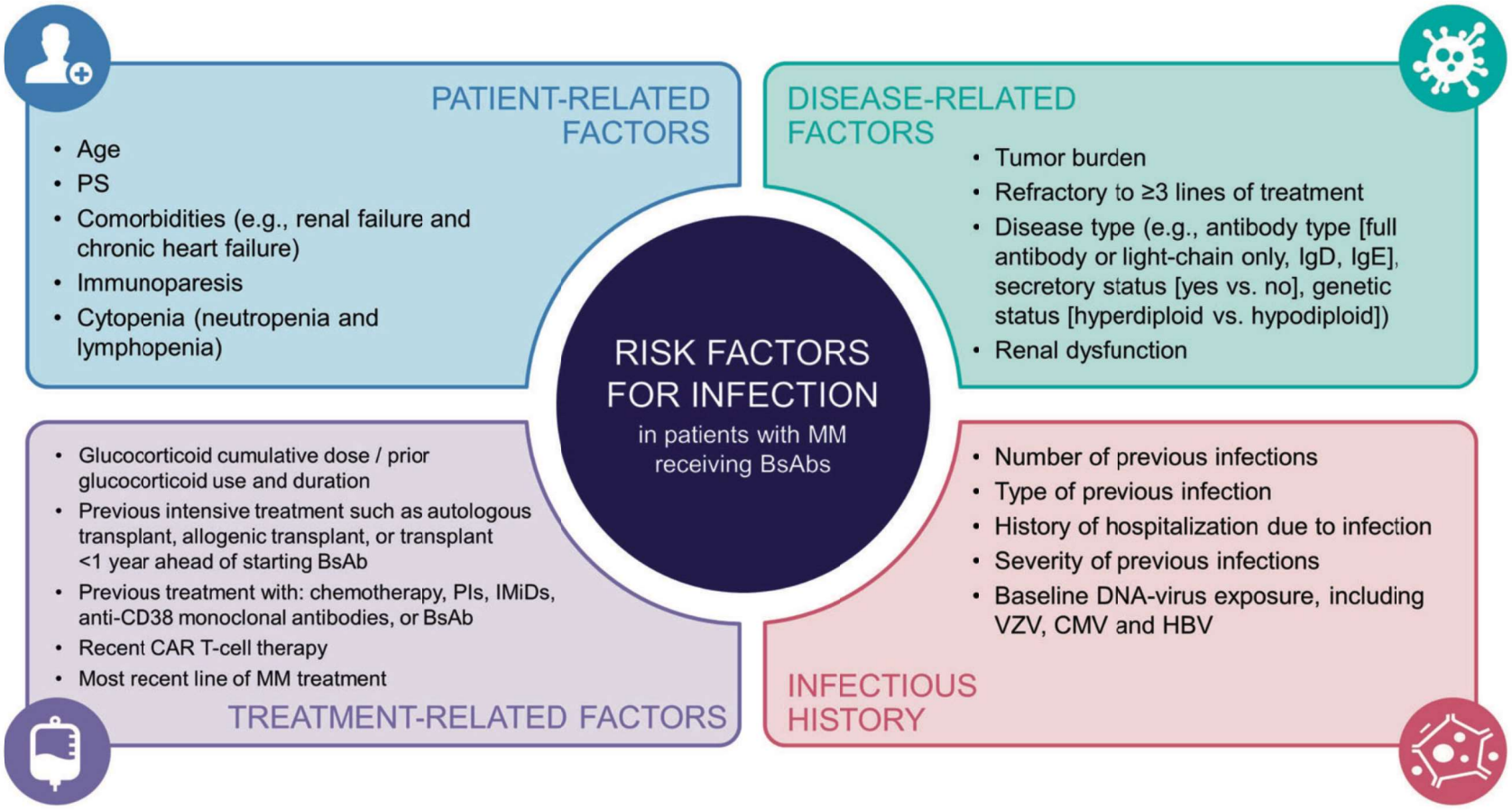
Gokarn et al. Bone Marrow Transplant. 2023 Feb;58(2):209-211.

Artesunate in GCV-intolerant alloHSCT

Artesunate usage in the cohort and its impact on CMV clearance			
Artesunate used In 27 of the total 78 episodes.	1st line (6 episodes)	Clearance in 2/6 episodes	33%
	2nd line (14 episodes)	Clearance in 2/14 episodes	14%
	3rd line (7 episodes)	Clearance in 1/7 episodes	14%
Artesunate clearance when used in 27 episodes	1st line (6 episodes)	Control of CMV* in 4/6 episodes	66%
	2nd line (14 episodes)	Control of CMV* in 10/14 episodes	71%
	3rd line (7 episodes)	Control of CMV* in 6/7 episodes	85%
Comparison of artesunate and ganciclovir when used as monotherapy in entire cohort of 78 episodes			
	Ganciclovir Monotherapy ($n = 28$)	Artesunate Monotherapy ($n = 4$)	
CMV cleared using monotherapy	14/28 (50% clearance rate with ganciclovir monotherapy)	2/4 (50% clearance rate with artesunate monotherapy)	

- **19% (5/27)** of CMV episodes cleared with artesunate
- **74% (20/27)** of CMV episodes were controlled with artesunate (no log increase in CMV copy numbers at 2 weeks and absence of progression to end organ CMV disease)
- Artesunate failure rate was 22% (6/27 episodes)

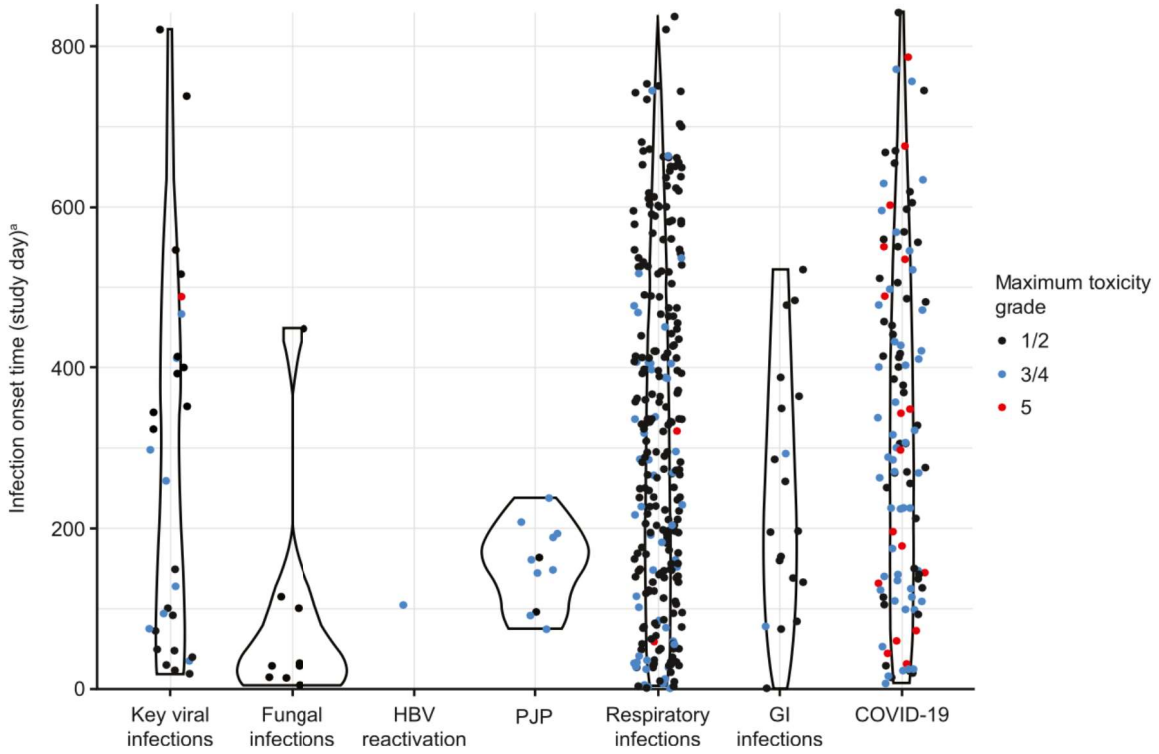
Gokarn et al. Bone Marrow Transplant. 2023 Feb;58(2):209-211.



Raje et al. Blood Cancer J. 2023 Aug 1;13(1):116

Incidence, timing, and management of infections in patients receiving teclistamab for the treatment of relapsed/ refractory multiple myeloma in the MajesTEC-1 study

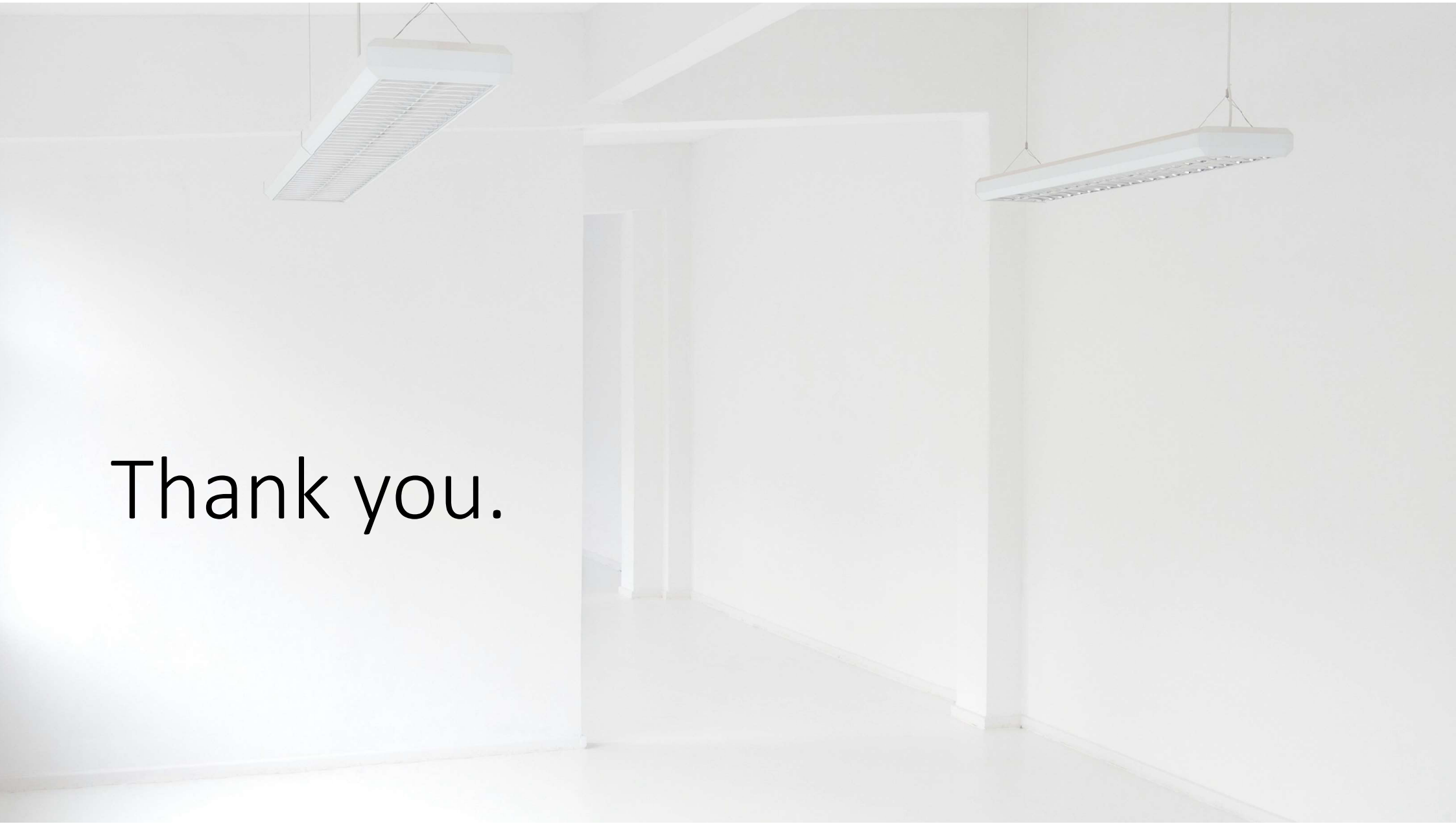
Ajay K. Nooka MD[1] | Cesar Rodriguez MD[2] | María Victoria Mateos MD, PhD[3] | Salomon Manier MD, PhD[4] | Katherine Chastain MD[5] | Arnob Banerjee MD, PhD[6] | Rachel Kobos MD[5] | Keqin Qi PhD[7] | Raluca Verona PhD[6] | Margaret Doyle MSc[8] | Thomas G. Martin MD[9] | Niels W. C. J. van de Donk MD, PhD[10]



Nooka et al. Cancer. 2023 Nov 14.

Take home points

- We have a fairly good idea of the patterns of infections at present. There will be increased clarity with ongoing follow-up and further trial data down the road
  - Perhaps we will have better means of risk stratifying some of the at-risk patients for certain infections
  - Implications – appropriate surveillance +/- prophylaxis programs based on risk-stratification
  - To consider host factors, antimicrobial prophylaxis use (and it's efficacy), CRS/ICANS treatment influence on infective risks
- A case of 'only time will tell'?
  - Then perhaps, time for another meta-analysis? 🙂


Thank you.