Comprehensive assessment of adverse event profiles associated with bispecific antibodies in multiple myeloma

by

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Abstract

Background: Multiple myeloma (MM) represents a hematological malignancy characterized by the uncontrolled proliferation of malignant plasma cells within the bone marrow. Ongoing research endeavors are focused on investigating the potential of Bispecific T Cell engagers (BiTEs) as a therapeutic approach for relapsed/refractory MM, demonstrating promising preliminary results.

Methods: We conducted a comprehensive review of the available biomedical literature, including abstracts and full publications, using PubMed, Scopus, and Nature databases until the beginning of 2023. BiTEs were classified into two groups: B-cell maturation antigen (BCMA) and non-BCMA targeting BiTEs, which included GPRC5D, and GPRC5D×BCMA. Our study included 23 different trials. Data about the frequencies of various adverse events (AEs) including hematological and non-BCMA hematological were collected. A pooled analysis based on Welch's t-test was then performed on all BiTEs to compare the safety profile of each agent from BCMA and non-BCMA. For clustering, we used t-distributed stochastic neighbor embedding (t-SNE).

Results: In this research, we looked at various studies involving a total of 1,899 patients with MM across twenty-three trials. Among them, 1,094 patients received treatment with BCMA inhibitors, while 677 patients were treated with non-BCMA inhibitors. Additionally, 65 patients were treated with a combination of Teclistamab and Talquetamab (Tec_Tal), and 63 patients received a combination of Talquetamab and Daratumumab (Tec_Dar). The median follow-up for all groups was 12.6 months. In terms of all-grade hematological AEs, neutropenia was observed in 43.87% of patients, anemia was observed in 43.96%, infections occurred in 44.05%, CRS was reported in 64.16%, and lymphopenia was observed in 40.33%. For grade 3/4 AEs, the percentages were as follows: neutropenia 40.03%, infections 18.18%, CRS 1.84%, anemia 28.48%, and lymphopenia 45.09%. Upon conducting a comprehensive pooled analysis, subtle disparities emerged between BCMA and non-BCMA BiTEs. More instances of CRS and CRS with Tocilizumab occurred with BCMA BiTEs vs non-BCMA BiTEs, $P<0.024$. Friedman's findings emphasized substantial distinctions between BCMA and non-BCMA agents for both overall and severe grade 3/4 AEs ($p<0.0001$). t-SNE was applied to examine the clustering patterns among agents across all grades and grade 3/4 AEs. The findings revealed that agents with all grades and grade 3/4 showed similar clustering patterns except for two agents.

Conclusion: The use of BiTEs in MM has demonstrated efficacy; however, these have been linked to a unique AE profile. Our results showed that non-BCMA were associated with less hematotoxicity (combined grade 3/4 AEs and hypogammaglobulinemia), whereas BCMA BiTEs were associated with less CRS rates. This is important information for treatment selection and mitigation strategy development aiming to optimize patient outcomes.

Keywords: BCMA, Pooled Analysis, Clustering

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abbreviation

These abbreviations will be utilized throughout the study:

BC: BCMA

NB: Non-BCMA (GPRC5D)

Talquetamab+Daratumumab**:** Tal_Dar

ND: Tal_Dar

B: BCMA×GPRC5D

G3/4: Grade 3/4

Agent names:

Teclistimab: Tec, TecU1(update 1), TecU2(update 2),

Elranatamab: Elr

F182112: F

REGN-5458 (linvoseltamab): REGN5458, R5458U1 (update 1),, R5458U2 (update 2),

AMG420: AMG4

AMG701 (pavurutamab): AMG7

CC-93269 (alnuctamab): Aln1(update 1), Aln2 (update 2)

ABBV-383 (TNB-383B): ABBV

Teclistamab + Talquetamab: Tec_Tal

Talquetamab: Tal405U1(update 1), Tal800U1 (update 1), Tal405U2 (update 2), Tal800U2 (update 2), TalqIV (IntravenousTalquetamab), Tal0.4 (0.4 mg/kg), Tal0.8 (0.8 mg/kg)

Cevostamab: Cevo

Adverse event: AE

Thrombocytopenia: TP

International Staging System class: ISS

High-risk cytogenetic abnormalities: HRCA

Anti-CD38 monoclonal antibody: MoAb

Immunomodulatory drugs: IMiDs

Proteasome inhibitor: PI

Prior BCMA-directed therapy: BDT

Extramedullary disease: EMD

Introduction

Multiple myeloma (MM) ranks as the second most prevalent hematological malignancy, and significant advancements in patient outcomes have been achieved with the introduction of novel therapeutic agents [1]. Over the past 25 years, the idea of using monoclonal antibodies (MAbs) to boost the immune system's ability to fight tumors and infectious diseases has sparked a surge of interest and creativity [2, 3, 4]. The antibodies have proven to be highly effective, and several monoclonal antibodies (MAbs) received approval from the FDA as therapeutic [5].

Bispecific T-cell engagers (BiTEs) (or Bispecific antibodies (BsAbs)) are increasingly establishing themselves as standard treatments for MM. The current research studies on BiTEs for the treatment of relapsed refractory MM demonstrated encouraging outcomes [6]. Improvements in treatment options, including the usage of immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies targeting CD38, and high-dose chemotherapy followed by autologous stem cell transplantation, significantly improved outcomes for patients with MM [7]. However, each treatment is associated with an adverse event (AE); similarly, BiTE, which is considered a potential treatment option, is associated with side effects. [8].

Several studies investigating alternative agents for MM treatment and analyzing the AEs associated with these agents have identified other significant factors related to treatment-induced AEs. Occasionally, treatments based on genetic factors can lead to AEs, as demonstrated in the study by Xu et al [9] delved into understanding the genetic basis of various combinations of AEs. This research revealed potential molecular mechanisms that explain the connections between drugs, genes, and AEs. The outcome contributed to the understanding of identifying the causes of AEs through genomics. Findings of the study [10] indicated a significant occurrence of peripheral neuropathy with the administration of bortezomib, lenalidomide, and dexamethasone (VRd) treatment, as well as with bortezomib treatment. Additionally, it is important to highlight various treatments for MM, as they are affected by gene expression [11]. Outcomes of another study [12] demonstrated that certain AEs could be influenced by both gender and geographical location. In addition, disparities in AEs observed in MM may result from a combination of factors, including genetics, treatment dosage and regimen, presence of other medical conditions, age, and gender. Results of the research [13] revealed that the utilization of distinct anti-MM drug regimens (AMDRs) in different regions significantly influenced the variations observed in toxicities.

Authors of the study [14] reported that individual agents, including Carfilzomib, Bortezomib, Daratumumab, Lenalidomide, Melphalan, Thalidomide, Ixazomib, Elotuzumab, Isatuximab, or Dexamethasone, exhibited a low toxicity profile. Moreover, distinct types of treatments, such as those for plasma cell dyscrasia, may increase the risk of developing severe COVID-19 (Coronavirus) infections [15]. Ongoing trials highlighted a different AE associated with BiTEs, including CRS, cytopenia, anemia, and infections [16]. Our study seeks to quantify and provide a comprehensive description of the reported AEs and toxicities associated with the use of bispecific BiTEs in the treatment of MM.

Methods

Data Curation

AEs: As defined by the FDA [4], the term AE refers to any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease caused using a medical treatment or procedure. In medical documentation and scientific analyses, AEs are unique representations of a specific event.

Database sources: To systematically organize various databases containing information on patients with relapsed refractory MM, we first extracted data from PubMed, Nature, the American Society of Clinical Oncology (ASCO), and the American Society of Hematology (ASH), focusing on BCMA and non-BCMA agents. We then ensured that this information was regularly updated from these sources. Additionally, we refined our dataset by concentrating on common AEs, gathering data from publicly available sources such as published articles and abstracts. Our analysis of BCMA agents included information from various sources such as: Teclistimab, derived from three separate papers [17, 18, 19], Elranatamab [20], F182112 [21], REGN-5458 [3, 22, 23], AMG420 [24], AMG720 [25], CC-93269 [26], and ABBV-383 [27]. For non-BCMA agents, our analysis encompassed studies involving Talquetamab [28, 29], results of Monumen TAL-1 for Talquetamab [30], and Cevostamab [31]. Additionally, data were obtained from studies combining two different types of medications such as Teclistamab + Talquetamab (BCMA×GPRC5D) [32], and Talquetamab + Daratumumab [33].

Imputations to address missing/nonreported events

Since the data originated from different populations for different agents, it was necessary to standardize them to ensure comparability on a uniform scale. This process involved normalizing each agent by its total population to scaling the values ranging within a similar interval, in this case between 0 and 1. To address this, after the normalization process, it was required to find an optimal approach for imputation. Various imputation methods, including filling with values such as minimum, half, maximum, 0, 1, or mean, or values drawn from mean ± standard deviation, or mean ± standard error of the mean, were examined. By employing box plots for visualization, we found the most reliable imputation strategy for our purpose. Ultimately, we determined that imputing with the minimum value for each AE (each row) yielded reasonable results.

Statistical Analysis

In this research, we employed a set of statistical tests, including both parametric and non-parametric approaches, to determine their comparative efficacy. The parametric tests included Welch's t-test provided by (Eq 3) below, while non-parametric tests comprised the Wilcoxon signed-rank test [34] and Friedman test [35].

Analysis of AEs safety through pooling of data

We conducted Welch's t-test to calculate p-values (α<0.05) for comparisons between different classes of AEs including hematological and non-hematological. For this purpose, a pooled analysis was conducted to obtain pooled mean (Eq1) and pooled variance (Eq 2) values, facilitating the calculation of standard deviation:

$$\overline{AE}^{l}_{p_i} = \frac{n_{i1}AE_{i1} + n_{i2}AE_{i2} + \cdots + n_{ij}AE_{ij} + \cdots + n_{ik}AE_{ik}}{n_{i1} + n_{i2} + \cdots + n_{ij} + \cdots + n_{ik}} \qquad (Eq1)\ Pooled\ mean$$

and

$$\boldsymbol{S^{2}}^{\boldsymbol{l}}_{\boldsymbol{p_j}} = \frac{\boldsymbol{(n_{1,j}-1)S^2_{1,j} + (n_{2,j}-1)S^2_{2,j} + \cdots + (n_{i,j}-1)S^2_{i,j} + \cdots + (n_{k,j}-1)S^2_{k,j}}}{\boldsymbol{n_{i1} + n_{i2} + \cdots + n_{ij} + \cdots + n_{ik}} \qquad (\boldsymbol{Eq2})\ \boldsymbol{Pooled\ variance}$$

where $n_{i,j}$ is the total number of agents involved with $AE_{j,i}$, for $i \in \{1,2,\ldots,k\}$ and each sepatate adverse event $j \in \{1,2,\ldots m\}$ and each BCMA or GPRC5D BiTes $l \in \{1,2\}$. Welch's t-test is a suitable method for handling data with different sample sizes [36]. The result of (Eq2) was applied in the computation of Welch's t-test. Welch's t-test was conducted on hematological AEs for all

$$\boldsymbol{t = \frac{\overline{AE}^{1}_{p_j} + \overline{AE}^{2}_{p_j}}{\sqrt{\frac{\left(S^{2}{}^{1}_{p_j}\right)^2}{n^1_j} + \frac{\left(S^{2}{}^{2}_{p_j}\right)^2}{n^2_j}}}} \qquad (\boldsymbol{Eq3})\ \boldsymbol{Welch's\ t-\ test}$$

grades within BCMA agents and GPRC5D agents. This involved performing Welch's t-test with pooled mean and pooled standard deviation. The same procedure was repeated for non-

hematological AEs for all grades within BCMA agents and GPRC5D agents. The process was replicated to compute Welch's t-test for grade 3 or higher AEs.

where $n_j^l = \boldsymbol{n_{i1}} + \boldsymbol{n_{i2}} + \cdots + \boldsymbol{n_{ij}} + \cdots + \boldsymbol{n_{ik}}$. To identify differences between BCMA and GPRC5D agents within each group, as well as between BCMA and GPRC5D agents overall, we utilized the Wilcoxon test. We implemented the Bonferroni p-value adjustment to correct for multiple comparisons. Furthermore, we performed the Wilcoxon test separately for the entire set of BCMA agents and GPRC5D agents, considering all grade AEs or grade 3/4 AEs. Afterward, we utilized the Friedman test for between-group comparisons of the agents. Initially, we applied for this test individually to BCMA agents and GPRC5D agents. Then, we combined the groups of BCMA and GPRC5D agents to perform the Friedman test. This analysis was conducted for both all-grade AEs and grade 3/4 AEs. The Friedman test, performed in R (version 4.3.2), yielded p-values (<0.05) for these comparisons, suggesting statistical significance.

Clustering

t-Distributed Stochastic Neighbor Embedding

Our dataset consisted of over forty dimensions, which made it challenging to analyze and identify common data characteristics. To address this complexity, we applied t-SNE as a non-linear dimension reduction and clustering technique to represent our data in two dimensions, facilitating easier visualization and analysis. In this process, we used t-SNE on our dataset after normalization and filling out missing values. The t-SNE strength lies in effectively projecting high-dimensional data onto lower-dimensional spaces while preserving crucial underlying structures [37]. The initial phase of the algorithm depends on transforming high-dimensional distances such as Euclidean distances between data points into conditional probabilities. This translation of data, accomplished through applying Stochastic Neighbor Embedding (SNE), is the foundation for accurately representing pairwise similarities within the lower-dimensional representation. Let A be a matrix of size $k \times m = 48 \times 23$ (AEs×agents) represented $A(a_1, a_2, \dots, a_m)$, where $a_j = \left(AE_{1j}, AE_{2j}, \dots, AE_{kj}\right)^T$. The conditional probability $P_{a_j|a_i}$ denotes the similarity between agent a_i and agent a_j based on their AEs, $(AE_{1i}, AE_{2i}, \dots, AE_{ki})^T$ and $\left(AE_{1j}, AE_{2j}, \dots, AE_{kj}\right)^T$, defined as follow [38]:

$$p_{a_j|a_i} = \frac{exp\left(\frac{-\|a_i - a_j\|^2}{2\sigma_i^2}\right)}{\sum_{k \neq i} exp\left(\frac{-\|a_i - a_k\|^2}{2\sigma_i^2}\right)} \qquad (Eq4) Conditional\ probability.$$

Subsequently, the probabilities in the original space are defined by the following equation:

$$p_{a_i,a_j} = \frac{\left(p_{a_i|a_j} + p_{a_j|a_i}\right)}{2m} \qquad (Eq5)\ Combined\ probability\ for\ t-SNE\ Eq.$$

This approach independently calculates the variance σ_i, which represents the effective number of neighbors, based on the pairwise distances between points. The variance is determined by the perplexity parameter with different values for all grade AEs and grade 3/4 AEs. To address concerns associated with overcrowding, t-SNE utilizes the student t-distribution with a single degree of freedom. Utilizing this distribution, the probability in the lower dimension, q_{a_i,a_j}, expressed in the following equation [38]:

$$q_{a_i,a_j} = \frac{\left(1 + \| \hat{a}_i - \hat{a}_j \|^2\right)^{-1}}{\sum_{a \neq b}\left(1 + \| \hat{a}_a - \hat{a}_b \|^2\right)^{-1}} \qquad (Eq6)\ t-SNE\ with\ t-Student.$$

where $\hat{a}_i$ denotes the estimator of a_i in lower dimensions, such as 2D or 3D. The positions of the points a a_i on the map are determined by minimizing the non-linear symmetric Kullback–Leibler divergence between the distributions P and Q. This is expressed in the following equation (Eq 6). Gradient descent is employed to minimize the Kullback–Leibler divergence concerning the points. This optimization process yields a map that effectively captures the similarities present in the high-

$$KL(P \parallel Q) = \sum_i \sum_j p_{a_i a_j} log \frac{P_{a_i a_j}}{q_{a_i a_j}} \qquad (Eq7)\ Kullback-Leibler$$

dimensional inputs [39, 40]

Clustering process

The t-SNE was applied to our dataset once to all grade AEs and once to grade 3/4 AEs. For AEs of all grades and grade 3/4, the t-SNE parameters were set as follows: the number of components = 2, perplexity = 2, random state = 12, and early exaggeration = 4.50451501 and city block similarity metric. We calculate the initial y_i with PCA to calculate $q_{a_i a_j}$ and then update its value with gradient descent over the Kullback-Leibler equation in both configurations. Our clustering

analysis compared AEs attributed to BCMA agents and non-BCMA agents. Clustering was performed by comparing AEs caused by BCMA agents and non-BCMA agents.

Results

Patients Characteristics

In this study, 1899 patients with MM were involved in twenty-three trials. A total of 1094 patients were treated with BCMA anti-agents including Tec, TecU1, TecU2, Elr, F, REGN5458, R5458U1, R5458U2, AMG420, AMG701 Aln1, Aln2, and ABBV compared to 677 patients treated with non-BCMA anti-agents including Tal405U1, Tal800U1, Tal405U2, Tal800U2, TalqIV, Tal0.4, Tal0.8 and Cevo. Additionally, 63 patients received BCMA× GPRC5D anti-agents Teclistamab and non-BCMA anti-agent Talquetamab, while 65 patients received GPRC5D anti-agent Talquetamab and Daratumumab. The following information refers to the total percentage of patients in all groups (BCMA, GPRC5D, BCMA×GPRC5D, Tal_Dar). The median age was 65 years (The average median age for each group: BCMA: 65.30, GPRC5D: 63.58, BCMA×GPRC5D: 67, Tal_Dar: 63), within which, 53.75% male (BCMA: 52.04%, GPRC5D: 56.04 %), 46.25% female (BCMA: 47.96 %, GPRC5D: 43.96%), 77.01% White (BCMA: 72.93%, GPRC5D: 81.09%), 12.05% Black or African American (BCMA: 12.06%, GPRC5D: 12.05%), 4.07% Asian (BCMA: 5.21%, GPRC5D: 2.93%), 4.01% other races (BCMA: 4.24%, GPRC5D: 3.93%), 12.59% not reported (BCMA: 12.59%), and 4.03% Hispanic (BCMA: 4.03%), and 95.97% not Hispanic or Latino (BCMA: 95.97%) (Table 1).

Table 1. Characteristics baseline for MM patients reported in 23 different studies including phase of studies and prior specific treatments with time of diagnosis for each patient.

	Tec	Tec U1	TecU 2	Elr	F	R5458 U2	R545 8U1	R54 58	AM G4	AM G7	Al n1	Al n2	AB BV	Tec_ Tal	Tal40 5U1	Tal80 0U1	Tal40 5U2	Tal80 0U2	Talq IV	Tal0. 4	Tal0. 8	Ce vo	Tal_ Dar
Target	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	B	NB	NB	NB	NB	NB	NB	NB	NB	ND
N	165	22	15	123	16	68	167	179	42	75	19	47	124	63	30	23	30	44	102	143	145	160	65
Age (Median)	64	70	66	68	64	64	64	66	65	63	64	63	68	67	61.5	60	62	64	65			64	63
Male	96	13		68	5		82		27			31	68		19	11	19	21	57			93	
Female	69	9		55	11		85		15			39	56		11	12	11	23	45			67	
White	134			72									98				25	35	82				
Black or African American	21			9									20				4	4	14				
Asian	3			16									1				0	3	2				
Other	7																1	2	4				
Not reported				26									5										
Hispanic													5										
Not Hispanicor Latino													119										
Median follow-up (Month)	14.1	3.1	1.3	14.7	3.1	2.4		3.6		1.7	3.65	2.6	10.8	14.4	7.5	3.7	11.7	4.2	4	14.9	8.6	6.1	11.5
Median time since diagnosis (Year)	6		7						5.2	5.9	6.2		7				5.6	6.4	6.6				
PLOT (range)	5	6	7	5	9	5	6	5	5	6	6	4	5	5			6	5	6	5	6	6	5
ECOG																							
0	55			45					24				40										
≥1	110			78					18				82										
ISS																							
I	87			28		10							19				12	16	34				
II	58			68		41							23				14	18	44				
III	20	5		19		16	31	81					38				4	9	24				
HCB	42	9	13	31			23	21	33				22	21			3	10	16				12
del(17p)	26																1	8	8				
t(4:14)	23																2	4	8				
t(14;16)	16																0	0	1				
EMD	28	14	10	39					0	20				27								34	
Previous therapy exposure																							
Triple-class	165	22		123								67	123		30	22	30	43	101				
Penta-drug	116	17		87								42	113	40	24	16	24	30	79				41
Refractoriness Status																							
Triplerefractory	128	20	24	119		9	150	145		51		43	102	49	23	15	23	33	87	106	100	136	38
Pentarefractory	50	13	19	52		35						15	44		6	5	6	9	36	41	33		
MoAb	148	22											120				30	39	97				50
IMiDs	152	21							20		16						28	42	98				
PI	142	21							16		17						25	36	92				
Refractory to last line of therapy	148			118	12	44			1		19	69	108				26	39	91				
BDT		16	10		9										9	4				21	16		35

Efficacy

Median follow-up for all groups was 12.6 months (BCMA: 13.2, GPRC5D: 11.36, BCMA × GPRC5D: 14.4, Tal_Dar: 11.5). The median time since diagnosis for all groups was 6.21 years. The number of previous lines of therapy (PLOT) for both groups of patients who received BCMA and GPRC5D was 5.6 (Table 1).

Those MM treatment response categories were developed by the International Myeloma Working Group (IMWG). Overall response rate (ORR) is defined as the proportion of patients responding to therapy with a complete response (CR) stringent complete response (sCR), very good partial response (VGPR), or partial response (PR), excluding stable disease, and is a direct indication of the effectiveness of the drug. On the other hand, CR is defined as no M component in serum or urine electrophoresis and 5% or fewer plasma cells in bone marrow aspiration. A PR is less favorable than a CR, an sCR, or VGPR, but worse than stable disease (SD). There is a PR if the serum monoclonal protein is reduced by 50%, and the urine monoclonal protein level is reduced by 90%, or by 200 mg/24 hours. Additionally, a 50% reduction in soft tissue plasmacytomas is required if the patient initially had one.

According to our findings (

Table 2), ORR was observed in 57.62% (BCMA: 47.55%, GPRC5D: 68.06%, BCMA× GPRC5D: 84.13%, Tal_Dar: 78.46%), complete response CR or stringent complete response sCR was 17% (BCMA: 18.91%, GPRC5D: 11.85%, BCMA× GPRC5D: 33.33%), very good partial response was 22.66% (BCMA: 12.21%, GPRC5D: 42.08%, BCMA× Tal_Dar: 3.17%), while partial response PR scored 11.49% (BCMA: 10.74%, GPRC5D: 14.13%, BCMA× Tal_Dar: 0%). Very good partial response was the highest among all other responses, specifically in the GPRC5D group. The median time to response was 1.06 months and the median time to best response was 4.6 months.

Table 2. Efficacy reported for different responses to each agent for MM patients reported in 23 different studies.

Agent	Tec	Tec U1	Tec U2	Elr	F	R5 45 8U 2	R5 45 8U 1	R5 45 8	A M G4	A M G7	Al n1	Al n2	AB BV	Tec_ Tal	Tal4 05U 1	Tal8 00U 1	Tal 40 5U 2	Tal 80 0U 2	Tal qI V	Tal0. 4	Tal0. 8	Ce vo	Tal_ Dar
Target	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	B	NB	NB	NB	NB	NB	NB	NB	NB	ND
ORR[a]	104	11	17	75	11	14	42	13	17	10	36	69	27	53	21	16	21	28	73	106	106	84	51
sCR/CR[b]	65	6	0	43	0	0	63	6	5	4	12	35	13	21	0	0	7	10	28	0	0	34	
VGPR	32	5	2	26	2	2	2	3	6	3	7	17	12	2	17	12	10	13	34	84	83	25	
[c]PR	7	0	0	6	9	0	0	4	6	3	17	17	2	0	4	4	4	5	11	22	23	25	
Median time to response (M)	1.2		0.5	1.2				1	1	1.0 5	1						0.9	1.2				1	1
Median time to best response	3.8								2.8								9.3	2.3					
Prior BCMA therapy			12																			58	
After BCMA therapy			10																				

[a]objective response rate

[b]complete response

[c]very good partial response

[c]partial response

Safety

At baseline, the ECOG with 0 performance was 39.83% (BCMA: 39.83%), while the ECOG with ≥1 performance status was 59.77% (BCMA: 59.77%). ISS of stages I, II, and III were 30.75% (BCMA: 26.38%, GPRC5D: 36.57%), 42.86% (BCMA: 42.32%, GPRC5D: 43.57%), and 22.56% (BCMA: 24.04%, GPRC5D: 19.11%), respectively. High-risk cytogenetics was 28.29% (BCMA: 33.44%, GPRC5D: 16.14%, BCMA× GPRC5D: 33.33%, TAL_DAR: 18.46%), [1]del(17p), t(4:14) and t(14:16) were respectively 11.28% (BCMA: 15.76%, GPRC5D: 9.79%), 8.63% (BCMA: 10.91%, GPRC5D: 7.87%), and 0.85% (BCMA: 2.42%, GPRC5D: 0.33%). EMD as the presence of any plasmacytoma (extramedullary and/or Para medullary with a soft-tissue component) was

[1] del(17p): deletion, t(4:14) and t(14:16): translocations.

present in 30.59% (BCMA: 30.11%, GPRC5D: 21.25%, BCMA× GPRC5D: 42.86%) of patients. Previous therapy exposures for Penta drug were in 72.60% (BCMA: 73.89%, GPRC5D: 75.04%, BCMA× GPRC5D: 63.49%, TAL_DAR: 63.08%) while for Triple-class was in 98.73% (BCMA: 98.98%, GPRC5D: 98.48%). Refractoriness statuses were reported in both BCMA and non-BCMA as the following: Triple class refractory was 75.21% (BCMA: 76.10%, GPRC5D: 75.87%, BCMA× GPRC5D: 77.78%, TAL_DAR: 58.46%), Penta refractory was 34.87% (BCMA: 45.60%, GPRC5D: 24.13%), MoAb refractory was 92.45% (BCMA: 95.49%, GPRC5D: 94.58%, BCMA× GPRC5D: 76.92%), IMiDs refractory was 86.32% (BCMA: 79.85%, GPRC5D: 94.96%) and PI refractory was 80.63% (BCMA: 77.27%, GPRC5D: 85.12%). Refractory to the last line of therapy and prior BCMA directed (BDT) were reported in 79.81% (BCMA: 76.67%, GPRC5D: 88.17%) and 37.20% (BCMA: 56.88%, GPRC5D: 18.28%, BCMA× GPRC5D: 53.85%). AEs for all grades in patients who received BCMA were 94.32% higher than those who received GPRC5D agents. Similarly, AEs for grades 3/4 were higher in BCMA agents, 77.47% than GPRC5D.

Hematological and non-hematological AEs were highlighted based on the total percentage of the patients who received BCMA, GPRC5D, BCMA×GPRC5D, and TAL_DAR agents in (Table 1). According to studies, AEs are reported at varying levels, however, the most common hematological AEs were: neutropenia 43.87% (BCMA: 40.14%, GPRC5D: 46.39%, BCMA× GPRC5D: 76.19%, TAL_DAR: 26.15%), Anemia 43.96% (BCMA: 38.73%, GPRC5D: 48.22%, BCMA× GPRC5D: 60.32%, TAL_DAR: 52.31%), lymphopenia 40.33% (BCMA:37.92 %, GPRC5D: 43.53%), leukopenia 33.85% (BCMA: 36.91%, GPRC5D: 31.81%) and thrombocytopenia 28.74% (BCMA: 27.05%, GPRC5D: 31.56%). Grade 3/4 hematological AEs were reported as the following: neutropenia 40.03% (BCMA: 38.94%, GPRC5D: 38.22%, BCMA× GPRC5D: 74.60%, TAL_DAR: 26.15%), anemia 28.48% (BCMA: 27.44%, GPRC5D: 26.98%, BCMA× GPRC5D: 42.86%), lymphopenia 45.09% (BCMA: 47.01%, GPRC5D: 41.90%), leukopenia 25.49% (BCMA: 31.21%, GPRC5D: 19.77%) and thrombocytopenia 17.47% (BCMA: 18.18%, 15.81).

Regarding other AEs, non-hematological AEs were CRS 64.16% (BCMA: 55.78%, GPRC5D: 73.88%, BCMA× GPRC5D: 80.95%, TAL_DAR: 78.46%), immune effector cell-associated neurotoxicity (ICAN) syndrome was 7.24% (BCMA: 6.42%, GPRC5D: 9.30%, BCMA× GPRC5D: 1.59%, TAL_DAR: 4.62%), CRS tx was 53.17% (BCMA: 42.48%, GPRC5D: 67.43%), CRS tx with tocilizumab was reported in 33.60% (BCMA: 22.86%, GPRC5D: 49.72%) and CRS tx with

steroids was 12.20% (BCMA: 12.66%, GPRC5D: 11.64%). Neurotoxicity in general was reported in 11.44 % of the BCMA group while the GPRC5D group did not report any case. Infection cases were 44.05% (BCMA: 48.34%, GPRC5D: 38.45%, TAL_DAR: 63.08%), 10.48% were Covid-19 (BCMA: 17.50%, GPRC5D: 5.23%) and 8.06 were pneumonia (BCMA: 17.22%, GPRC5D: 1.96%). Hypogammaglobulinemia was reported in 49.08% (BCMA:44.13%, GPRC5D: 52.37%), Hypogammaglobulinemia tx with IVIG was 35.85% (BCMA: 39.39%, GPRC5D: 32.31%). Grade 3/4 CRS was 1.84% (BCMA: 1.30%, GPRC5D: 2.56%, BCMA× GPRC5D: 3.17%), grade 3/4 ICAN 3.03% (BCMA: 3.03%). Grade 3/4 infection 18.18% (BCMA: 27.32%, GPRC5D: 10.91%, GPRC5D: 21.54%) mostly reported as 5.51% (BCMA: 13.78%, GPRC5D: 0%) COVID-19, and pneumonia 2.85% (BCMA: 6.36%, GPRC5D: 1.09%), see (Table 3) below. These AEs occurred in several studies the number of each AE that appeared in the studies counted as follow: CRS in 23, neutropenia grade3/4 in 17, CRS grade3/4 15, Infections in 15, Infections in grade3/4 15, Anemia in 14, Anemia grade3/4 in 13, ICANS in 13, Thrombocytopenia grade3/4 in 10, CRS tx with tocilizumab in 10, Thrombocytopenia in 8, CRS tx with steroids in 9, Lymphopenia grade3/4 in 8, Lymphopenia in 7, CRS tx in 7, Leukopenia grade3/4 in 6, Leukopenia in 5, and Hypogammaglobulinemia in 5.

Table 3. Adverse events (Safety) including hematological, non- hematological, and general adverse events reported for each agent reported in 23 studies.

Agent	Tec	Tec U1	Tec U2	Elr	F	R5458U1	R5458U2	R5458	AMG4	AMG7	Aln1	Aln2	ABBV	Tec_Tal	Tal405U1	Tal800U1	Tal405U2	Tal800U2	TalqIV	Tal0.4	Tal0.8	Cevo	Tal_Dar
Target	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	BC	B	NB	NB	NB	NB	NB	NB	NB	NB	ND
Neutropenia	117			60	10	11	48			17		24	46	48	20	10	20	16	48			29	25
Anemia	86			60	5		61	63		32		24	36	38			18	19	59			51	34
Lymphopenia	57			33	12								19				12	17	53				
Leukopenia	29				9												12	8	38				
[a]TP	66			38			35			15			29				11	10	36				
Neutropenia G3/4	106	8		60	7	9	46				10	21	42	47	18	8	18	14	27			26	17
Anemia G3/4	61	2		46			50	55			8	12	20	27			9	10	34			35	
Lymphopenia G3/4	54	21		31	11								16				12	17	48				
Leukopenia G3/4	12	8			8												9	6	16				
TP G3/4	35	7		29			27			1	4		15				7	5	13				
CRS[b]	119	9	10	71	13	26	80	83	16	46	17	37	71	51	22	18	23	35	50	113	109	128	51
Fatigue	46			45		29	57	58		19			37				10	12	37			26	29
Fatigue G3/4	4			4		3		0					1				1	0	1			3	
Nausea	45			33		22							36				9	7	23			35	
Infections	126			86				93	14	13			51		11	3	14	15	12	83	94	68	41
Infections G3/4	74			49				52	8		5		6		1	1	2	3	10	31	23	30	14
ICANS[c]	5	5		4				3				1		1			3	2	6	16	16	21	3
Death	68	5		55					4	4	8		33				0	3	0				

[a]Thrombocytopenia.

[b]Cytokine releases syndrome.

[c]Immune effect or cell-associated neurotoxicity syn

Other events reported as general AEs for any grade (**Error! Reference source not found.Error! Reference source not found.**) include: diarrhea 28.68% (BCMA: 32.21%, GPRC5D: 25.15%), fatigue 32.21% (BCMA: 32.69%, GPRC5D: 28.28%, TAL_DAR: 44.62%), nausea 25.73% (BCMA: 28.87%, GPRC5D: 22.58%), decrease appetite 22.12% (BCMA: 33.3%, GPRC5D: 18.39%), dysgeusis 55.92% (GPRC5D: 52.67%, TAL_DAR: 75.38%), dry mouth 38.51% (GPRC5D: 34.29%, TAL_DAR: 55.38), injection-site erythema 15.94% (BCMA: 26.44%, GPRC5D: 8.94%), pyrexia 25.07% (BCMA: 25.51%, GPRC5D: 24.63%), headache 23.78% (BCMA: 21.11%, GPRC5D: 26.44%), arthralgia 20.87% (BCMA: 19.78%, GPRC5D: 21.59%), constipation 14.64% (BCMA: 20.61%, GPRC5D: 12.65%) and cough 21.59% (BCMA: 20.44%, GPRC5D: 22.45%). Patients who received treatment with autologous stem cell transplantation, allogenic stem cell transplantation, or both were reported in 79.50% (BCMA: 77.14%, GPRC5D: 83.43%). Plasma cells in bone marrow were 23.47% (BCMA: 29.30%, GPRC5D: 17.64%).

Grade 3/4 general AEs were reported as the following: diarrhea 1.63% (BCMA: 2.29%, GPRC5D: 1.14%), fatigue 1.90% (BCMA: 2.18%, GPRC5D: 1.55%), nausea 0.32% (BCMA: 0.74%, GPRC5D: 0%), decrease appetite 1.28% (BCMA: 0.81%, GPRC5D: 1.44%). injection-site erythema 0%, pyrexia 0.67% (BCMA: 1.56%, GPRC5D: 0%), headache 0.70% (BCMA: 0.74%, GPRC5D: 0.65%), arthralgia 0.71% (BCMA: 0.30%, GPRC5D: 0.98%), constipation 0.49% (BCMA: 0%, GPRC5D: 0.65%) and cough 0%. There were three different reported types of death, death was reported at 20.60% (BCMA: 20.60%) and some studies reported death; due to progressive disease, 6.81% (BCMA: 6.81%) due to AEs, 6.50% (BCMA: 6.50%) due to infections, 1.94% (BCMA: 4.85%) due to COVID-19, and 0.90% (BCMA: 3.14%) related to medications. Deaths are generally reported mainly in the BCMA group.

Statistical results

The pooled analysis of our research indicated that the following AEs are mostly reported with a 95% confidence interval (CI); CRS 64.16% (CI: 35.7, 68.4), neutropenia grade 3/4 40.03% (15.3,41.6), CRS grade 3/4 1.84% (0.7, 2.3), infections 44.05% (26.0, 70.5), infections grade 3/4 18.18% (8.2, 33.0), anemia 43.96% (29, 54.7), anemia grade 3/4 28.48% (16.3, 40.5), ICANS 7.24% (2.6, 10.6), TP) grade 3/4 28.74% (5.8, 22.8), CRS tx with tocilizumab 33.60% (10.07, 43.13), Thrombocytopenia 28.74% (14.5, 45.5), CRS tx with steroids 12.20% (2.6,20.7), lymphopenia grade 3/4 45.09% (12.4, 40.1), lymphopenia 40.33% (11.3, 46.7), leukopenia

grade3/4 25.49% (6.1, 13.6), leukopenia 33.85% (2.4, 36), CRS tx 53.17% (7.9, 76.4), and hypogammaglobulinemia 49.08% (-20.4, 99.2), those reports here are ordered based on the frequency that reported on studies.

The Friedman test results for comparing BCMA, GPRC5D, and the combination of BCMA, GPRC5D, BCMA× GPRC5D, and TAL_DAR groups together for all grades were obtained as follows: $P < 0.05$, 0.00008, and $P \ll 0.05$, respectively. Conducting the Friedman test for grade 3/4 AEs among agents stratified into BCMA, GPRC5D, and then BCMA, GPRC5D, BCMA× GPRC5D, and TAL_DAR groups together yielded the following results: 0.00005, 0.007, and 0.00001. Employing the Wilcoxon test for pairwise comparisons within each group of agents involved several steps. Initially, we applied the Wilcoxon test independently to assess the statistical significance of differences between BCMA and GPRC5D groups (**Error! Not a valid bookmark self-reference.**) across all grades (Table 5) in Appendix). Subsequently, we extended this analysis by employing the Wilcoxon test on BCMA, GPRC5D, BCMA× GPRC5D, and TAL_DAR groups together, considering AEs for all grades.

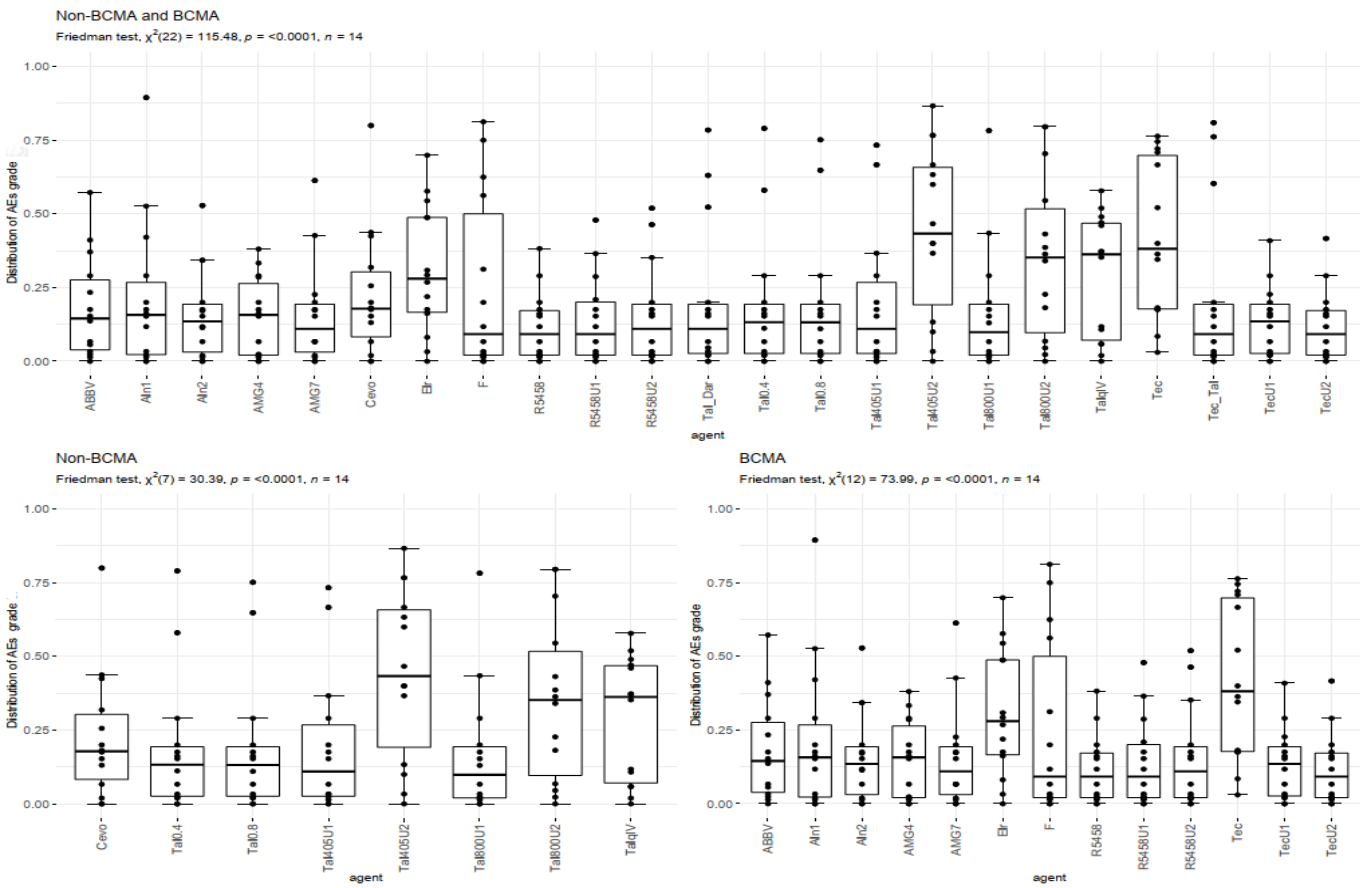

Figure 1. . Comparison between agents for all grade AE's using Friedman test. The top panel provides boxplot comparison between all agents, the bottom left panel shows only non-BCMA agents, and the bottom right panel illustrates BCMA agents. Statistics including Chi square, p-value and degree freedom is shown on top of each panel.

We then conducted separate Wilcox tests on BCMA and GPRC5D for grade 3/4 (Figure 2), yielding statistical significance in (Table 6).

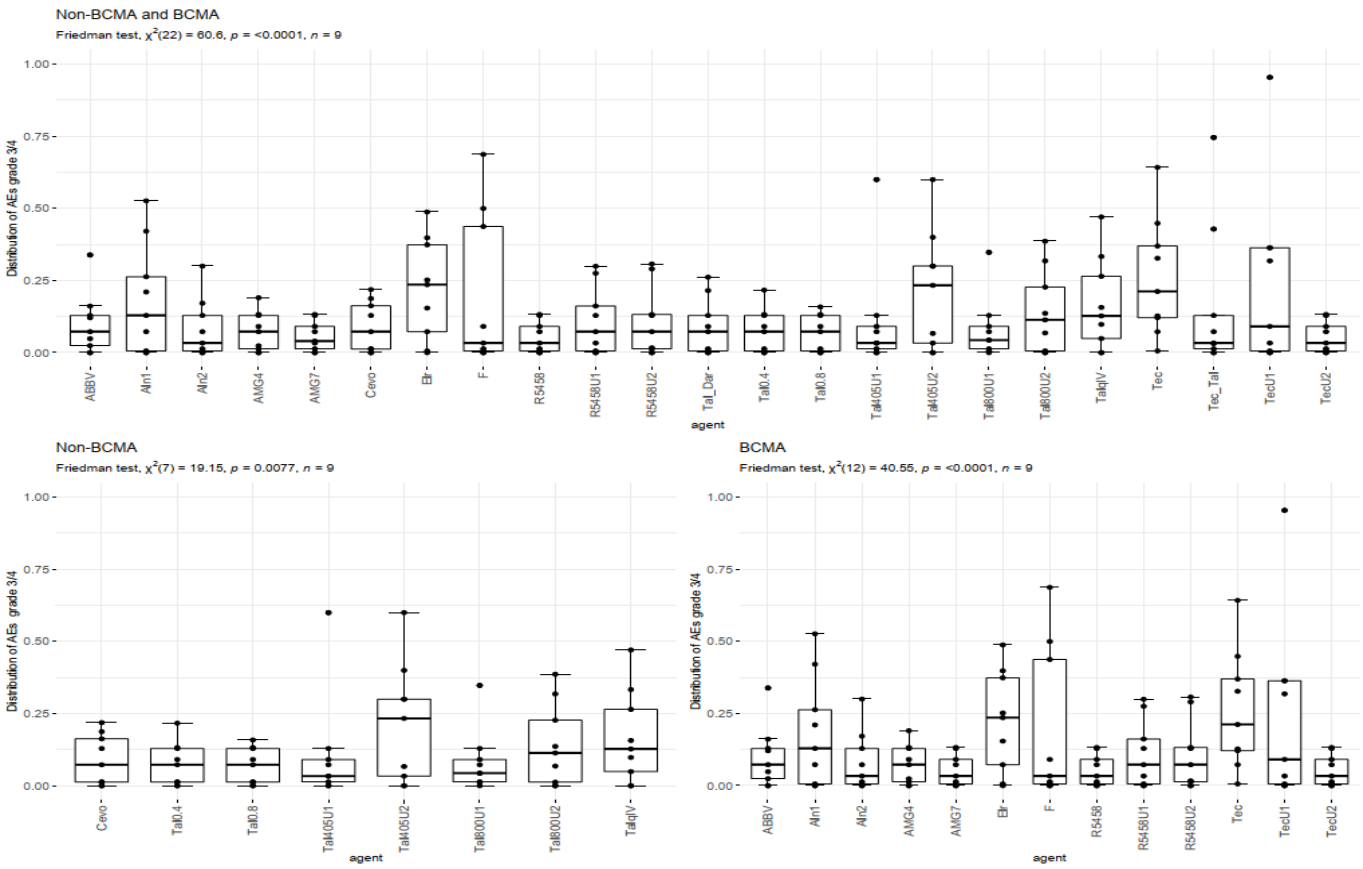

Figure 2 . Comparison between agents for all grade AE's using Friedman test. The top panel provides boxplot comparison between all agents, the bottom left panel shows only non-BCMA agents, and the bottom right panel illustrates BCMA agents. Statistics including Chi square, p-value and degree freedom is shown on top of each panel.

Clustering

Our analysis including twenty-three BCMA, GPRC5D, BCMA× GPRC5D, and TAL_DAR agents are shown in different colors in **Error! Reference source not found.**. Upon clustering these a gents, we found differences in their AE performance across all grades. For fine-tuning in some parameters we used this study [41] to find the suitable hyperparameters for our proposal. As a result of running the code multiple times, we observe that these agents' group as follows:

Group 1: R5458U2, R5458U1, R5458, Aln1, Aln2, AMG4, AMG7, ABBV, TecU1, TecU2 and Cevo

Group 2: TalqIV, Tal405U2, Tal800U2, Tec and Elr

Group 3: F, Tal405U1, Tal800U1, Tec_Tal, Tal0.4, Tal0.8 and Tal_Dar

Similarly, upon clustering these agents based on AEs of grade3/4, we observe that these agents group as follows:

Group 1: R5458U2, R5458U1, R5458, Aln1, Aln2, AMG4, AMG7, ABBV, TecU1, TecU2, Cevo and Tal_Dar

Group 2: TalqIV, Tal405U2, Tal800U2, Tec, Elr and Aln1

Group 3: F, Tal405U1, Tal800U1, Tec_Tal, Tal0.4 and Tal0.8

The difference between clustering in Grade 3/4 and all grades is that Tal_Dar from Group 3 in all grades moves to Group 1 in Grade 3/4, while Aln1 from Group 1 in all grades moves to Group 2 in Grade 3/4.

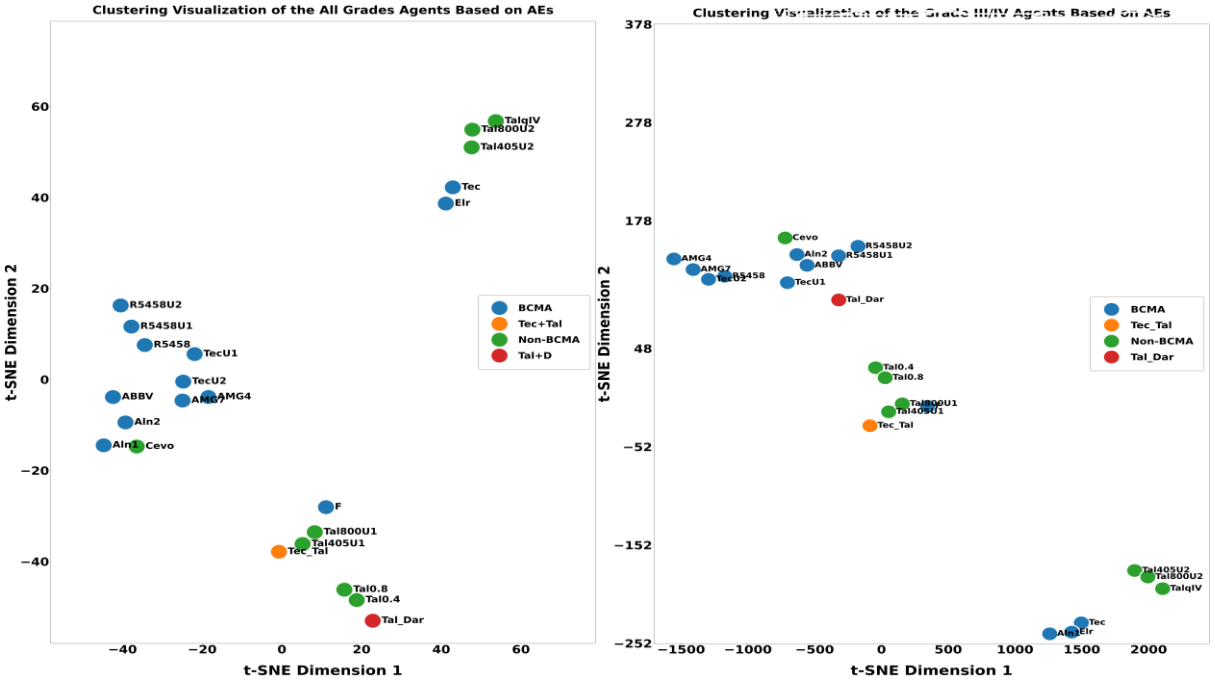

Figure 3. Results of Clustering using t-SNE algorithm for all grade AEs (Left Panel) and grade 3/4 AEs (Right Panel), separately

Discussion

Studies on Teclistamab showed that cytopenia (reduced blood cell counts) and infections were common. AEs related to T-cell redirection were mostly mild to moderate in severity [19]. Elranatamab showed robust and long-lasting responses along with a favorable safety profile; However, the most common AEs observed included infections, CRS, anemia, and neutropenia [20]. A BCMA, F182112, presented a new immunotherapeutic approach for the treatment of relapsed refractory MM [21]. Studies on another BCMA BiTe, REGN5458, primarily emphasized efficacy and treatment responses [3, 26, 25]; Although, the most frequently observed hematologic AEs were anemia, neutropenia, and thrombocytopenia; Among non-hematologic AEs, CRS was the most reported. Specific cases of polyneuropathy were reported in patients treated with AMG 420, also a BCMA BiTe, with 7% of patients experiencing the AE [42]. Another study [43] shows administration of Alnuctamab improved the safety profile meanwhile CRS was limited to grades 1/2 events. In the study by D'souza *et al.* [27], they administered escalating doses of ABBV-383 and found that serious CRS events occurred in 18% of patients across the entire study population. Among these, 26% were in the group receiving doses of ≥ 40 mg during the escalation phase. AEs associated with Talquetamab treatment often led to CRS, skin-related problems, and dysgeusia (altered taste sensation), though, these AEs were mainly mild in severity or low grades [28]. Talquetamab demonstrated considerable therapeutic efficacy in individuals with MM who had received extensive prior treatments and were facing relapse or refractory conditions [30]. When administered as an independent treatment, cevostamab continues to show clinically significant effectiveness in a substantial group of patients who have undergone extensive prior treatments for relapsed refractory MM [31]. The observed increase in overall response rate seems to be linked to the targeted dose, without a corresponding increase in the rate of CRS. In this study [32] authors explained that when combining BCMA and non-BCMA treatments, such as Teclistamab + Tqalquetamab, they found a safety profile that was easy to handle and consistent with the safety of each treatment. Additionally, using Talquetamab with daratumumab, which reduces the need for steroids, resulted in strong and lasting responses, suggesting a hopeful outlook for the median progression-free survival (mPFS) in relapsed refractory MM [33].

In our study, we specified reported AEs associated with BiTEs. BiTEs operate by connecting T-cells through CD3 and specific antigens on MM cells, thereby triggering the apoptotic machinery of T cells against malignant myeloma cells. In our study, we focused on the analysis of the most important AEs (hematological and non-hematological).

We found higher rates of neutropenia, anemia, lymphopenia, leukopenia, CRS, ICANS, CRS tx, CRS tx with tocilizumab, CRS tx with steroids, hypogammaglobulinemia, and CRS grade3/4 in non-BCMA than BCMA agents including Teclistimab, and Talquetamab. The statistical result is shown in (Table 5) and also in

Table 4 and Table 6. Another study [44] implemented a non-parametric statical test to see differences between several groups of data, meanwhile, we applied both parametric and non-parametric tests on our data to find more accurate results. In the study [1], the authors focused solely on infections linked to the usage of BiTEs in the context of MM, also in this [45] research the main focus is on infections as AEs. In contrast, our study thoroughly investigated all AEs and toxicities. We utilized a comprehensive analysis approach that covered the entire range of these AEsa. Notably, a prior study [46] derived a death rate of 0.01% through the amalgamation of rates from eleven distinct studies. In contrast, our investigation, benefitting from a more extensive dataset, revealed a death rate of 0% in our cohort. Within the framework of their research [47], the authors highlighted elevated occurrences of grade ≥3 infections among patients treated with BCMA compared to non-BCMA. However, our meticulous pooled analysis failed to discern any discernible distinctions between patients treated with BCMA and those treated with non-BCMA in terms of infection rates.

Clustering

Clustering is a fundamental technique in data analysis that involves grouping data points based on shared characteristics. The goal is to organize complex datasets into meaningful and interpretable subsets, helping to understand the underlying structures within the data. Clustering can be achieved using various algorithms, each with a different approach to defining and finding clusters efficiently. Common definitions of clusters include groups with small distances between members, dense regions of data space, intervals, or specific statistical distributions. Thus, clustering can be viewed as a multi-objective optimization problem. The choice of clustering algorithm and parameter

settings (e.g., the number of clusters) depends on the dataset and the intended use of the results. Analyzing clusters involves trial and error, requiring modifications in data preprocessing and model parameters until the desired results are achieved.

Visualizing high-dimensional datasets poses a significant challenge because high-dimensional plots are less intuitive than two- or three-dimensional ones due to increased visual complexity. In our study, we explored various linear and non-linear dimension reduction methods, including Principal Component Analysis (PCA), Kernel Principal Component Analysis (kPCA), Locally Linear Embedding (LLE), Isomap, and t-SNE. Through comparative analysis, t-SNE emerged as the most effective method for our dataset due to its ability to capture complex patterns and relationships in reduced-dimensional space. t-SNE transforms affinities of data points into probabilities: Gaussian joint probabilities in the original space and Student's t-distributions in the embedded space.

One of the primary strengths of t-SNE lies in its ability to faithfully represent the local structure of high-dimensional data in a reduced-dimensional space [39]. This means that points close to the original feature space remain clustered after dimensionality reduction, making t-SNE particularly advantageous for visualizing complex datasets. This facilitates the identification of inherent groupings and relationships between data points that might otherwise be obscured in high-dimensional representation. Preserving local neighborhoods provides valuable insights into the data, enabling researchers to explore and analyze complex structures within the dataset. Due to its sensitivity to local structure, t-SNE has several advantages over existing approaches:

1. Visualizing the structure at multiple scales on one map.
2. Identifying data that exists in multiple, differing, or clustered locations.
3. Increasing points' space at the center and reducing crowding.
4. Not thrown off by outliers as easily as the results of some other dimension reduction techniques.

t-SNE method is a principal technique for data visualization and clustering [48]. We applied t-SNE in the form of revealing the local structure of the data, making the data helpful in visualizing clusters and identifying patterns.

Limitations

Our analysis faced limitations due to a significant number of unreported missing values in the underlying studies. Some studies, especially those focused on infection-related AEs, either omitted or did not fully report these details, leading to many missing values. Additionally, some studies, driven by specific goals, neglected to report essential details, concentrating only on efficacy and a few AEs. Many abstracts also reported retests of other publications without providing baseline characteristics, further contributing to missing values in our analyses. Missing data poses a threat to the integrity of clinical research, potentially leading to biased results and reduced statistical power [49]. We address how to tackle the missing value on section Imputations to address missing/nonreported events.

Wattenon-Aerg, et al [40] discussed the challenges of interpreting cluster sizes in t-SNE plots, especially when clusters have different standard deviations. Their study showed that clusters with different sizes in bounding box measurements can appear similar in t-SNE plots. This is because the t-SNE algorithm adapts to regional density variations, expanding densely populated clusters and contracting sparser ones, which equalizes cluster sizes. This density equalization is an intentional feature of t-SNE, not a distortion of distances. Therefore, t-SNE plots do not accurately represent the relative sizes of clusters, highlighting a limitation for size-related analyses.

Another limitation of t-SNE is interpreting distances between clusters, particularly with varying numbers of points and different perplexity values. In our conductions, using lower perplexity values can create the illusion of central clusters, while higher values can inaccurately make one cluster appear smaller. Van der Maaten and Hinton [39] suggested perplexity values between 5 and 50 for consistent global geometry representation. However, this range did not produce satisfactory results for our data, which likely had multiple clusters with varying elements. Perplexity is a global parameter, and finding one value that captures distances across all clusters is challenging. Different settings of parameters occur in different shapes and distances but mostly in the same clusters. Consequently, distances between well-separated clusters in a t-SNE plot may be meaningless.

Unlike PCA, where axes in the low-dimensional space have specific meanings, t-SNE works differently. The axes in t-SNE's low-dimensional space lack distinct interpretation, allowing for arbitrary rotations without affecting the t-SNE cost function. Additionally, t-SNE does not establish explicit mappings between high-dimensional and low-dimensional spaces. Instead, it

focuses on maintaining the relative distances between points, ensuring that neighboring points in the input space stay close in the low-dimensional space.

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Appendix

Table 4. Appendex Comparison for all grade AEs together.

BCMA and non-BCMA together

Agent	Agent	P-val	Agent	Agent	P-val	Agent	Agent	P-val
ABBV	Elr	0.008	AMG7	TecU2	0.036	R5458U2	TalqIV	0.038
ABBV	R5458	0.036	Cevo	R5458	0.022	R5458U2	Tec	0.002
ABBV	Tal405U2	0.003	Cevo	Tal405U2	0.014	Tal_Dar	Tal405U2	0.011
ABBV	Tal800U2	0.05	Cevo	Tec	0.018	Tal_Dar	Tec	0.008
ABBV	Tec	0.002	Cevo	TecU2	0.022	Tal0.4	Tal405U2	0.014
ABBV	TecU2	0.036	Elr	R5458	0.003	Tal0.4	Tal800U2	0.043
Aln1	Tal405U2	0.007	Elr	R5458U1	0.003	Tal0.4	Tec	0.005
Aln1	Tal800U2	0.008	Elr	R5458U2	0.003	Tal0.8	Tal05U28	0.011
Aln1	Tec	0.012	Elr	Tal_Dar	0.038	Tal0.8	Tal800U2	0.043
Aln2	Elr	0.004	Elr	Tal0.4	0.031	Tal0.8	Tec	0.004
Aln2	Tal405U2	0.002	Elr	Tal0.8	0.025	Tal405U1	Tal405U2	0.004
Aln2	Tal800U2	0.006	Elr	Tal405U1	0.038	Tal405U1	Tal800U2	0.036
Aln2	TalqIV	0.009	Elr	Tal800U1	0.021	Tal405U1	Tec	0.002
Aln2	Tec	0.003	Elr	Tec	0.012	Tal405U2	Tal800U1	0.003
AMG4	Elr	0.017	Elr	TecU1	0.011	Tal405U2	Tal800U2	0.012
AMG4	Tal405U2	0.008	Elr	TecU2	0.003	Tal405U2	TalqIV	0.035
AMG4	Tal800U2	0.01	R5458	Tal405U2	0.003	Tal405U2	Tec_Tal	0.014
AMG4	TalqIV	0.038	R5458	Tal800U1	0.181	Tal405U2	TecU1	0.004
AMG4	Tec	0.006	R5458	Tal800U2	0.002	Tal405U2	TecU2	0.003
AMG7	Elr	0.005	R5458	TalqIV	0.004	Tal800U1	Tal800U2	0.008
AMG7	R5458	0.036	R5458	Tec	0.002	Tal800U1	TalqIV	0.025
AMG7	Tal405U2	0.002	R5458U1	Tal405U2	0.003	Tal800U1	Tec	0.003
AMG7	Tal800U2	0.002	R5458U1	Tal800U2	0.002	Tal800U2	TecU1	0.006
AMG7	TalqIV	0.017	R5458U1	TalqIV	0.004	Tal800U2	TecU2	0.002
AMG7	Tec	0.002	R5458U1	Tec	0.002	TalqIV	TecU1	0.015
R5458U2	Tal405U2	0.003	Tec	TecU1	0.005	TalqIV	TecU2	0.004
R5458U2	Tal800U2	0.008	Tec	TecU2	0.002	Tec	Tec_Tal	0.021

Table 5. Appendex comparison for all grade AE's BCMA and non-BCMA.

BCMA	BCMA	p	BCMA	BCMA	p	non-BCMA	non-BCMA	p	non-BCMA	non-BCMA	p
ABBV	Elr	0.008	AMG7	Tec	0.002	Cevo	Tal405U2	0.014	Tal405U1	Tal800U2	0.036
ABBV	R5458	0.036	AMG7	TecU2	0.036	Tal0.4	Tal405U2	0.014	Tal405U2	Tal800U1	0.003
ABBV	Tec	0.002	Elr	R5458	0.003	Tal0.4	Tal800U2	0.043	Tal405U2	Tal800U2	0.012
ABBV	TecU2	0.036	Elr	R5458U1	0.003	Tal0.8	Tal405U2	0.011	Tal405U2	TalqIV	0.035
Aln1	Tec	0.012	Elr	R5458U2	0.003	Tal0.8	Tal800U2	0.043	Tal800U1	Tal800U2	0.008
Aln2	Elr	0.004	Elr	Tec	0.012	Tal405U1	Tal405U2	0.004	Tal800U1	TalqIV	0.025
Aln2	Tec	0.003	Elr	TecU1	0.011						
AMG4	Elr	0.017	Elr	TecU2	0.003						
AMG4	Tec	0.006	R5458	Tec	0.002						
AMG7	Elr	0.005	R5458U1	Tec	0.002						
AMG7	R5458	0.036	R5458U2	Tec	0.002						
Tec	TecU2	0.002	Tec	TecU1	0.005						

Table 6. Appendex comparison for grade 3/4 AE's.

BCMA and non-BCMA together

Agent	Agent	p-val	Agent	Agent	p-Val	BCMA	BCMA	p
ABBV	Elr	0.035	Elr	TecU2	0.036	ABBV	Elr	0.035
ABBV	Tal405U2	0.022	R5458	Tal405U2	0.022	ABBV	Tec	0.021
ABBV	Tec	0.021	R5458	Tal800U2	0.036	Aln1	Tec	0.042
Aln1	Tec	0.042	R5458	TalqIV	0.022	Aln2	Elr	0.036
Aln2	Elr	0.036	R5458	Tec	0.014	Aln2	Tec	0.014
Aln2	Tal405U2	0.022	R5458U1	Tal405U2	0.022	AMG4	Elr	0.035
Aln2	Tal800U2	0.036	R5458U1	Tec	0.014	AMG4	Tec	0.021
Aln2	TalqIV	0.035	R5458U2	Tec	0.021	AMG7	Elr	0.036
Aln2	Tec	0.014	Tal_Dar	Tec	0.014	AMG7	Tec	0.014
AMG4	Elr	0.035	Tal0.4	Tec	0.014	Elr	R5458	0.036
AMG4	Tec	0.021	Tal0.8	Tec	0.014	Elr	R5458U1	0.036
AMG7	Elr	0.035	Tal405U1	Tec	0.021	Elr	R5458U2	0.035
AMG7	Tal405U2	0.035	Tal405U2	Tal800U1	0.042	Elr	TecU2	0.036
AMG7	Tal800U2	0.035	Tal405U2	Tal800U2	0.035	R5458	Tec	0.014
AMG7	TalqIV	0.022	Tal405U2	TecU2	0.022	R5458U1	Tec	0.014
AMG7	Tec	0.021	Tal800U1	Tec	0.014	R5458U2	Tec	0.021
Cevo	Elr	0.035	Tal800U2	Tec	0.039	Tec	TecU2	0.014
Cevo	Tec	0.021	Tal800U2	TecU2	0.036	**non-BCMA**	**non-BCMA**	**P**
Elr	R5458	0.036	TalqIV	TecU2	0.022	Tal405U2	Tal800U1	0.042
Elr	R5458U1	0.036	Tec	TecU2	0.014	Tal405U2	Tal800U2	0.035
Elr	R5458U2	0.035	Elr	Tal0.4	0.036			
Elr	Tal_Dar	0.036	Elr	Tal0.8	0.036			
			Elr	Tal800U1	0.035			