Cardiovascular Toxicities Associated with Bi-specific T-cell Engager Therapy

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Supplementary Methods

Database Structure

In FAERS, each case reported in the database may be the subject of several submissions (corresponding to the initial report and subsequent updates). In our analysis, we de-duplicated the database and retained only the latest (most updated) versions of any given case. For each case, the list of drugs that the patient was using is provided. The reporting party classifies drugs as being primary suspects, secondary suspects, or concomitantly taken drugs. In this analysis, a case was classified as having experienced a BiTE-related AE only if the primary suspected drug was a BiTE product.

Database Cleaning

First, we identified all reports of adverse events where one of the two FDA-approved bispecific T-cell engagers (BiTEs), Blinatumomab and Teclistamab, was listed as primary suspected drug. We then chose a 20% random sample of reports where the primary suspected drug was not a BiTE product. A single case may be the subject of several reports on FAERS (identified through a common case ID). For these cases which were the subject of multiple reports, we chose to keep only the latest (most updated) version of each. Then, because all of our analyses utilized age and sex adjustments, we excluded all records with a missing age or sex variable. Because FAERS reports may include a miniscule fraction of erroneous age entries with unlikely age values, only records with an age of up to 100 years were included.

We then excluded records of BiTE-related products where the indication for the BiTE product was unclear (e.g., “neoplasm”) or where it was used for a solid tumor (since BiTE products are not eligible for use in solid tumors to date and their use in such settings is likely experimental and reserved for patients with severe disease).

Because the deduplication process is imperfect (that is, it may fail to identify all duplicate cases because they may be labelled using different case IDs), we added a second deduplication step wherein all reports sharing the same age, sex, country of origin, event date, drugs, and adverse events were

deduplicated. The Medical Dictionary for Regulatory Activities (MedDRA) classifies off-label uses of drugs as adverse events; therefore, a report may be submitted purely because the related product was used in an off-label manner. All such reports (where the only adverse event recorded was “Off-label use”) were removed as this is not the subject of our analysis.

Additionally, all records where the reported adverse event was equivalent to the reported indication of the drug, and which thus likely represent erroneous reporting, were excluded. Finally, some reports only included the adverse event “Death”. This may be the case if the cause of death is not clear. Because such reports are not possible to classify as cardiovascular or non-cardiovascular in nature, they were excluded from the analysis.

Definitions of Adverse Events & Disease Status

Adverse events within the Food and Drug Administration Adverse Event Reporting System (FAERS) are classified according to the Medical Dictionary for Regulatory Activities (MedDRA). Specifically, adverse events are entered using one or more “Preferred Terms” (PTs). Several PTs may correspond to a single adverse event. For example, both the “cardiac failure” and “ventricular failure” PTs refer to heart failure. These PTs fall under broader (higher-level) concepts called “High Level Terms” (HLTs) which themselves fall under yet broader concepts called “High Level Group Terms” (HLGTs) and which themselves fall under “System Organ Classes” (SOCs).

SOCs refer to broader concepts that indicate the involvement of a specific organ system (e.g., the “Cardiac” SOC would include all PTs that involve the heart as an organ system, including all those that refer to heart failure, atrial fibrillation, myocardial infarction, etc.). Standardized Medical Queries (SMQs) refer to a pre-defined collection of PTs that are used to facilitate analyses of adverse events. For example, the SMQ “Cardiac failure” is inclusive of the PTs “Left ventricular failure”, “Cor pulmonale”, “Cardiac failure”, etc. SMQs may be “broad” or “narrow”. The former is meant to be as inclusive and

sensitive as possible, whereas the latter is meant to be as focused and specific as possible. For this analysis, narrow SMQs were used.

The same system is used to classify indications in the database. In our analysis, disease status was adjusted for in the regression models because the presence of a malignancy correlates with both the use of a bispecific T-cell engager (BiTE) product and the development of adverse cardiovascular events. Three variables were used for this purpose. For Blinatumomab, we adjusted for the presence of disease using one of 6 HLGTs ("Leukaemias", "Lymphomas Hodgkin's disease", "Lymphomas NEC", "Lymphomas non-Hodkgin's B-cell", "Lymphomas non-Hodgkin's T-cell", and "Lymphomas non-Hodgkin's unspecified histology"). For Teclistamab, we adjusted for the presence of disease using the HLGT "Plasma cell neoplasms". For the analysis comprising overall BiTE therapy, we included all 7 of the aforementioned terms.

Statistical Models

When used in the context of a safety surveillance system, logistic regression models produce reporting odds ratios (aRORs), which is the ratio between two values (odds). The numerator is the odds of reporting the AE of interest with the drug of interest (BiTE). The denominator is the odds of reporting the same AE with all other drugs in the database (termed the "background" rate). In our analysis, we included all cases reporting BiTE and compared them to a 20% random sample of non-BiTE reports. The random sampling of non-BiTE products was required due to the enormity of the database. Given the still very large sample size afforded by a 20% random sample of non-BiTE reports, this has a negligible influence on statistical power and comparisons.

Supplementary Table 1. Definitions of adverse events according to the Medical Dictionary for Regulatory Activities.

Adverse event	Terms used for its identification
Altered mental status	"Encephalopathy", "Alcoholic encephalopathy", "Autoimmune encephalopathy", "Chronic traumatic encephalopathy", "Contrast encephalopathy", "Diabetic encephalopathy", "Early infantile epileptic encephalopathy with burst-suppression", "Encephalopathy allergic", "Encephalopathy neonatal", "Epileptic encephalopathy", "Hashimoto's encephalopathy", "Hepatic encephalopathy", "Hepatic encephalopathy prophylaxis", "Hyperammonaemic encephalopathy", "Hypertensive encephalopathy", "Hypoglycaemic encephalopathy", "Hyponatraemic encephalopathy", "Hypoxic ischaemic encephalopathy neonatal", "Hypoxic-ischaemic encephalopathy", "Immune effector cell encephalopathy score", "Immune-mediated encephalopathy", "Leukoencephalopathy", "Metabolic encephalopathy", "Mitochondrial neurogastrointestinal encephalopathy", "Posterior reversible encephalopathy syndrome", "Postresuscitation encephalopathy", "Progressive encephalopathy, hypsarrhythmia and optic atrophy syndrome", "Progressive multifocal leukoencephalopathy", "Radiation induced encephalopathy", "Septic encephalopathy", "Toxic encephalopathy", "Toxic leukoencephalopathy", "Uraemic encephalopathy", "Vascular encephalopathy", "Wernicke's encephalopathy", "Delirium", "Delirium febrile", "Delirium tremens", "Dementia of the Alzheimer's type, with delirium", "Intensive care unit delirium", "Post-injection delirium sedation syndrome", "Postoperative delirium", "Disorientation", "Somnolence", "Radiation somnolence syndrome", "Somnolence neonatal", "Mental status changes", "Mental status changes postoperative", "Mini mental status examination abnormal", "Confusional state"
Arterial thromboembolism	Embolic and thrombotic events, arterial (SMQ)
Atrial fibrillation or flutter	"Atrial fibrillation", "Atrial flutter"
Bleeding	Haemorrhages (SMQ)
Bradyarrhythmia	Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)
Cardiac adverse events	All preferred terms corresponding to the System Organ Class "Cardiac Disorders"
Cerebrovascular disease	Central nervous system vascular disorders (SMQ)
Coronary disease	Ischaemic heart disease (SMQ)
Cytokine release syndrome	"Cytokine release syndrome", "Cytokine storm"

Adverse event	Terms used for its identification
Disseminated intravascular coagulation	"Disseminated intravascular coagulation"
Dyslipidemia	Dyslipidaemia (SMQ)
Endocarditis	"Endocarditis", "Abiotrophia defectiva endocarditis", "Endocarditis candida", "Endocarditis enterococcal", "Endocarditis haemophilus", "Endocarditis histoplasma", "Endocarditis pseudomonal", "Endocarditis Q fever", "Endocarditis staphylococcal", "Endocarditis viral", "Fungal endocarditis", "Lupus endocarditis", "Prosthetic valve endocarditis", "Septic endocarditis", "Streptococcal endocarditis", "Subacute endocarditis"
GBS	Guillain-Barre syndrome (SMQ)
Gait disturbance	"Ataxia", "Cerebellar ataxia", "Cerebral ataxia", "Hemiataxia", "Vestibular ataxia", "Autoimmune cerebellar ataxia", "Ataxia with vitamin E deficiency", "Decreased gait velocity", "Gait apraxia", "Gait deviation", "Gait disturbance", "Gait inability", "Gait spastic", "Parkinsonian gait", "Propulsive gait", "Tandem gait test abnormal"
Headache	"Headache", "Cervicogenic headache", "Cluster headache", "Cold-stimulus headache", "Drug withdrawal headache", "Exertional headache", "External compression headache", "Hypnic headache", "Ictal epileptic headache", "Medication overuse headache", "Menstrual headache", "New daily persistent headache", "Postictal headache", "Post-traumatic headache", "Primary cough headache", "Primary headache associated with sexual activity", "Procedural headache", "Sinus headache", "Tension headache", "Thunderclap headache", "Vascular headache", "Migraine", "Migraine postdrome", "Migraine with aura", "Migraine without aura", "Hemiplegic migraine", "Basilar migraine", "Migrainous infarction", "Ophthalmic migraine", "Ophthalmoplegic migraine", "Status migrainosus", "Retinal migraine", "Vestibular migraine", "Chronic paroxysmal hemicrania", "Occipital neuralgia", "SUNA syndrome", "SUNCT syndrome"
Heart failure	Cardiac failure (SMQ)
Hypertension	Hypertension (SMQ)
Hypotension	"Hypotension", "CT hypotension complex", "Dialysis hypotension", "Diastolic hypotension", "Neonatal hypotension", "Orthostatic hypotension", "Post procedural hypotension", "Procedural hypotension"
Infection	All preferred terms corresponding to the System Organ Class "Infections and Infestations"
Myocardial infarction	Myocardial infarction (SMQ)

Adverse event	Terms used for its identification
Myocarditis	"Myocarditis", "Autoimmune myocarditis", "Chronic myocarditis", "Coxsackie myocarditis", "Cytomegalovirus myocarditis", "Enterovirus myocarditis", "Eosinophilic myocarditis", "Giant cell myocarditis", "Hypersensitivity myocarditis", "Immune-mediated myocarditis", "Lupus myocarditis", "Malarial myocarditis", "Myocarditis bacterial", "Myocarditis helminthic", "Myocarditis infectious", "Myocarditis meningococcal", "Myocarditis mycotic", "Myocarditis post infection", "Myocarditis septic", "Myocarditis syphilitic", "Myocarditis toxoplasmal", "Radiation myocarditis", "Viral myocarditis"
Neurotoxicity	All preferred terms corresponding to the System Organ Class "Nervous system disorders"
Pericardial effusion	"Pericardial effusion", "Cardiac tamponade"
Pericarditis	"Pericarditis", "Pericarditis adhesive", "Pericarditis constrictive", "Pleuropericarditis", "Myopericarditis", "Autoimmune pericarditis", "Immune-mediated pericarditis"
QT Prolongation	"Electrocardiogram QT interval abnormal", "Electrocardiogram QT prolonged", "Long QT syndrome"
Seizure	Convulsions (SMQ)
Shock	Shock (SMQ)
Speech disturbance	"Speech disorder", "Poverty of speech", "Pedantic speech", "Disorganised speech", "Slow speech", "Repetitive speech", "Speech disorder developmental", "Speech latency", "Dysarthria", "Aphasia", "Acquired epileptic aphasia", "Primary progressive aphasia", "Transient aphasia"
Sudden death	"Sudden death", "Sudden cardiac death"
Supraventricular Tachycardia	Supraventricular tachyarrhythmias (SMQ)
Tachyarrhythmia	Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)
Thromboembolic disease	Embolic and thrombotic events (SMQ)
Tremor	"Tremor", "Action tremor", "Dystonic tremor", "Essential tremor", "Holmes tremor", "Intention tremor", "Orthostatic tremor", "Parkinsonian rest tremor", "Postural tremor", "Psychogenic tremor", "Resting tremor", "Tremor neonatal"
Valvular disease	"Aortic valve disease mixed", "Aortic valve incompetence", "Aortic valve sclerosis", "Aortic valve stenosis", "Bicuspid aortic valve", "Congenital aortic valve incompetence", "Congenital aortic valve stenosis",

Adverse event	Terms used for its identification
	"Subvalvular aortic stenosis", "Supravalvular aortic stenosis", "Heyde's syndrome", "Williams syndrome", "Aortic valve calcification", "Aortic valve prolapse", "Aortic valve disease", "Aortic valve atresia", "Degenerative aortic valve disease", "Aortic valve thickening", "Aortic annulus rupture", "Unicuspid aortic valve", "Congenital mitral valve incompetence", "Congenital mitral valve stenosis", "Mitral valve disease mixed", "Mitral valve incompetence", "Mitral valve prolapse", "Mitral valve stenosis", "Mitral valve calcification", "Mitral valve sclerosis", "Mitral valve disease", "Parachute mitral valve", "Mitral valve atresia", "Mitral perforation", "Mitral face", "Degenerative mitral valve disease", "Systolic anterior motion of mitral valve", "Myxomatous mitral valve degeneration", "Ischaemic mitral regurgitation", "Mitral valve thickening", "Mitral valve dysplasia", "Pulmonary valve incompetence", "Pulmonary valve stenosis", "Pulmonary valve stenosis congenital", "Congenital pulmonary valve atresia", "Pulmonary valve calcification", "Pulmonary valve sclerosis", "Congenital pulmonary valve disorder", "Pulmonary valve disease", "Bicuspid pulmonary valve", "Pulmonary valve thickening", "Congenital tricuspid valve stenosis", "Tricuspid valve incompetence", "Tricuspid valve stenosis", "Congenital tricuspid valve atresia", "Tricuspid valve calcification", "Tricuspid valve sclerosis", "Tricuspid valve disease", "Tricuspid valve prolapse", "Congenital tricuspid valve incompetence", "Degenerative tricuspid valve disease", "Tricuspid valve thickening", "Straddling tricuspid valve", "Tricuspid valve disease mixed", "Tricuspid valve thrombosis", "Cardiac valve replacement complication", "Cardiac valve vegetation", "Heart valve calcification", "Cardiac valve sclerosis", "Cardiac valve disease", "Heart valve stenosis", "Congenital heart valve disorder", "Cardiac valve abscess", "Shone complex", "Heart valve incompetence", "Cardiac valve rupture", "Carcinoid heart disease", "Congenital heart valve incompetence", "Cardiac valve discolouration", "Cardiac valve thickening", "Degenerative multivalvular disease", "Lambl's excrescences", "Cardiac valve fatty infiltration", "Prosthetic cardiac valve regurgitation"
Vascular adverse events	All preferred terms corresponding to the System Organ Class "Vascular disorders"
Vasculitis	Vasculitis (SMQ)
Venous thromboembolism	Embolic and thrombotic events, venous (SMQ)
Ventricular extrasystole	"Ventricular parasystole", "Ventricular extrasystoles"
Ventricular fibrillation	"Ventricular fibrillation"
Ventricular tachyarrhythmia	Ventricular tachyarrhythmias (SMQ)

Adverse event	Terms used for its identification
Ventricular tachycardia	"Ventricular tachycardia", "Torsade de pointes"
All of the above terms refer to terms within the "Preferred Terms" level of the MedDRA heirarchy unless noted otherwise. "Standardized Medical Queries" (SMQs) and "System Organ Classes" refer to higher-level concepts in the MedDRA heirarchy which multiple Preferred Terms corresponding to the adverse event are placed under.	
SMQ: Standardized Medical Query	

Supplementary Figure 1. Time to onset of selected cardiovascular adverse events associated with bispecific T-cell engagers, by event type. Each line represents the cumulative proportion of adverse events that occurred by a given time point. A cubic root transformation was applied to the X-axis to aid in visualization.