Disclaimer

The following report(s) provides findings from an FDA-initiated query using its Sentinel pilot. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand the capabilities of the Sentinel pilot.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from the Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request ID cder_ahr_wp005_nsdp_v01

Request ID: cder_ahr_wp005_nsdp_v01

Request Description: This request investigated rates of six nervous system disorders and reasons for censoring among bortezomib users in the Sentinel Distributed Database (SDD) using cumulative distribution function (CDF) and Kaplan-Meier curves.

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis Tool (CIDA), version 3.0.3, and a Rapid Analytic Development and Response (RADaR) module.

Data Source*:* Data from June 1, 2008 to September 30, 2015 for 16 Data Partners contributing to the SDD were included in this request (see Appendix A for a list of data availability dates). The request was distributed to Data Partners on September 6, 2016.

Study Design*:* This request was designed to calculate rates of events among new users and the number of new users that were censored from the study for various reasons. New users were censored when at least one of the following events occurred:

1. Occurrence of event of interest
2. End of query period (September 30, 2015)
3. End of Data Partner data (see Appendix A for data availability dates for each Data Partner)
4. Disenrollment in medical coverage
5. End of exposure episode
6. Evidence of death

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Exposure of Interest: The exposure of interest was bortezomib, which was defined using Healthcare Common Procedure Coding System (HCPCS) procedure codes (see Appendix B for a list of HCPCS codes used to define each exposure event). In order to be included in the cohort of new users, patients were required to be continuously enrolled in health plans with medical coverage for at least 183 days before bortezomib use, during which gaps in coverage of up to 45 days were allowed. New use was defined as no bortezomib use in the prior 183 days. Moreover, patients were required not to have had any of the following events in the 183 days before bortezomib use: amyotrophic lateral sclerosis (ALS), Alzheimer's disease, amyloidosis, frontotemporal lobar degeneration (FTLD), or Parkinson's disease. Please see Appendix C for a list of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes used to define each event.

Follow-Up Time: Follow-up began on the day that the exposure of interest occurred and continued until the first occurrence of any of the above-mentioned censoring categories. Multiple exposure episodes were bridged into one exposure episode if they occurred within 90 days of each other. An exposure extension period of 90 days was added onto the end of each exposure episode length after the gaps were bridged. By definition of the exposure episode, it was not possible for patients to be censored due to the end of the exposure episode until day 91 of follow-up time (1 day of exposure from bortezomib injection + 90 days from exposure extension). Patients were not required to be enrolled during the 90-day exposure extension period. Only the first valid exposure episode per patient that occurred during the study period was included. Please see Appendix D for a pictorial display of how the exposure episodes are created.

Events of Interest: The events of interest were ALS, Alzheimer's disease, amyloidosis, dementia, FTLD, and Parkinson's disease, which were defined using ICD-9-CM diagnosis codes. Please see Appendix C for a list of codes used to define each event.

Please see Appendix E for a list of parameters used in this request.

Overview for Request ID cder_ahr_wp005_nsdp_v01
Limitations: Algorithms used to define exposures and outcomes are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind. **Notes:** Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, please refer to the documentation (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse).

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Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U).

Cohort Definition (drug/exposure)- indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the MP algorithm: (0) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1. Summary of Bortezomib Use and Events of Interest in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Event of Interest	Members who are Eligible for Cohort Inclusion	Member-Years	New Bortezomib Users	Bortezomib Injections	Average Bortezomib Injections / New User	Total Years at Risk	Total Days at Risk	Median Days at Risk	Number of Events among New Users	Number of Events / 10K Years at Risk
Amyotrophic Lateral Sclerosis										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,484.0	5,290,290	174	4	2.76
Alzheimer's Disease										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,446.9	5,276,720	172	100	69.22
Amyloidosis										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,339.4	5,237,456	171	354	246.87
Dementia										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,327.1	5,232,964	171	471	328.75
Frontotemporal Lobar Degeneration										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,484.2	5,290,341	174	5	3.45
Parkinson's Disease										
	159,753,526	429,963,003.4	24,832	449,325	18.09	14,462.9	5,282,580	173	62	42.87

Table 2a. Censoring Reasons Among Patients with Amyotrophic Lateral Sclerosis (ALS) in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Amyotrophic Lateral Sclerosis (ALS)

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,213	523	1,159	1,794	2,262	2,700	2,975	3,214	3,378	3,498	3,593	3,676	3,756
Evidence of Death	1,939	307	665	992	1,212	1,380	1,493	1,592	1,649	1,701	1,741	1,772	1,795
End of Data Partner Data	884	108	212	312	396	478	531	585	628	659	680	702	722
End of Query Period	2,331	290	605	865	1,069	1,258	1,412	1,552	1,664	1,751	1,805	1,864	1,921
End of Exposure Episode	17,476	0	0	0	2,966	5,083	7,909	10,810	12,420	13,789	14,626	15,212	15,594
Occurrence of Event	4	1	1	2	2	2	3	3	3	3	3	3	3
Number of Unique Patients Censored	24,832	978	2,122	3,200	6,944	9,745	13,051	16,368	18,262	19,843	20,846	21,579	22,095
Number of Patients Still at Risk	.	23,854	22,710	21,632	17,888	15,087	11,781	8,464	6,570	4,989	3,986	3,253	2,737
KM/Survival Probability	.	0.960615	0.914546	0.871134	0.720361	0.607563	0.474428	0.340851	0.264578	0.200910	0.160519	0.131000	0.110221

KM: Kaplan-Meier

Table 2b. Censoring Reasons Among Patients with Alzheimer's Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Alzheimer's Disease

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,204	523	1,159	1,793	2,257	2,695	2,970	3,209	3,373	3,493	3,587	3,670	3,750
Evidence of Death	1,928	307	664	985	1,204	1,371	1,484	1,581	1,638	1,690	1,730	1,761	1,784
End of Data Partner Data	883	108	212	312	396	478	531	585	628	659	680	702	722
End of Query Period	2,323	290	605	865	1,069	1,257	1,411	1,551	1,661	1,748	1,802	1,861	1,918
End of Exposure Episode	17,407	0	0	0	2,956	5,068	7,883	10,776	12,384	13,748	14,579	15,163	15,542
Occurrence of Event	100	19	31	45	56	65	74	77	79	81	82	82	84
Number of Unique Patients Censored	24,832	996	2,151	3,235	6,975	9,778	13,081	16,391	18,283	19,861	20,858	21,589	22,104
Number of Patients Still at Risk	.	23,836	22,681	21,597	17,857	15,054	11,751	8,441	6,549	4,971	3,974	3,243	2,728
KM/Survival Probability	.	0.959891	0.913378	0.869725	0.719112	0.606234	0.47322	0.3399243	0.2637323	0.2001852	0.1600354	0.1305976	0.1098582

KM: Kaplan-Meier

Table 2c. Censoring Reasons Among Patients with Amyloidosis in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Amyloidosis

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,155	518	1,150	1,780	2,241	2,674	2,945	3,183	3,344	3,459	3,553	3,634	3,711
Evidence of Death	1,900	302	656	976	1,190	1,355	1,466	1,564	1,620	1,669	1,708	1,739	1,762
End of Data Partner Data	872	108	212	312	394	474	526	580	623	653	673	694	713
End of Query Period	2,294	290	604	861	1,062	1,247	1,397	1,535	1,644	1,727	1,781	1,836	1,892
End of Exposure Episode	17,239	0	0	0	2,929	5,022	7,810	10,675	12,254	13,602	14,425	15,007	15,384
Occurrence of Event	354	121	169	206	246	286	298	310	325	331	338	339	339
Number of Unique Patients	24,832	1,089	2,273	3,372	7,106	9,913	13,185	16,476	18,347	19,903	20,897	21,622	22,130
Number of Patients Still at Risk	.	23,743	22,559	21,460	17,726	14,919	11,647	8,356	6,485	4,929	3,935	3,210	2,702
KM/Survival Probability	.	0.956145	0.908465	0.864208	0.713837	0.600797	0.469032	0.3365013	0.261155	0.1984939	0.1584649	0.1292687	0.1088112

KM: Kaplan-Meier

Table 2d. Censoring Reasons Among Patients with Dementia in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Dementia

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,127	521	1,149	1,771	2,223	2,652	2,918	3,150	3,312	3,432	3,526	3,605	3,682
Evidence of Death	1,868	304	656	964	1,174	1,336	1,442	1,534	1,590	1,641	1,680	1,711	1,734
End of Data Partner Data	873	108	211	311	393	475	528	581	623	654	675	695	715
End of Query Period	2,293	290	602	860	1,061	1,247	1,398	1,535	1,643	1,728	1,782	1,838	1,895
End of Exposure Episode	17,180	0	0	0	2,913	4,991	7,770	10,638	12,230	13,575	14,397	14,974	15,344
Occurrence of Event	471	123	198	254	302	348	380	397	407	415	423	431	434
Number of Unique Patients	24,832	1,096	2,301	3,403	7,115	9,908	13,180	16,467	18,347	19,909	20,903	21,630	22,134
Number of Patients Still at Risk	.	23,736	22,531	21,429	17,717	14,924	11,652	8,365	6,485	4,923	3,929	3,202	2,698
KM/Survival Probability	.	0.955863	0.907337	0.862959	0.713475	0.600999	0.469233	0.3368637	0.261155	0.1982523	0.1582233	0.1289465	0.1086501

KM: Kaplan-Meier

Table 2e. Censoring Reasons Among Patients with Frontotemporal Lobar Degeneration in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Frontotemporal Lobar Degeneration

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,211	523	1,159	1,793	2,261	2,699	2,974	3,212	3,376	3,496	3,591	3,674	3,754
Evidence of Death	1,939	307	665	992	1,212	1,380	1,493	1,592	1,649	1,701	1,741	1,772	1,795
End of Data Partner Data	884	108	212	312	396	478	531	585	628	659	680	702	722
End of Query Period	2,331	290	605	865	1,069	1,258	1,412	1,552	1,664	1,751	1,805	1,864	1,921
End of Exposure Episode	17,477	0	0	0	2,966	5,082	7,908	10,810	12,420	13,789	14,626	15,212	15,594
Occurrence of Event	5	1	2	4	4	4	4	5	5	5	5	5	5
Number of Unique Patients	24,832	978	2,123	3,201	6,945	9,745	13,050	16,368	18,262	19,843	20,846	21,579	22,095
Number of Patients Still at Risk	.	23,854	22,709	21,631	17,887	15,087	11,782	8,464	6,570	4,989	3,986	3,253	2,737
KM/Survival Probability	.	0.960615	0.914506	0.871094	0.720321	0.6075628	0.474468	0.3408505	0.264578	0.2009101	0.1605187	0.1310003	0.1102207

KM: Kaplan-Meier

Table 2f. Censoring Reasons Among Patients with Parkinson's Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015, by Days at Risk and Event

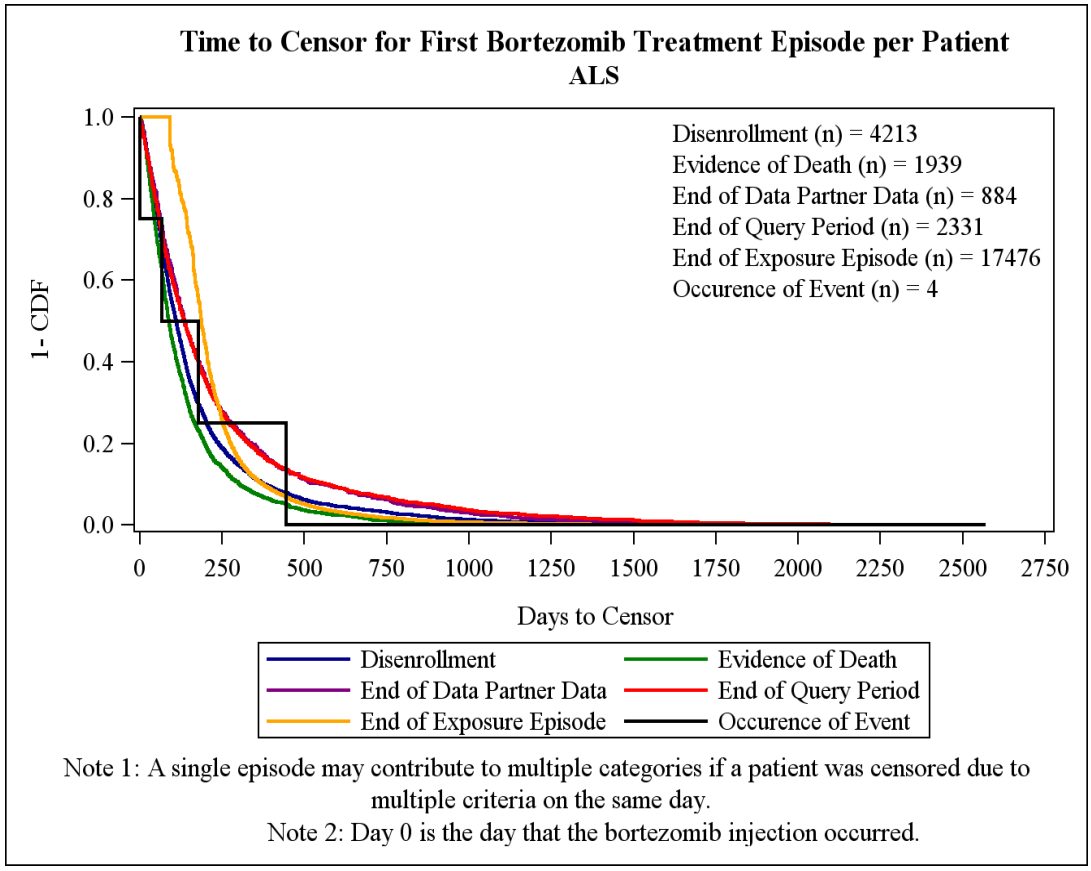
Please note that a single patient may contribute to multiple censoring categories if a patient was censored due to multiple criteria on the same day.

Patients Censored for Each Reason by Days at Risk
Parkinson's Disease

Censoring Reason	Total Number of Patients Censored	Days at Risk 30	60	90	120	150	180	210	240	270	300	330	360
Disenrollment	4,207	523	1,158	1,792	2,259	2,697	2,972	3,211	3,374	3,494	3,589	3,671	3,751
Evidence of Death	1,932	307	662	987	1,207	1,375	1,487	1,586	1,643	1,695	1,735	1,766	1,789
End of Data Partner Data	883	108	212	312	396	478	531	585	627	658	679	701	721
End of Query Period	2,327	290	605	865	1,067	1,256	1,410	1,550	1,661	1,748	1,802	1,861	1,918
End of Exposure Episode	17,433	0	0	0	2,963	5,074	7,892	10,791	12,398	13,763	14,597	15,180	15,562
Occurrence of Event	62	7	18	28	36	40	45	49	52	55	55	55	57
Number of Unique Patients	24,832	984	2,136	3,221	6,966	9,765	13,066	16,385	18,278	19,858	20,858	21,587	22,105
Number of Patients Still at Risk	.	23,848	22,696	21,611	17,866	15,067	11,766	8,447	6,554	4,974	3,974	3,245	2,727
KM/Survival Probability	.	0.960374	0.913982	0.870288	0.719475	0.606757	0.473824	0.3401659	0.2639336	0.2003061	0.1600354	0.1306782	0.109818

KM: Kaplan-Meier

Figure 1a.Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for ALS in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

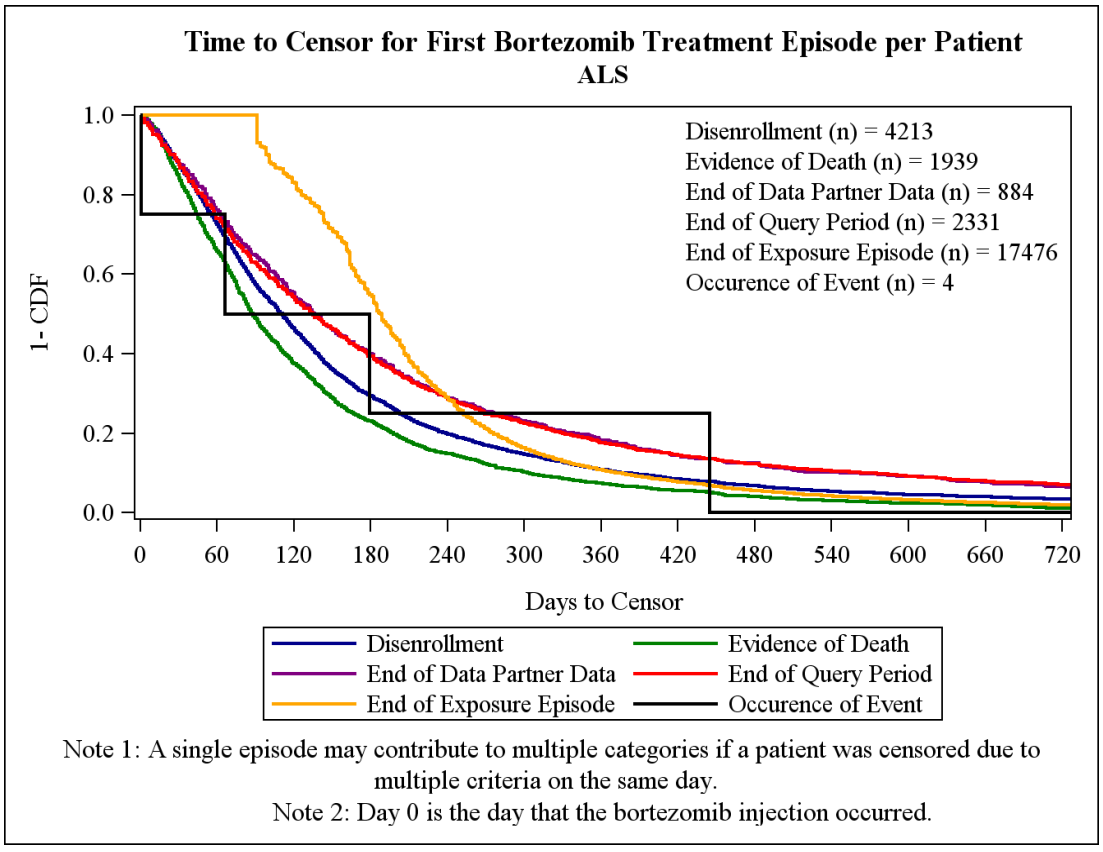


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 1b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for ALS in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

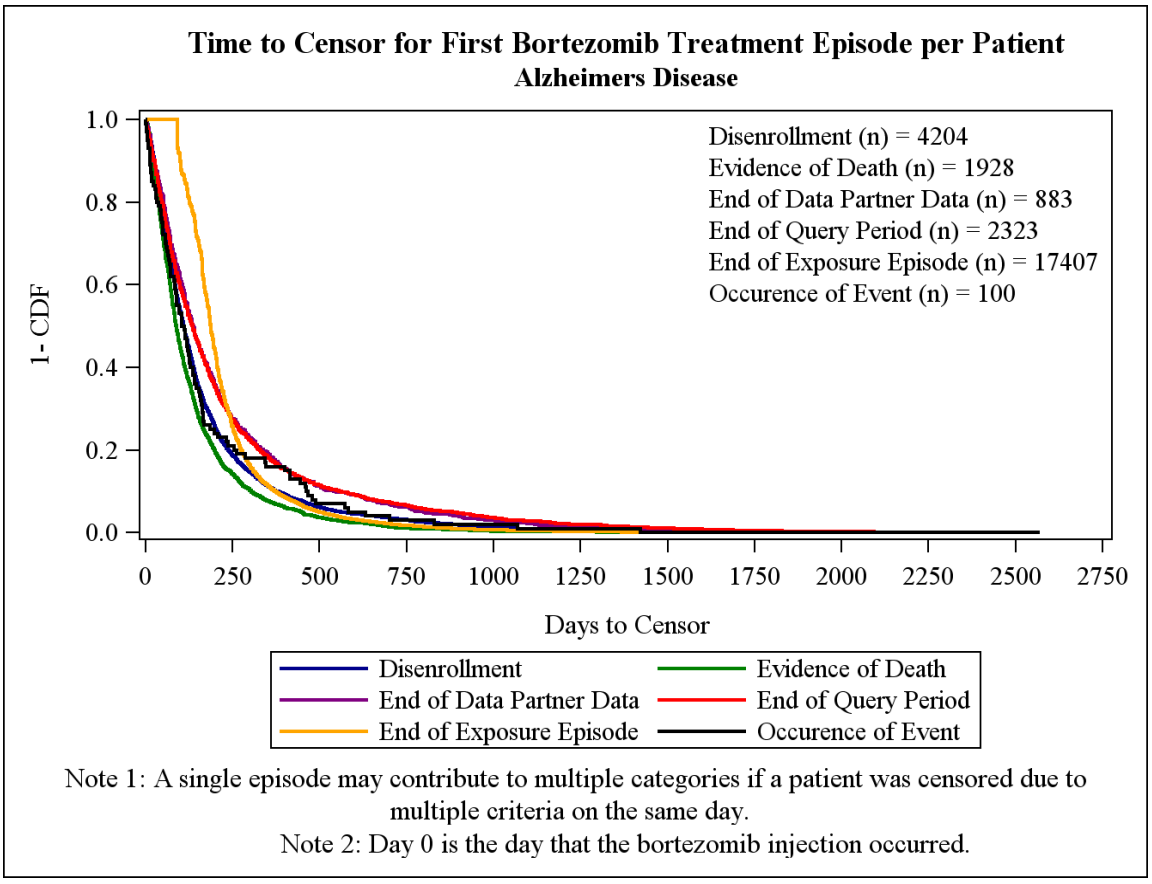
Figure 1a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 2a.Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Alzheimers Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

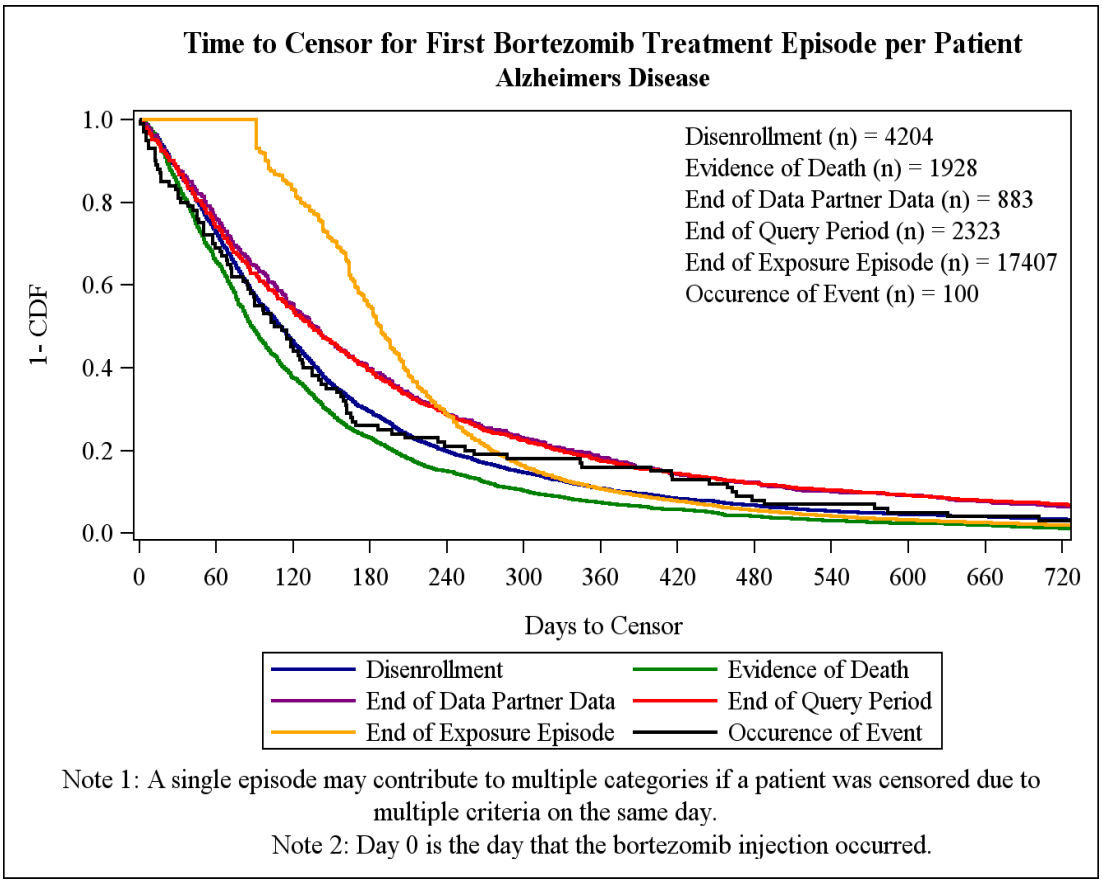


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

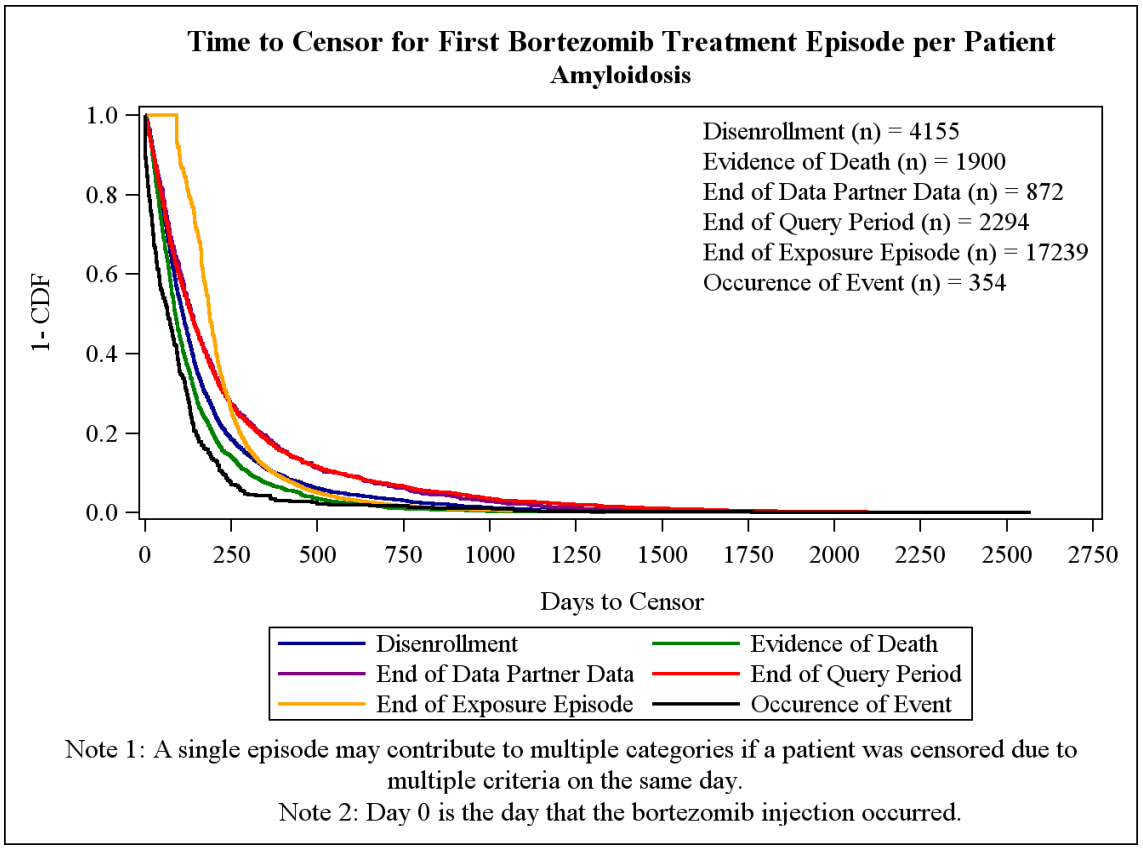
Figure 2b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Alzheimers Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 2a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.
Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 3a. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Amyloidosis in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

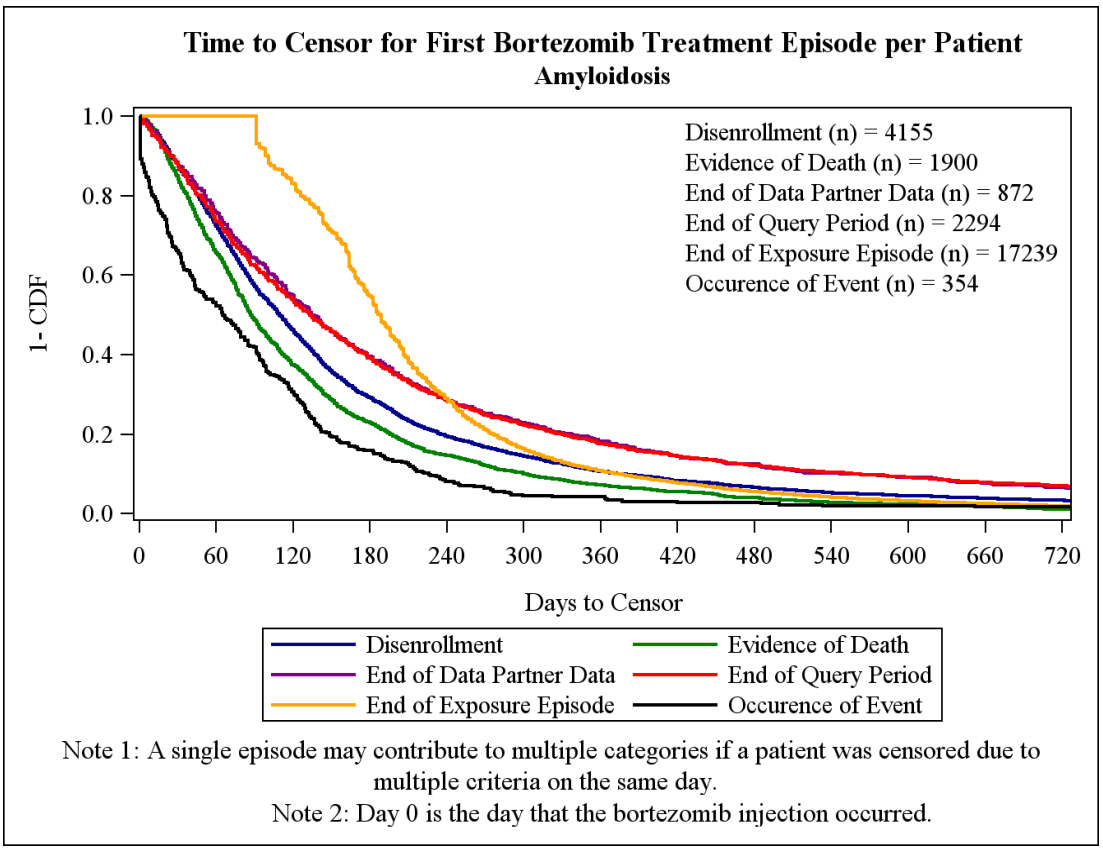


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

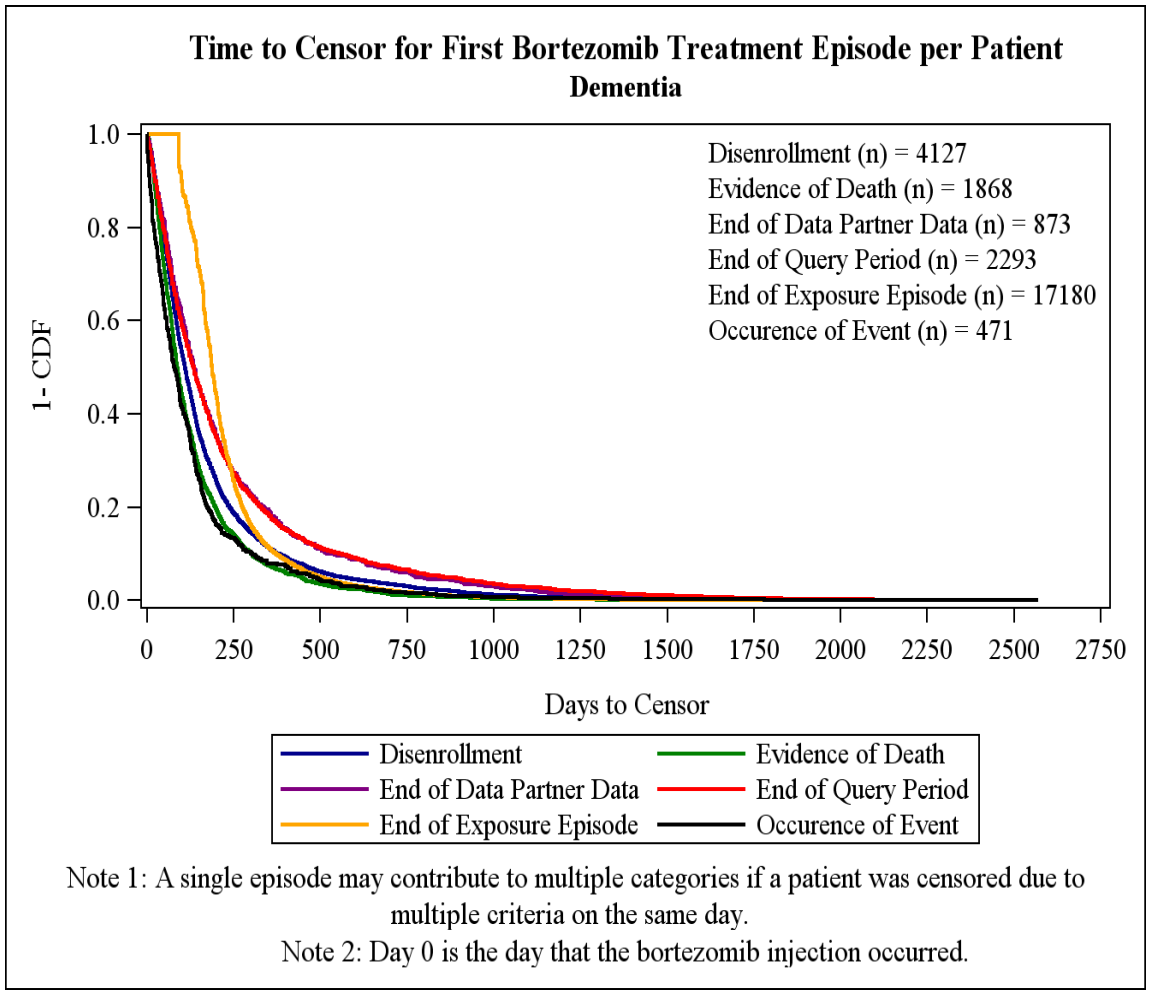
Figure 3b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Amyloidosis in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 3a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.
Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 4a. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Dementia in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

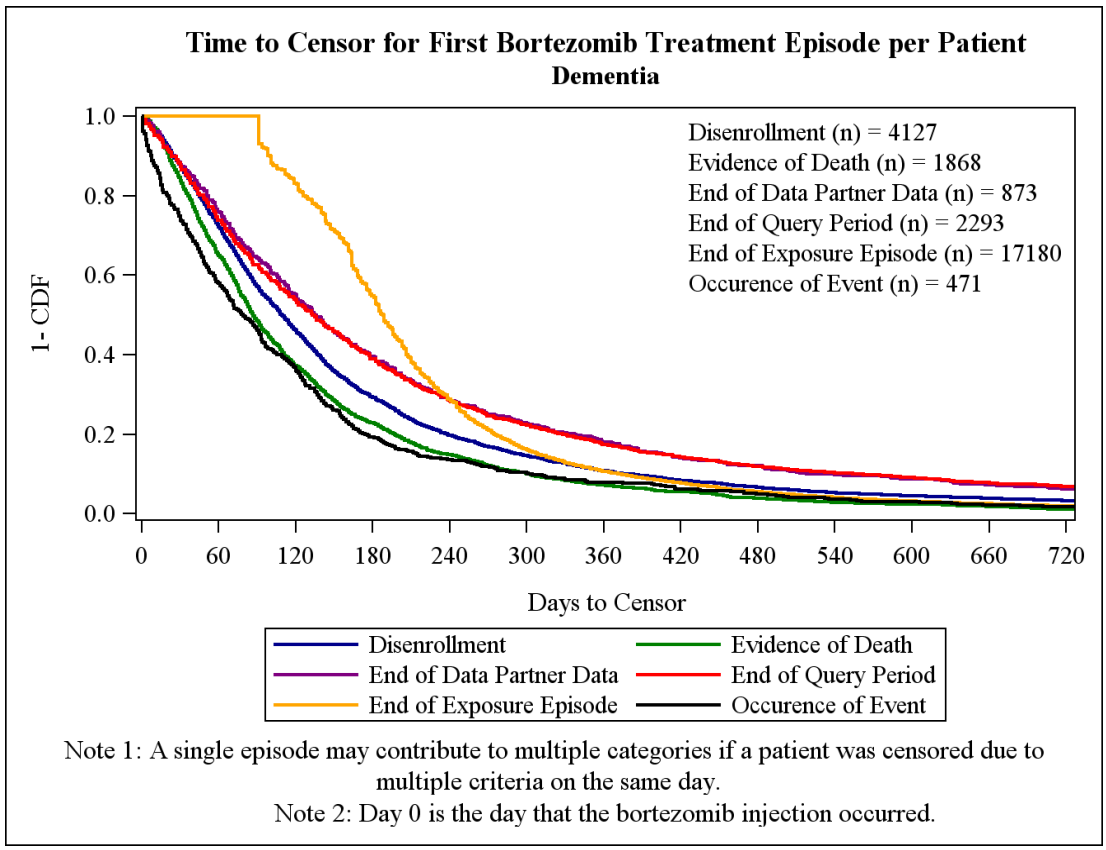


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

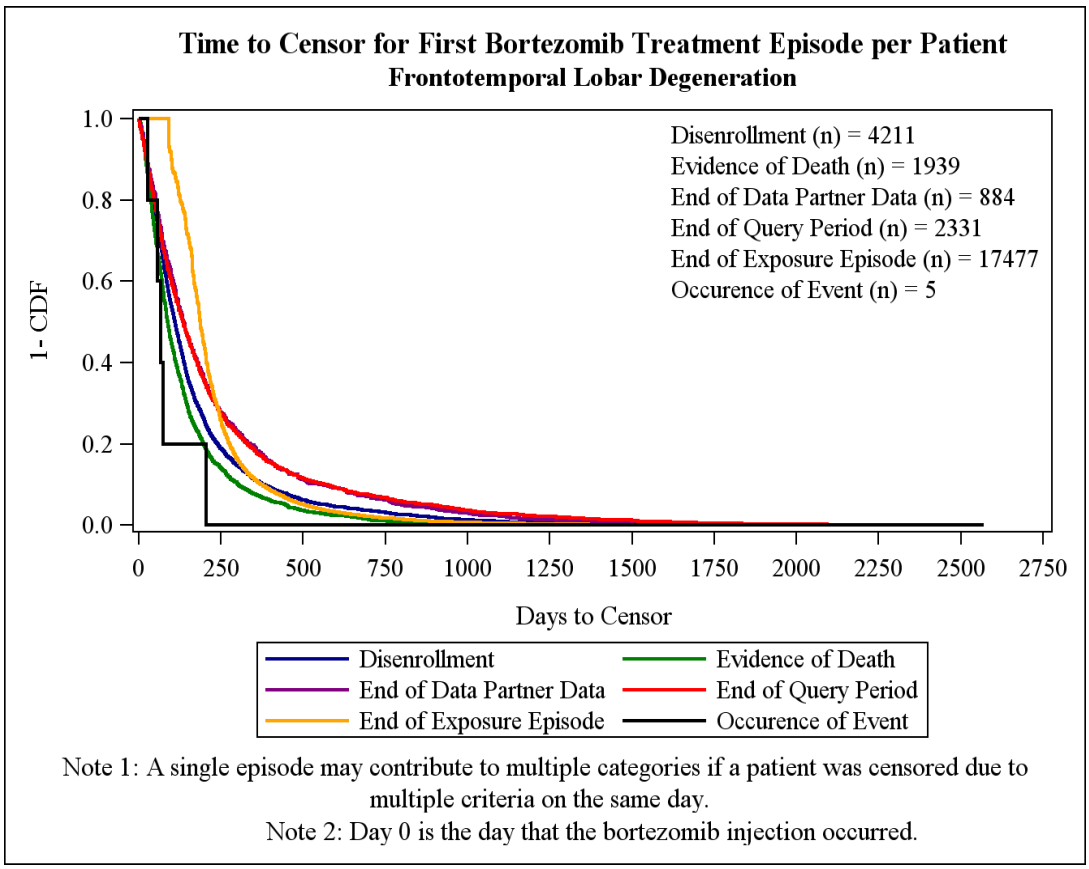
Figure 4b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Dementia in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 4a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.
Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 5a. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Frontotemporal Lobar Degeneration in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

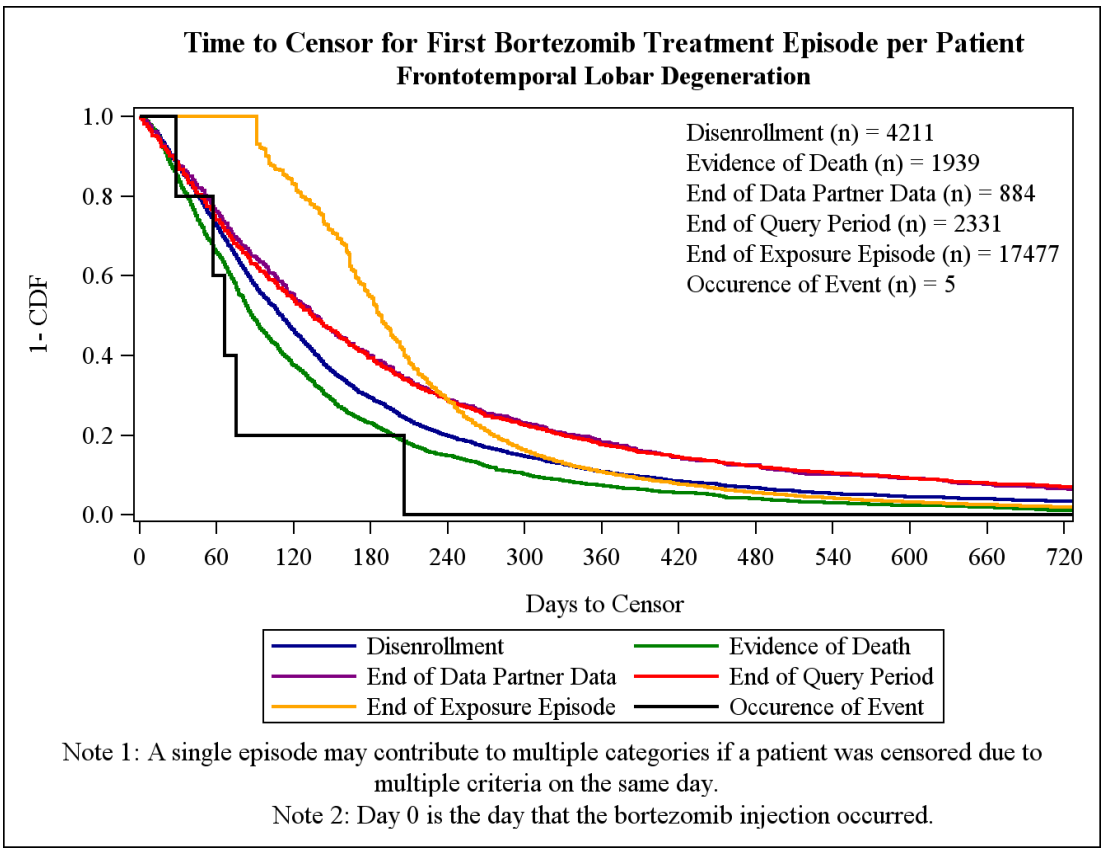


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

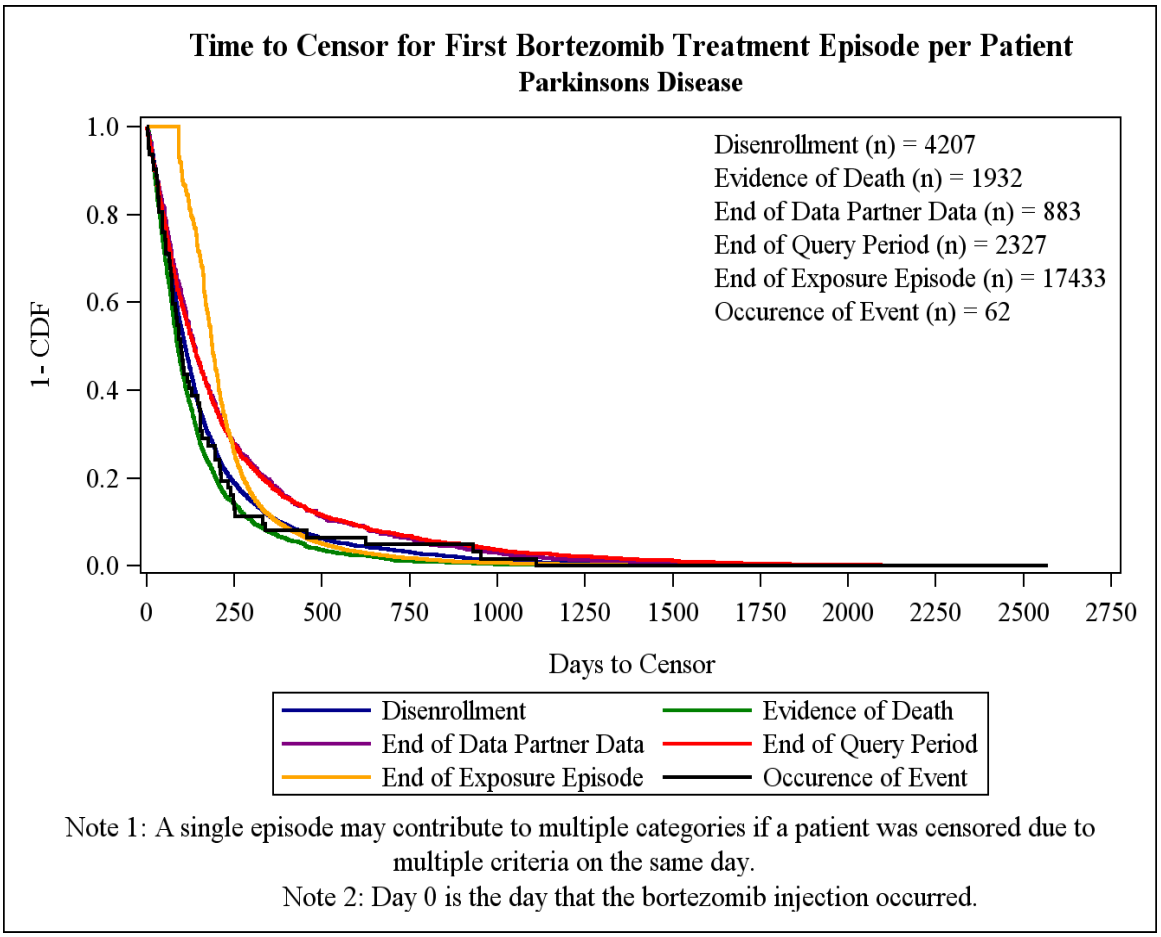
Figure 5b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Frontotemporal Lobar Degeneration in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 5a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.
Note 2: Day 0 is the day that the bortezomib injection occurred.

Figure 6a. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Parkinsons Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

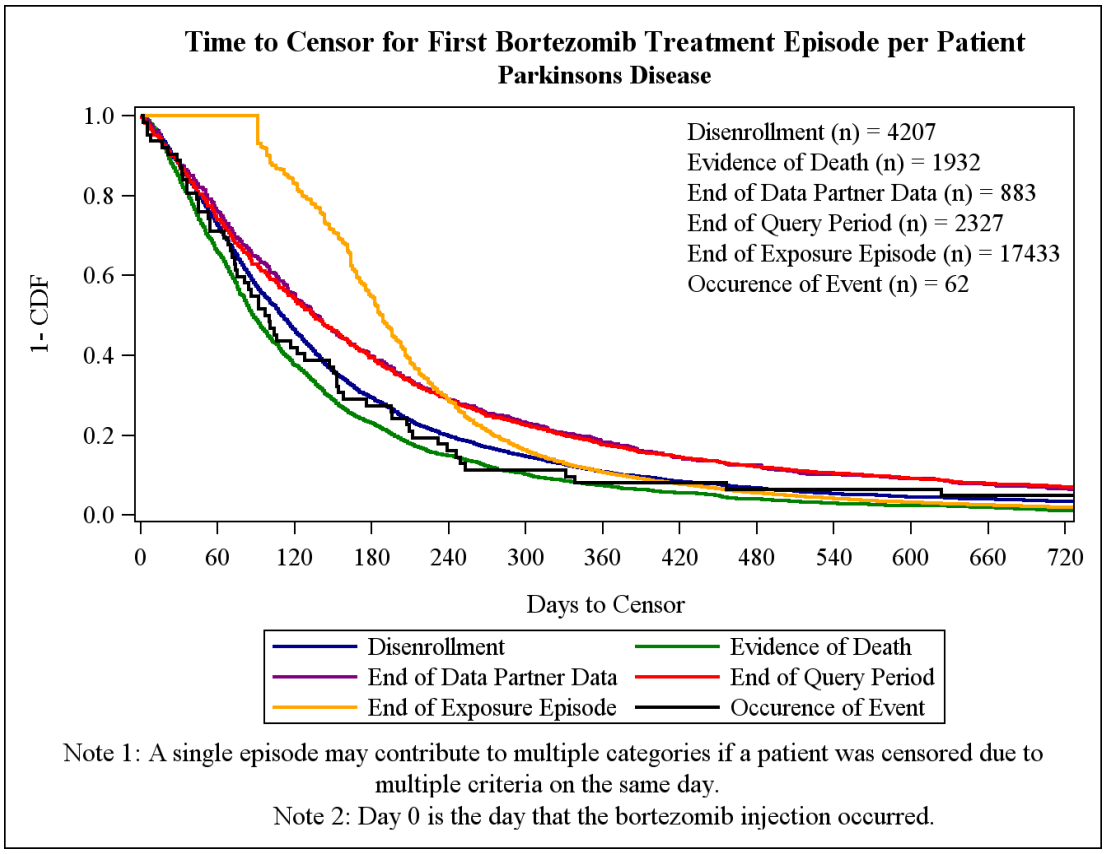


Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.

Note 2: Day 0 is the day that the bortezomib injection occurred.

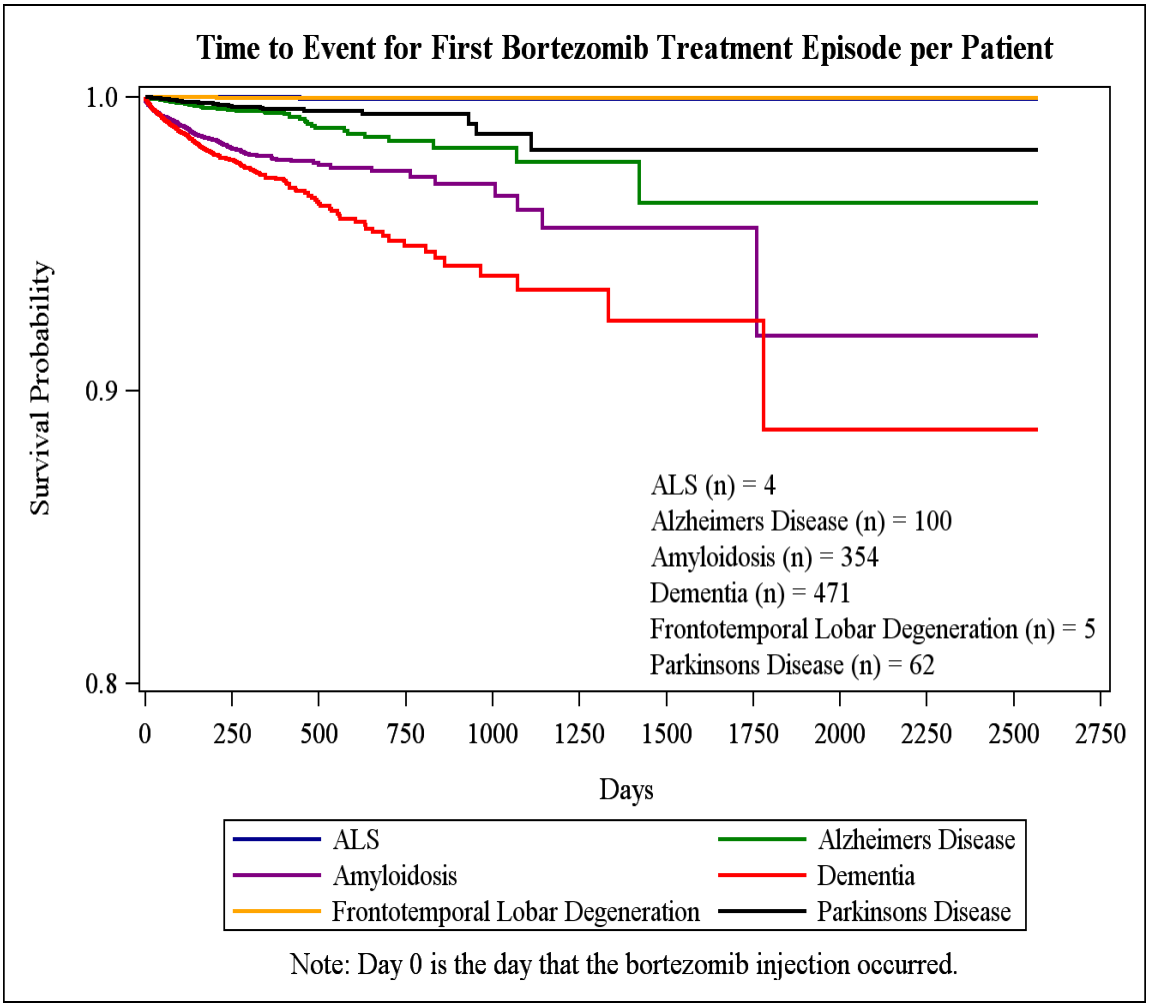
Figure 6b. Cumulative Distribution Function (CDF) Curves Depicting Time to Censor for First Bortezomib Treatment Episode per Patient for Parkinsons Disease in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 6a with Truncated X-Axis



Note 1: A single episode may contribute to multiple categories if a patient was censored due to multiple criteria on the same day.
Note 2: Day 0 is the day that the bortezomib injection occurred.

Figures 7a. Kaplan-Meier Curves Depicting Time to Event during First Bortezomib Treatment Episode per Patient in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015



Figures 7b. Kaplan-Meier Curves Depicting Time to Event during First Bortezomib Treatment Episode per Patient in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Figure 7b with Truncated X-Axis

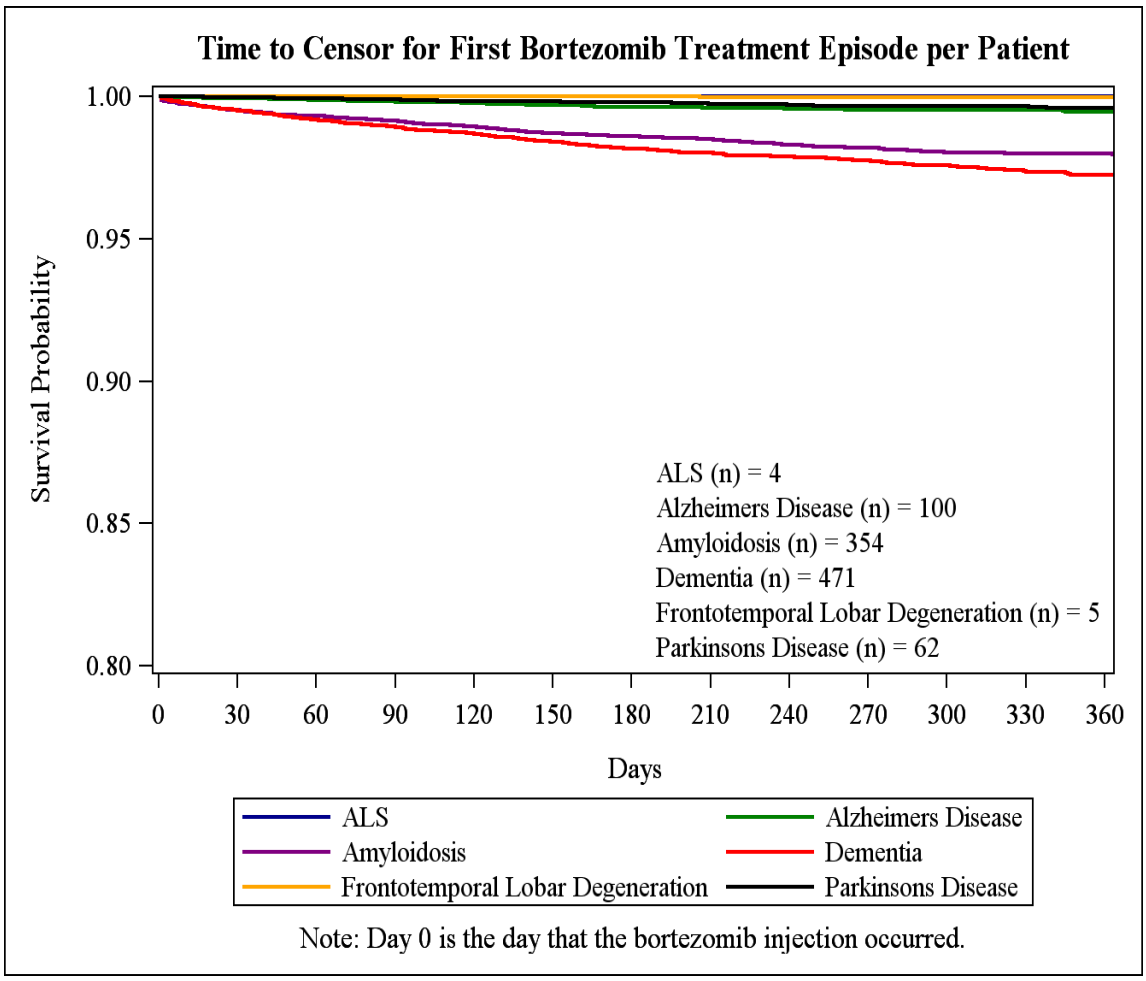


Figure 8. Kaplan-Meier Curves Depicting Time to Event during First Bortezomib Treatment Episode per Patient in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

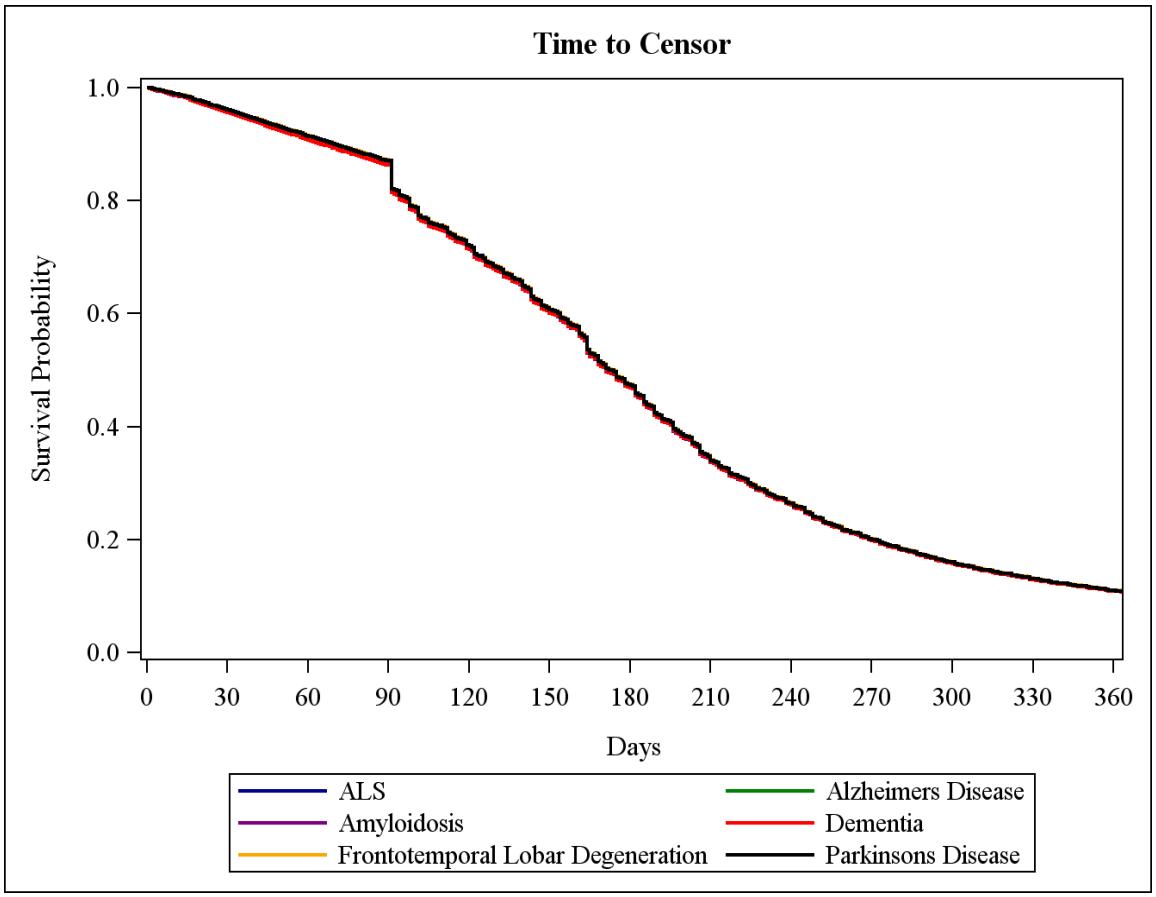


Figure 9. Kaplan-Meier Curves Depicting Time to Event during First Bortezomib Treatment Episode per Patient in the Sentinel Distributed Database (SDD) between June 1, 2008 and September 30, 2015

Survival Probability for Each Event

Event	Days at Risk											
	30	60	90	120	150	180	210	240	270	300	330	360
ALS	0.960615	0.914546	0.871134	0.720361	0.607563	0.474428	0.340851	0.264578	0.200910	0.160519	0.131000	0.110221
Alzheimer's Disease	0.959891	0.913378	0.869725	0.719112	0.606234	0.473220	0.339924	0.263732	0.200185	0.160035	0.130598	0.109858
Amyloidosis	0.956145	0.908465	0.864208	0.713837	0.600797	0.469032	0.336501	0.261155	0.198494	0.158465	0.129269	0.108811
Dementia	0.955863	0.907337	0.862959	0.713475	0.600999	0.469233	0.336864	0.261155	0.198252	0.158223	0.128947	0.108650
Frontotemporal Lobar Degeneration	0.960615	0.914506	0.871094	0.720321	0.607563	0.474468	0.340851	0.264578	0.200910	0.160519	0.131000	0.110221
Parkinson's Disease	0.960374	0.913982	0.870288	0.719475	0.606757	0.473824	0.340166	0.263934	0.200306	0.160035	0.130678	0.109818

Appendix A: Latest Date of Available Data for Each Data Partner (DP) Until Request End Date (September 30, 2015)

DP ID	Start Date	End Date[1]
DP001	1/1/2008	9/30/2015
DP002	1/1/2012	6/30/2015
DP003	1/1/2006	4/30/2015
DP004	1/1/2004	10/31/2014
DP005	1/1/2000	6/30/2015
DP006	1/1/2000	2/28/2015
DP007	1/2/2000	7/31/2014
DP008	1/2/2000	6/30/2012
DP009	6/1/2007	7/31/2015
DP010	1/1/2000	10/31/2015
DP011	1/1/2000	11/30/2015
DP012	1/1/2005	9/30/2015
DP013	1/1/2000	12/31/2014
DP014	1/1/2000	11/30/2015
DP015	1/1/2008	6/30/2015
DP016	1/1/2000	12/31/2014

[1]End date represents the earliest of: (1) query end date, or (2) last day of the most recent month for which all of a Data Partner's data tables (enrollment, dispensing, etc.) have at least 80% of the record count relative to the prior month

Appendix B: List of Healthcare Common Procedure Coding System (HCPCS) Procedure Codes Used to Define Bortezomib Use

Code	Description	Code Category	Code Type
J9041	Injection, bortezomib, 0.1 mg	Procedure	HCPCS
S0115	Bortezomib, 3.5 mg	Procedure	HCPCS

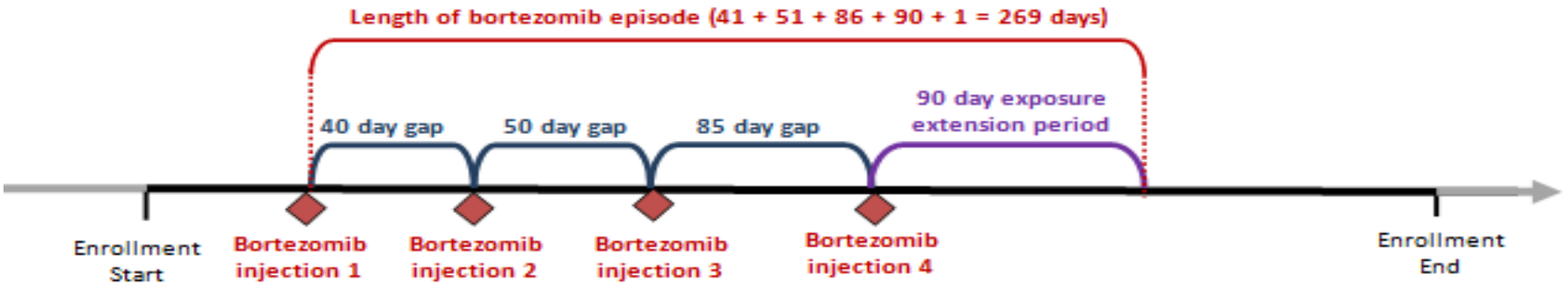
Appendix C: List of International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) Diagnosis Codes Used to Define Events

Code	Description	Code Category	Code Type
	Amyotrophic Lateral Sclerosis		
335.20	Amyotrophic lateral sclerosis	Diagnosis	ICD-9-CM
	Alzheimer's Disease		
331.0	Alzheimer's disease	Diagnosis	ICD-9-CM
	Parkinson's Disease		
332	Parkinson's disease	Diagnosis	ICD-9-CM
332.0	Paralysis agitans	Diagnosis	ICD-9-CM
332.1	Secondary Parkinsonism	Diagnosis	ICD-9-CM
	Frontotemporal Lobar Degeneration		
331.1	Frontotemporal dementia	Diagnosis	ICD-9-CM
331.19	Other frontotemporal dementia	Diagnosis	ICD-9-CM
	Amyloidosis		
277.3	Amyloidosis	Diagnosis	ICD-9-CM
277.39	Other amyloidosis	Diagnosis	ICD-9-CM
277.30	Amyloidosis, unspecified	Diagnosis	ICD-9-CM
	Dementia		
290	Dementias	Diagnosis	ICD-9-CM
290.0	Senile dementia, uncomplicated	Diagnosis	ICD-9-CM
290.1	Presenile dementia	Diagnosis	ICD-9-CM
290.10	Presenile dementia, uncomplicated	Diagnosis	ICD-9-CM
290.11	Presenile dementia with delirium	Diagnosis	ICD-9-CM
290.12	Presenile dementia with delusional features	Diagnosis	ICD-9-CM
290.13	Presenile dementia with depressive features	Diagnosis	ICD-9-CM
290.2	Senile dementia with delusional or depressive features	Diagnosis	ICD-9-CM
290.20	Senile dementia with delusional features	Diagnosis	ICD-9-CM
290.21	Senile dementia with depressive features	Diagnosis	ICD-9-CM
290.3	Senile dementia with delirium	Diagnosis	ICD-9-CM
290.4	Vascular dementia	Diagnosis	ICD-9-CM
290.40	Vascular dementia, uncomplicated	Diagnosis	ICD-9-CM
290.41	Vascular dementia, with delirium	Diagnosis	ICD-9-CM
290.42	Vascular dementia, with delusions	Diagnosis	ICD-9-CM
290.43	Vascular dementia, with depressed mood	Diagnosis	ICD-9-CM
	Dementia		
291.2	Alcohol-induced persisting dementia	Diagnosis	ICD-9-CM
292.82	Drug-induced persisting dementia	Diagnosis	ICD-9-CM
294.1	Dementia in conditions classified elsewhere	Diagnosis	ICD-9-CM
294.10	Dementia in conditions classified elsewhere without behavioral disturbance	Diagnosis	ICD-9-CM
294.11	Dementia in conditions classified elsewhere with behavioral disturbance	Diagnosis	ICD-9-CM
294.2	Dementia, unspecified	Diagnosis	ICD-9-CM
294.20	Dementia, unspecified, without behavioral disturbance	Diagnosis	ICD-9-CM
294.21	Dementia, unspecified, with behavioral disturbance	Diagnosis	ICD-9-CM
331.0	Alzheimer's disease	Diagnosis	ICD-9-CM

Appendix C: List of International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) Diagnosis Codes Used to Define Events

Code	Description	Code Category	Code Type
331.1	Frontotemporal dementia	Diagnosis	ICD-9-CM
331.11	Pick's disease	Diagnosis	ICD-9-CM
331.19	Other frontotemporal dementia	Diagnosis	ICD-9-CM
331.2	Senile degeneration of brain	Diagnosis	ICD-9-CM
331.82	Dementia with Lewy bodies	Diagnosis	ICD-9-CM
046.1	Jakob-Creutzfeldt disease	Diagnosis	ICD-9-CM

Appendix D: Design Diagram of Exposure Episodes



Multiple exposure episodes were bridged into one exposure episode if they occurred within 90 days of each other. An exposure extension period of 90 days was added onto the end of each exposure episode length after the gaps were bridged. By definition of the exposure episode, it was not possible for patients to be censored due to the end of the exposure episode until day 91 of follow-up time (1 day of exposure from bortezomib injection + 90 days from exposure extension). Patients were not required to be enrolled during the 90-day exposure extension period. Only the first valid exposure episode per patient that occurred during the study period was included.

Appendix E: Specifications Defining Parameters for this Request

The Center for Drug Evaluation and Research (CDER) has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) tool (version 3.0.3) to investigate the rate of six outcomes during bortezomib use. Additionally, CDER has requested the development of a Rapid Analytic Development and Response (RADaR) module, which investigates censoring among bortezomib users and creates associated cumulative distribution function (CDF) and Kaplan-Meier curves.

Query Period: June 1, 2008 - September 30, 2015
Coverage Requirement: Medical coverage
Enrollment Requirement: 183 days
Enrollment Gap: 45 days

	Exposure							
Scenario	**Exposure**	**Care Setting**	**Incident with Respect to**	**Washout**	**Episode Gap**	**Exposure Extension Period**	**Censor Due to Evidence of Death**	**Cohort Definition**
1	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period
2	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period
3	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period
4	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period

Appendix E: Specifications Defining Parameters for this Request								
5	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period
6	Bortezomib	Inpatient or outpatient	Bortezomib	183 days	90 days	90 days	Yes	Include the first valid incident treatment episode during query period
Note: International Classification on Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and Healthcare Common Procedure Coding System (HCPCS) codes are provided by Optum360.								

Appendix E: Specifications Defining Parameters for this Request

		Exclusion Criteria				Outcome			
Scenario	Exposure	Exclusions	Care Setting/ PDX	Lookback Start	Lookback End	Outcome	Care Setting/ PDX	Incident with Respect to	Washout
1	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	ALS	Any care setting	N/A	0 days
2	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	Alzheimer's disease	Any care setting	N/A	0 days
3	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	Amyloidosis	Any care setting	N/A	0 days
4	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	Dementia	Any care setting	N/A	0 days
5	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	Frontotemporal lobar degeneration	Any care setting	N/A	0 days
6	Bortezomib	ALS, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyloidosis	Any care setting	-183	-1	Parkinson's disease	Any care setting	N/A	0 days

Note: International Classification on Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and Healthcare Common Procedure Coding System (HCPCS) codes are provided by Optum360.

N/A: Not applicable