Adverse Events Associated With the Use of Sipuleucel-T Reported to the US Food and Drug Administration’s Adverse Event Reporting System, 2010-2017

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Abstract

IMPORTANCE Sipuleucel-T was the first therapeutic cancer vaccine approved by the US Food and Drug Administration (FDA) in 2010. Although almost a decade has passed since its approval for the treatment of asymptomatic or minimally symptomatic castration-resistant prostate cancer (CRPC), there remains a paucity of literature describing safety data in the postmarketing period.

OBJECTIVE To describe the postmarketing safety experience for sipuleucel-T.

DESIGN, SETTING, AND PARTICIPANTS In this case series study, US reports for sipuleucel-T submitted to the FDA's Adverse Event Reporting System were searched and reviewed between April 29, 2010, and December 31, 2017. This system is a spontaneous safety surveillance database for drug and therapeutic biologic products. The analysis of 3216 reports and select case reviews were undertaken between February and November 2018.

MAIN OUTCOMES AND MEASURES Descriptive statistics were used to assess adverse event reports for sipuleucel-T. Empirical Bayes Geometric Means (EBGM) and their 90% confidence intervals (CIs) were computed to identify disproportionate (ie, at least twice the expected) reporting of sipuleucel-T–event pairs. Selected adverse events and death reports were individually reviewed.

RESULTS In total, 3216 reports were identified for sipuleucel-T, of which 2014 (62.6%) were serious. For all included reports, the patients' median (interquartile range) age was 73 (67-79) years, and 3149 were specified to be males. Chills (n = 318), malaise (n = 196), pyrexia (n = 189), culture positive (n = 184), fatigue (n = 180), and nausea (n = 173) were among the most commonly reported adverse events. Infusion-related reactions (EBGM, 12.1; 90% CI, 9.4-15.3), infections, vascular events, and transient ischemic attacks (EBGM, 2.9; 90% CI, 2.2-3.9) were reported disproportionately. Among 249 deaths for which relevant dates were available, 128 (51.4%) were reported within 30 days of a sipuleucel-T infusion, of which 81.2% included a specified cause of death; of these 104 deaths, there were 37 neoplasms (35.6%), 25 cardiac disorders (24.0%), 18 nervous system disorders (17.3%), and 9 infections (8.7%).

CONCLUSIONS AND RELEVANCE Reported adverse events were generally consistent with the safety experience observed in prelicensure studies and described in the sipuleucel-T package insert. Off-label use among overtly symptomatic men with CRPC, reporting bias, or lack of product effectiveness may have influenced the reporting of deaths within 30 days of treatment initiation. With this overview of sipuleucel-T experience, the present study serves as a resource for health care professionals and patients as they weigh the risks and benefits of treatment in the context of all available therapeutic options for CRPC.

Key Points

Question What is the postmarketing safety profile of sipuleucel-T in the United States?

Findings The US Food and Drug Administration’s Adverse Event Reporting System received 3216 reports for sipuleucel-T from 2010 through 2017. This case series study identified disproportionate reporting for infusion-associated reactions, infections, certain thromboembolic events, and transient ischemic attacks.

Meaning The spectrum of adverse events reported for sipuleucel-T was consistent with the safety experience described in clinical studies and the package insert, and no new safety concerns were identified.

+ Invited Commentary

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Introduction

Sipuleucel-T (Provenge), an autologous active cellular immunotherapy, was the first therapeutic cancer vaccine approved by the US Food and Drug Administration (FDA) (April 29, 2010) for the treatment of asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer (CRPC). The safety database leading to product approval included 904 patients (601 patients treated with sipuleucel-T; 303 controls) from 4 randomized, placebo-controlled clinical trials.\textsuperscript{1,2} The most common adverse events (AEs) among patients treated with sipuleucel-T were chills, fatigue, fever, back pain, nausea, arthralgia, and headache. Serious AEs occurred in 24% of treated men and 25% of controls.\textsuperscript{1} However, an imbalance in the occurrence of cerebrovascular events (3.5% of patients treated with sipuleucel-T vs 2.6% of controls) led the US FDA to require the sponsor to conduct the observational phase IV study Provenge Registry for Observation, Collection, and Evaluation of Experience Data (PROCEED) to further quantify the risk of cerebrovascular events, including hemorrhagic/ischemic strokes and transient ischemic attacks (TIAs), following sipuleucel-T therapy.\textsuperscript{3} The trial\textsuperscript{4} was closed to patient accrual, and the results published in the peer-reviewed literature are awaited.

As of 2019, 30 000 men have been prescribed sipuleucel-T.\textsuperscript{5} With few exceptions, including 1 institutional retrospective review (36 patients treated with sipuleucel-T) and a clinical trial of androgen-dependent prostate cancer (117 patients treated with sipuleucel-T),\textsuperscript{6,7} most of the safety information in the literature\textsuperscript{8-11} is limited to review articles that refer to the clinical trials originally submitted in support of product approval.\textsuperscript{12-14} We sought to summarize the safety experience of sipuleucel-T in the postmarketing period by assessing US reports submitted to the FDA's Adverse Event Reporting System (FAERS).

Methods

FAERS Database

We used the FAERS database to assess AEs reported for sipuleucel-T; FAERS is a spontaneous, passive surveillance system designed for health care professionals, pharmaceutical companies, and consumers to report AEs, medication errors, and product quality matters associated with drugs and biologic products.\textsuperscript{15} The database includes information on patient demographics, medical history, concomitant medications, description and outcome of the AE, and source of the report. All AEs are coded according to the international Medical Dictionary for Regulatory Activities.\textsuperscript{16,17} These coded terms are arranged in a hierarchy of 5 categories that include broad (system organ class [SOC]) and specific categories (eg, preferred term [PT]). A PT can describe signs or symptoms, a diagnosis, an indication for treatment, laboratory tests, procedures, and aspects of medical, social, or family history.\textsuperscript{16} A single FAERS report is assigned 1 or more PTs and the corresponding SOC(s) for each PT. Each PT is considered independently of any other. A report is considered serious when the patient outcome results in death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability, or birth defect.\textsuperscript{18} The FAERS reports are submitted as expedited (15-day) reports (reports for both serious and unexpected [unlabeled] AEs required to be submitted by industry to the US FDA within 15 days of receipt), direct reports (any report submitted directly to the US FDA from outside of industry, eg, health care professionals or consumers), or nonexpedited (periodic) reports (reports for serious labeled events and nonserious events) submitted by industry to the US FDA on a regular basis. This safety review was exempt from institutional review board approval or informed patient consent because it met the criteria for exemption from the Office for Protection From Research Risks, as specified under Department of Health and Human Services regulations.\textsuperscript{19} This report followed the reporting guideline for case series.
Eligibility Criteria
We searched US reports submitted to FAERS between April 29, 2010, and December 31, 2017, with sipuleucel-T included as a suspect product. A suspect product is a drug or biologic considered by the reporter to be associated with the reported AE. We excluded 2 reports involving females and 8 duplicate or invalid reports encountered during the manual case review.

Statistical Analysis
Descriptive Analyses
We separately assessed all reports (serious and nonserious) and serious reports only. Overall frequencies and stratified analyses by seriousness were undertaken using Stata/IC 13.1 (StataCorp LLC). Case review and analyses were conducted between February and November 2018.

Data Mining (Disproportionality Analyses)
We used the Multi-Item Gamma Poisson Shrinker algorithm in the Oracle Empirica Signal system to conduct empirical Bayes data mining to assess disproportionality in AE reporting for sipuleucel-T compared with all other therapeutic biologics and drugs in the FAERS database.20-22 The analyses (data lock point, February 2, 2018) were adjusted for age group (≤1, 2-4, 5-12, 13-16, 17-29, 30-45, 46-64, 65-75, 76-85, and ≥86 years and unknown age) and calendar year in which the report was received at the US FDA. The main statistical scores computed were the empirical Bayes Geometric Mean (EBGM) and the 90% confidence interval (EB05, EB95). An elevated data mining statistic should be interpreted as a potential signal for further evaluation.21,23 The EBGM does not reflect the magnitude of association between sipuleucel-T and an AE but provides an estimate of the relative reporting of an event for sipuleucel-T relative to all other drugs and events in the FAERS database. An EB05 of 2.0 or higher is commonly used by the US FDA as a criterion for considering an AE a potential signal because such a value suggests a high probability of the product-event pair occurring at least twice as often as expected under the assumption that product-events are randomly paired.21 The analysis performed in Empirica relies on the most recent follow-up report for a given case and on a duplicate detection algorithm (the most recent follow-up serves to represent the group). Therefore, the number of reports in the FAERS database may differ slightly from those available for data mining analyses.

Case Reviews
On the basis of findings from data mining analyses and premarketing experience, we reviewed reports for selected AEs, including, but not limited to, thromboembolic and vascular events such as deep vein thrombosis (DVT), pulmonary embolism (PE), TIA, stroke, and myocardial infarction (MI).24 We also reviewed all death reports (n = 314) to identify the stated cause of death; when this information was not available, we assigned a cause of death if apparent in the case history. We calculated time to death from the date of last sipuleucel-T infusion. For cases with missing day of infusion or death, we imputed the day as 15. If only the calendar year was available, we imputed the month as June; if partial information was available, we used the month midway between the known month of infusion (or death), using the earliest possible month for the unknown month of infusion or latest possible month for the unknown month of death. Overall, we imputed dates on 39 death reports (12.4% of all death reports).

Results
We identified a total of 3216 reports following sipuleucel-T administration, of which 2014 (62.6%) were serious (Table 1). The median (interquartile range [IQR]) patient age was 73 (67-79) years, and 3149 patients were specified to be males. Most reports were submitted by physicians or other health care professionals; some reports involved patients enrolled in clinical trials or in the postmarketing PROCEED study.1,4
Of 3216 reports, 9800 PTs were included. The most frequently reported PTs included chills (n = 318), malaise (n = 196), pyrexia (n = 189), culture positive (n = 184), fatigue (n = 180), and nausea (n = 173) (Table 2). Except for culture positive, these PTs were also frequent among serious reports in addition to disease progression (potentially confounded by the indication for therapy) and asthenia.

### Data Mining (Disproportionality Analyses)

Sipuleucel-T–event pairs reported at least twice as often as expected (EB05 ≥ 2.0) are provided in Table 3. We observed disproportionate reporting for labeled PTs, including vomiting (EBGM, 2.7; 90% CI, 2.4-3.1), chills (EBGM, 15.8; 90% CI, 14.4-17.3), pyrexia (EBGM, 4.5; 90% CI, 4.0-5.1), culture pos...

### Table 1. Description of US Reports Submitted to the US FDA Adverse Event Reporting System for Sipuleucel-T Between April 29, 2010, and December 31, 2017

| Report Type | No. (%) | All Reports | Serious Reports Only |
|-------------|---------|-------------|----------------------|
| Total       | 3216 (100) | 2014 (100) |
| Sex         |         |             |                      |
| Male        | 3149 (97.9) | 1952 (96.9) |
| Not specified | 67 (2.1) | 62 (3.1) |
| Age, y      |         |             |                      |
| <50         | 12 (0.4) | 4 (0.2) |
| 50-64       | 448 (13.9) | 286 (14.2) |
| 65-74       | 1065 (33.1) | 696 (34.5) |
| 75-84       | 860 (26.7) | 582 (28.9) |
| ≥85         | 249 (7.7) | 174 (8.6) |
| Not specified | 582 (18.1) | 272 (13.5) |
| Received at FDA, calendar year | | |
| 2010        | 44 (1.4) | 44 (2.2) |
| 2011        | 203 (6.3) | 199 (9.9) |
| 2012        | 317 (9.9) | 309 (15.3) |
| 2013        | 599 (18.6) | 390 (19.4) |
| 2014        | 261 (8.1) | 254 (12.6) |
| 2015        | 294 (9.1) | 279 (13.9) |
| 2016        | 665 (20.7) | 256 (12.7) |
| 2017        | 833 (25.9) | 283 (14.1) |
| Source of report | | |
| Health professional | 1426 (44.3) | 920 (45.7) |
| Physician | 1077 (33.5) | 712 (35.4) |
| Consumer/other specified | 547 (17.0) | 276 (13.7) |
| Registered nurse | 101 (3.1) | 72 (3.6) |
| Pharmacist | 43 (1.3) | 24 (1.2) |
| Not specified | 22 (0.7) | 10 (0.5) |
| Type of report | | |
| Expedited, 15 d | 1586 (49.3) | 1573 (78.1) |
| Not expedited | 1601 (49.8) | 412 (20.5) |
| Direct | 29 (0.9) | 29 (1.4) |
| Reported outcome, serious reports | | |
| Death | 314 (9.8) | 314 (15.6) |
| Nonfatal: hospitalization, disability, life-threatening, or required intervention | 1099 (34.2) | 1099 (54.6) |
| Nonfatal: other serious outcomes* | 600 (18.7) | 600 (29.8) |
| Not specified | 1 (<0.1) | 1 (<0.1) |
| Not applicableb | 1202 (37.4) | 0 |

Abbreviation: FDA, Food and Drug Administration.

* Defined as important medical events based on appropriate medical judgment that may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the other specified outcomes.

b Refers to nonserious reports. Reports that do not meet criteria for seriousness as defined in the Code of Federal Regulations (ie, death, hospitalization, life-threatening, disability, congenital anomaly, required intervention, or other serious outcome) are considered nonserious.
positive (EBGM, 157.1; 90% CI, 138.8-177.4), infusion-related reaction (EBGM, 12.1; 90% CI, 9.4-15.3), and citrate toxicity (EBGM, 153.1; 90% CI, 99.1-228.1). We also identified anemia (EBGM, 3.0; 90% CI, 2.6-3.5), infections (eg, sepsis [EBGM, 2.8; 90% CI, 2.3-3.4], bacteremia [EBGM, 7.6; 90% CI, 5.2-11.6]), device-associated infections (eg, device-related infection [EBGM, 29.9; 90% CI, 25.5-34.8] and device-related sepsis [EBGM, 48.9; 90% CI, 33.2-69.9]), and urinary tract infection (EBGM, 3.8; 90% CI, 3.2-4.5)), presyncope (EBGM, 3.6; 90% CI, 2.5-5.1), blood pressure decrease (EBGM, 3.6; 90% CI, 2.8-4.5), tachycardia (EBGM, 4.8; 90% CI, 3.7-6.1), unresponsive to stimuli (EBGM, 3.3; 90% CI, 2.4-4.5), and thromboembolic events (eg, PE [EBGM, 3.1; 90% CI, 2.4-3.8], thrombosis in device [EBGM, 27.7; 90% CI, 19.3-38.7], DVT [EBGM, 3.2; 90% CI, 2.6-4.0], and jugular vein thrombosis [EBGM, 16.9; 90% CI, 4.1-45.0]) as reported disproportionately.

We observed disproportionate reporting for local infusion site signs and symptoms, including extravasation, hematoma, swelling, and reaction when all (serious and nonserious) reports were considered. This pattern was similarly observed for TIA, tremor, oral paresthesia (the latter likely reflecting citrate toxicity associated with leukapheresis), and product- or device-associated AEs, such as microbial product contamination, device occlusion, catheter site pain, catheter site infection, and complication associated with device. In addition, the data mining analyses detected disproportionate reporting for AEs not described in the US package insert (USPI), including leukocytosis, malaise, systemic inflammatory response syndrome (SIRS), abnormal mononuclear cell count, dehydration, hyponatremia, hypokalemia, malnutrition, hypovolemia, atelectasis, and pallor.

**Case Review**

**Death Reports**

Of 314 reported deaths, the median (IQR) age of patients was 74 (68-81) years. Most deaths occurred in the age groups of 65 to 74 years (106 patients [33.8%]) and 75 to 84 years (95 patients [30.3%]) (Table 4). There were 249 reports (79%) for which the time interval from last sipuleucel-T infusion and death was available or could be imputed (39 [12.4%]). More than half the deaths (128 [51.4%]) occurred within 30 days of a sipuleucel-T infusion, an additional 59 deaths (23.7%) between 31 and 90 days, and 42 deaths (16.9%) after 180 days (Table 4). Similar proportions (53.8%, 23.3%, and 16.2%, respectively) were estimated when only reports with known dates were considered (n = 210). Most death reports were attributable to neoplasms (83 [33.3%]), cardiac disorders (38 [15.3%]), nervous system disorders (33 [13.3%]), and infections and infestations (14 [5.6%]). Among the 128 deaths reported within 30 days of a sipuleucel-T infusion, 104 patients (81.2%) had a specified cause of death.
Table 3. Data Associated With PTs With a Disproportionality EB05 Score of 2.0 or Higher Grouped by SOC for US Adverse Event Reports Submitted to the US FDA Adverse Event Reporting System for Sipuleucel-T, Overall and According to Seriousness, April 29, 2010, to December 31, 2017

| SOC and PT                                      | All Reports<sup>a,b</sup> | Serious Reports Only | Labeled Event<sup>c</sup> |
|------------------------------------------------|---------------------------|----------------------|---------------------------|
| Blood and lymphatic system disorders            |                           |                      |                           |
| Anemia                                         | 125                       | 119                  | Yes                       |
| Leukocytosis                                    | 15                        | 14                   | No                        |
| Normochromic normocytic anemia                  | 6                         | 6                    | Yes                       |
| Anemia of chronic disease                       | 6                         | 6                    | Yes                       |
| Cardiac disorders<sup>d</sup>                   |                           |                      |                           |
| Tachycardia                                     | 42                        | 33                   | Yes                       |
| Sinus tachycardia                               | 8                         | 6                    | Yes                       |
| Gastrointestinal disorders                      |                           |                      |                           |
| Vomiting                                       | 140                       | 97                   | Yes                       |
| Oral paresthesia                                | 9                         | 6                    | Yes                       |
| Nausea                                         |                           | 125                  | Yes                       |
| General disorders and administration site conditions |                       |                      |                           |
| Chills                                         | 317                       | 166                  | Yes                       |
| Malaise                                        | 192                       | 114                  | No                        |
| Pyrexia                                        | 191                       | 120                  | Yes                       |
| Feeling cold                                    | 16                        | 12                   | Yes                       |
| Infusion site extravasation                     | 14                        | 14                   | Yes                       |
| SIRS                                           | 11                        | 11                   | No                        |
| Complication associated with device            | 10                        | 10                   | Yes                       |
| Infusion site pain                              | 7                         | 7                    | Yes                       |
| Infusion site swelling                          | 6                         | 6                    | Yes                       |
| Catheter site pain                              | 5                         | 5                    | Yes                       |
| Infusion site hematoma                          | 5                         | 5                    | Yes                       |
| Infusion site reaction                          | 5                         | 5                    | Yes                       |
| Infections and infestations                     |                           |                      |                           |
| Device-related infection                        | 110                       | 94                   | Yes                       |
| Urinary tract infection                         | 88                        | 70                   | Yes                       |
| Infection                                       | 64                        | 64                   | Yes                       |
| Sepsis                                         | 62                        | 62                   | Yes                       |
| Bacteremia                                      | 24                        | 23                   | Yes                       |
| Staphylococcal bacteremia                       | 22                        | 22                   | Yes                       |
| Device-related sepsis                           | 20                        | 20                   | Yes                       |
| Catheter site infection                         | 10                        | 10                   | Yes                       |
| Staphylococcal sepsis                           | 8                         | 8                    | Yes                       |
| Injury, poisoning, and procedural complications  |                           |                      |                           |
| Infusion-related reaction                       | 65                        | 47                   | Yes                       |
| Citrate toxicity                                | 16                        | 11                   | Yes                       |
| Investigations                                  |                           |                      |                           |
| Culture positive                                | 180                       | 180                  | Yes                       |
| Hemoglobin decreased                            | 91                        | 74                   | Yes                       |
| Blood pressure decreased                        | 48                        | 34                   | Yes                       |
| Mononuclear cell count abnormal                 | 39                        | 5                    | No<sup>e</sup>             |
| Hematocrit decreased                            | 33                        | 30                   | Yes                       |
| Body temperature increased                      | 32                        | 24                   | Yes                       |
| Microbiology test abnormal                      | 21                        | 154                  | Yes                       |
| Staphylococcus test positive                    | 13                        | 12                   | Yes                       |
| Neutrophil count abnormal                       | 7                         | 7                    | No                        |
| Blood culture positive                          | 6                         | 6                    | Yes                       |
| Gram stain positive                             | 4                         | 4                    | Yes                       |

(continued)

<sup>a</sup> EB05 = 90% confidence interval
<sup>b</sup> EB05 < 2.0
<sup>c</sup> Yes
<sup>d</sup> Yes
<sup>e</sup> No
The following PTs (all reports) within the specified SOC had an EB05 of 2.0 or higher.

Table 3. Data Associated With PTs With a Disproportionality EB05 Score of 2.0 or Higher Grouped by SOC for US Adverse Event Reports Submitted to the US FDA Adverse Event Reporting System for Sipuleucel-T, Overall and According to Seriousness, April 29, 2010, to December 31, 2017 (continued)

| SOC and PT | All Reportsa,b | Serious Reports Only | Labeled Eventc |
|-----------|----------------|----------------------|----------------|
| Metabolism and nutrition disorders |               |                      |                |
| Dehydration | 106 (3.1 [2.6-3.6]) | 93 (2.7 [2.3-3.2]) | No             |
| Hyponatremia | 28 (3.9 [2.8-5.2]) | 28 (3.5 [2.6-4.8]) | No             |
| Hypokalemia | 22 (4.3 [3.0-6.0]) | 22 (3.9 [2.7-5.4]) | No             |
| Malnutrition | 12 (4.1 [2.5-6.3]) | 12 (3.8 [2.4-5.7]) | No             |
| Hypovolemia | 11 (4.2 [2.6-6.6]) | 11 (3.8 [2.4-5.9]) | No             |

Musculoskeletal and connective tissue disorders

- Back pain: 111 (2.8 [2.4-3.2]), 69 (2.9 [2.4-3.6]), Yes
- Bone pain: 32 (3.9 [2.9-5.2]), 24 (4.6 [3.6-5.3]), Yes

Nervous system disordersd

- Tremor: 66 (2.6 [2.1-3.2]), EB05 < 2.0, EB05 < 2.0, Yes
- Transient ischemic attack: 30 (2.9 [2.2-3.9]), EB05 < 2.0, EB05 < 2.0, Yes
- Unresponsive to stimuli: 25 (3.3 [2.4-4.5]), 24 (2.9 [2.0-3.9]), No
- Presyncope: 20 (3.6 [2.5-5.1]), 17 (3.4 [2.3-4.9]), Yes
- Carotid artery stenosis: 7 (3.8 [2.1-6.6]), EB05 < 2.0, EB05 < 2.0, No

Product

- Thrombosis in device: 23 (27.7 [19.3-38.7]), 11 (6.3 [3.5-14.0]), Yes
- Device occlusion: 18 (7.3 [4.7-12.4]), EB05 < 2.0, EB05 < 2.0, Yes
- Product contamination microbial: 7 (8.6 [3.2-30.1]), EB05 < 2.0, EB05 < 2.0, Yes
- Product sterility lacking: 5 (44.7 [5.9-106.6]), 5 (36.3 [4.6-91.5], Yes

Renal and urinary disorders

- Hematuria: 48 (3.1 [2.4-3.9]), 46 (3.2 [2.5-4.0]), Yes

Respiratory, thoracic, and mediastinal disorders

- Pulmonary embolism: 52 (3.1 [2.4-3.8]), 52 (2.7 [2.2-3.4], Yes
- Atelectasis: 23 (6.2 [4.4-8.7]), 23 (5.3 [3.8-7.4], No
- Hypoxia: 22 (2.9 [2.1-4.1]), EB05 < 2.0, EB05 < 2.0, Yes

Surgical and medical procedures

- Hospitalization: 105 (5.1 [4.3-5.9]), 105 (4.6 [3.9-5.4], Outcome
- Hospice care: 15 (5.0 [3.7-7.5]), 10 (3.8 [2.3-6.1], Outcome

Vascular disorders

- Deep vein thrombosis: 53 (3.2 [2.6-4.0]), 53 (2.9 [2.3-3.6], Yes
- Pallor: 30 (7.5 [5.4-10.4]), 18 (4.9 [3.3-7.0], No
- Hematoma: 26 (3.6 [2.6-4.9]), EB05 < 2.0, EB05 < 2.0, Yes
- Poor venous access: 22 (36.0 [24.9-50.6]), 8 (26.7 [7.9-50.9], Yes
- Thrombophlebitis superficial: 8 (6.1 [3.1-16.9]), 8 (5.5 [2.9-13.9], Yes
- Jugular vein thrombosis: 7 (16.9 [4.1-45.0]), 7 (13.6 [3.6-39.0], Yes

Abbreviations: EBGM, empirical Bayes Geometric Mean; EB05, lower bound of EBGM 90% CI; FDA, Food and Drug Administration; PT, preferred term; SIRS, systemic inflammatory response syndrome; SOC, system organ class.

a The following PTs (all reports) within the specified SOC had an EB05 of 2.0 or higher but were not included in the table because there is potential confounding by the following indications: General disorders and administration site conditions: disease progression (n = 139); investigations: prostate-specific antigen increased (n = 66), blood alkaline phosphate increased (n = 23); neoplasms: prostate cancer (n = 52), prostate cancer metastatic (n = 49), metastases to bone (n = 45), metastases to central nervous system (n = 20), neoplasm progression (n = 18), metastases to liver (n = 17), metastasis (n = 13), metastases to spine (n = 7), metastases to lymph nodes (n = 6), and metastases to meninges (n = 6); nervous system disorders: spinal cord compression (n = 23); and renal disorders: hydronephrosis (n = 24), urinary tract obstruction (n = 8), ureteric obstruction (n = 7), bladder obstruction (n = 7). Although back pain, bone pain, and hematuria could also be associated with confounding by indication, these symptoms and signs are also common in conditions unrelated to prostate cancer; therefore, we maintained these entities in the table.
b The following PTs (all reports) within the specified SOC had an EB05 of 2.0 or higher but were not included in the table owing to nonspecific terminology. General disorders and administration site conditions: ill-defined disorder (n = 137), adverse reaction (n = 11); investigations: investigation (n = 8).
c Indicates whether the adverse event (represented by the specified PT) is a labeled event or consistent with a labeled event. The product label instructs patients to report catheter-associated symptoms (eg, swelling, redness) to a health care professional; therefore, we considered all device- or catheter-associated events as labeled events, including hematura.
d Although the EB05 was lower than 2.0, reports of myocardial infarction (n = 38) were reviewed owing to the inclusion of cardiovascular disorders in the “Warnings and Precautions” section of the product label (EBGM [serious reports], 0.53; 90% CI, 0.40-0.68).
e Not a labeled event with respect to peripheral blood; labeled event with respect to characterization of product.
f Although EB05 was lower than 2.0, reports of peripheral blood were reviewed owing to the inclusion of cerebrovascular disease in the “Warnings and Precautions” section of the product label. Data for all serious reports were as follows: ischemic stroke (n = 6; EBGM, 1.7; 90% CI, 0.9-3.0); hemorrhagic stroke (n = 5; EBGM, 1.3; 90% CI, 0.7-2.3); embolic stroke (n = 6; EBGM, 2.9; 90% CI, 1.5-5.0). All reports were serious.

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of death; of these 104 deaths, 37 (35.6%) were associated with neoplasms, followed by cardiac disorders (25 [24.0%]), nervous system disorders (18 [17.3%]), and infection (9 [8.7%]).

Tachycardia
Among 33 serious reports of tachycardia (median [IQR] age, 79 [72-85] years; n = 32), the median time to onset from last sipuleucel-T infusion was 8 days (IQR, 0-13 days, with day 0 representing events occurring on the day of infusion; n = 29). Twelve reports (36.0%) were associated with an infusion reaction occurring within 1 day of infusion. Four reports of tachycardia were potentially associated with underlying heart disease (new-onset atrial fibrillation, chest pain, acute MI, and ischemia). The remaining reports were associated with fever and infection (n = 9) or dehydration (n = 5).

Table 4. Characterization of Deaths for US Adverse Event Reports Submitted to the US FDA Adverse Event Reporting System for Sipuleucel-T, April 29, 2010, to December 31, 2017

| Characteristic                                           | Total, No (%) |
|----------------------------------------------------------|---------------|
| Total death reports                                      | 314 (100)     |
| Total death reports with date of last sipuleucel-T infusion and date of death |
| Without imputation                                       | 210 (66.9)    |
| With imputation                                          | 249 (79.3)    |
| Age, y<sup>a</sup>                                        |               |
| <50                                                      | 1 (0.3)       |
| 50-64                                                    | 31 (9.9)      |
| 65-74                                                    | 106 (33.8)    |
| 75-84                                                    | 95 (30.3)     |
| ≥85                                                      | 32 (10.2)     |
| Not specified                                            | 49 (15.6)     |
| Time from last infusion to death, d<sup>b</sup>           |               |
| <31                                                      | 128 (51.4)    |
| 31-90                                                    | 59 (23.7)     |
| 91-180                                                   | 20 (8.0)      |
| >180                                                     | 42 (16.9)     |
| Cause of death according to SOC<sup>c</sup>              |               |
| Total deaths<sup>c</sup>                                 |               |
| Neoplasms                                                | 83 (33.3)     |
| Cardiac disorders                                        | 38 (15.3)     |
| Nervous system disorders                                 | 33 (13.3)     |
| Infections and infestations                              | 14 (5.6)      |
| General                                                  | 8 (3.2)       |
| Respiratory tract                                        | 7 (2.8)       |
| Vascular                                                 | 4 (1.6)       |
| Renal                                                    | 3 (1.2)       |
| Other specified                                          | 5 (2.0)       |
| Not specified                                            | 54 (21.7)     |
| Deaths occurring within 30 d of sipuleucel-T infusion<sup>c</sup> |
| Neoplasm                                                 | 37 (28.9)     |
| Cardiac                                                  | 25 (19.5)     |
| Neurologic                                               | 18 (14.1)     |
| Infections and infestations                              | 9 (7.0)       |
| General                                                  | 3 (2.3)       |
| Respiratory tract                                        | 5 (3.9)       |
| Vascular                                                 | 3 (2.3)       |
| Other specified                                          | 4 (3.1)       |
| Not specified                                            | 24 (18.8)     |

Abbreviations: FDA, US Food and Drug Administration; SOC, system organ class.
<sup>a</sup> Based on total deaths (n = 314).
<sup>b</sup> Based on 249 deaths (with available dates of death and last sipuleucel-T infusion, including imputed dates).
<sup>c</sup> Causes of death associated with fewer than 3 cases were grouped in the “other specified” category to maintain patient anonymity.
Myocardial Infarction
There were 38 reports (all serious) of MI, of which 2 were excluded from these descriptive analyses based on MI occurring prior to sipuleucel-T infusion or the diagnosis being ruled out, as described in the report. The median (IQR) age of the remaining 35 patients was 74 (71-81) years, and 1 patient was an unspecified age. Cardiac risk factors (eg, hypertension, diabetes, coronary artery disease, or hyperlipidemia) were specified in 68% of reports. Most events occurred after the second (n = 14) or third (n = 11) dose of sipuleucel-T; 6 events occurred after the first dose, and 5 reports did not specify the timing of subsequent MI. Most MIs occurred within 1 week of a sipuleucel-T infusion (19 [53%], with 12 of these reports describing MI on the same day as an infusion) or 8 to 30 days after an infusion (n = 11).

Transient Ischemic Attack
We identified a total of 30 (serious and nonserious) reports of TIA following at least 1 dose of sipuleucel-T. The median (IQR) age at time of the event was 75 (67-79) years, and the median (range) time to the event, which was assessable in all but 4 reports, was 5 (0-11) days.

Stroke
All 17 reports of stroke (6 embolic, 5 hemorrhagic, and 6 ischemic) occurring among 16 patients were serious. One patient was diagnosed as having an embolic stroke 6 days after his second dose of sipuleucel-T and an ischemic stroke 15 days later. Stroke occurred after the first (n = 3), second (n = 4), or third (n = 7; includes 5 patients in the PROCEED study) sipuleucel-T infusion. Overall, the median (IQR) time from the last sipuleucel-T dose to stroke was 25 (6-206) days among 14 patients with information. The median (IQR) time to stroke was 7 (0-14) days among those not stated to be in the study and 490 days (range, 206-996 days) among those participating in the PROCEED study.

Other Thromboembolic Events
Forty-one of the 53 DVT reports (77%) and 47 of the 52 PE reports (90%) occurred within 30 days of a sipuleucel-T infusion. All 7 cases of jugular vein thrombosis occurred in association with a central venous catheter (CVC).

Systemic Inflammatory Response Syndrome
There were 11 serious reports of SIRS submitted between 2012 and 2015 that occurred after the first, second, or third sipuleucel-T infusion. The median (IQR) age of these patients was 78 (67-86) years, and the median (IQR) time from infusion to SIRS was 0 (0-11) days. Nine reports documented administration of intravenous antibiotics and included other PTs, such as sepsis, bacteremia, bacterial infection, pneumonia, catheter site infection, and device-related sepsis, suggesting an infectious cause leading to SIRS. This syndrome was also reported in conjunction with infusion reaction, congestive heart failure, and PE.

Unresponsive to Stimuli
Serious reports of unresponsive to stimuli (n = 23) were associated with preterminal events (n = 7; eg, progression of CRPC, intracerebral bleed, or cardiopulmonary arrest), infusion reactions (n = 6), falls (n = 3), and other isolated cases of seizure, TIA, drug reaction (other than to sipuleucel-T), infection, and illicit drug use. Five of the infusion reactions occurred on the day of sipuleucel-T receipt during or shortly following the infusion (1 case did not specify event timing). Two reports described unresponsive events during the leukapheresis procedure.

Other AEs
Leukocytosis was reported in association with infection, infusion reaction, progression of metastatic disease, thrombosis, subdural hematoma, and acute kidney injury or obstruction. Malaise, hyponatremia, hypokalemia, malnutrition, hypovolemia, and atelectasis were secondary
manifestations of various underlying labeled disease processes and also associated with progression of metastatic prostate cancer, the indication for therapy. There were 5 serious reports involving patients unable to undergo sipuleucel-T infusion on the scheduled date because their mononuclear cell counts were outside the required range (sipuleucel product).

**Discussion**

The present study represents the largest postmarketing safety assessment, to our knowledge, of sipuleucel-T since its entry in the US market in 2010. The reported AEs were generally consistent with the safety experience observed in prelicensure studies and described in the USPI.\textsuperscript{12,13,24} Except for asthenia, dizziness, and fall, the most frequently reported AEs (chills, malaise, pyrexia, and culture positive) were also identified in our data mining analyses. Fall, typically an accidental event, is not included in the USPI, whereas asthenia, dizziness, and fatigue are labeled events.\textsuperscript{24} We found that more than 50% of reported deaths occurred within 30 days of a sipuleucel-T infusion, although, based on the information available in the FAERS reports, an association between death and sipuleucel-T could not be established. In data mining analyses, we identified disproportionate reporting (at least twice the expected) for anemia, infection, thromboembolic events, and general symptoms, all of which (or related term) are included in the USPI.

Various metabolic abnormalities and SIRS represent unlabeled events reported more frequently than expected. However, metabolic abnormalities and SIRS were noted to be secondary manifestations of labeled events, most commonly infections and infusion reactions. A nonspecific clinical response, SIRS reflects the manifestation of a dysregulated inflammatory response triggered by infectious or noninfectious conditions.\textsuperscript{25,26} The infusion of sipuleucel-T is associated with an immunostimulatory response that could conceivable result in a dysregulated inflammatory response. The majority of SIRS events occurred within 1 day of infusion, with most SIRS reports reflecting an underlying infection or infusion reaction. In the literature, the term SIRS has been found to lack specificity and sensitivity and has largely been replaced by alternate terminology.\textsuperscript{27-29} This may explain why FAERS reports with a SIRS diagnosis were not observed after 2015. Other unlabeled AEs that were primarily noted in serious reports included pallor, unresponsive to stimuli, dehydration, malaise, and leukocytosis. Pallor would be an expected clinical sign of anemia, the latter a recognized and labeled sequela of sipuleucel-T that also was disproportionately reported. Unresponsive to stimuli mostly described preterminal events and infusion reactions. Similar to dehydration and malaise, leukocytosis reflected other underlying conditions.

Infections were among the most notable disproportionately reported AEs, with infections associated with CVCs among the most frequently reported. Catheter-associated infections have been previously reported to occur in 12% of patients treated with sipuleucel-T (64% severe or life-threatening) in contrast to the 1% observed among those without a CVC.\textsuperscript{30} Although the frequency of CVC infection appears elevated compared with that generally seen in other settings,\textsuperscript{31,32} comparisons across studies are limited because of varying study methods, measures of association, indications for CVCs, duration of use, and patient populations.

Thromboembolic events, including TIA, PE, thrombosis in device, and jugular vein thrombosis, were also disproportionately reported. Prostate cancer, advancing age, androgen-deprivation therapy and its duration, advanced cancer stage, and tumor burden are risk factors for thrombosis (including cerebrovascular disease)\textsuperscript{33-35}; these risks could have contributed to the thromboembolic events observed after administration of sipuleucel-T. Although TIA was reported disproportionately, PTs for cerebrovascular accident or stroke were not. We found a long latency period for stroke among reports indicating patient participation in the PROCEED study (median, 490 days) in contrast to those not specifying trial participation (median, 7 days). In the preapproval study by Kantoff and colleagues,\textsuperscript{13} a median follow-up of 34.1 months was reported, and the median time to cerebrovascular events was 210 days. However, reporting sensitivity for cerebrovascular events may have been heightened among clinical trial participants with active follow-up and in the postmarketing
PROCEED study, during which events were actively solicited. It is possible that cerebrovascular accidents and strokes may have been underreported to FAERS if they had a long latency period and were not recognized as possibly being associated with sipuleucel-T.

A few deaths (0.5%) were observed within 30 days of receiving sipuleucel-T in the preapproval trials, during which most deaths occurred more than 1 year after treatment. In the present study, we found that prostate cancer accounted for most deaths occurring within 30 days of a sipuleucel-T infusion, possibly reflecting increased sensitivity of passive surveillance systems for events occurring in close proximity to the exposure, patients not meeting labeled indications for treatment, or lack of product effectiveness. Several treatment alternatives for metastatic CRPC became available after sipuleucel-T approval in 2010. Therefore, after 2010, patients may have been more heavily pretreated, thereby presenting for sipuleucel-T treatment with more refractory or symptomatic disease and an ensuing shorter survival time compared with individuals participating in the preapproval clinical trials. However, a recent study using a US insurance database found that 69% of patients received sipuleucel-T as first-line treatment, suggesting that many patients receiving sipuleucel-T are naive to other therapies for CRPC. In the present study, cardiac death was the second most common cause of death, although cardiac-related AEs (eg, MI, arrhythmia) were not disproportionately reported except for tachycardia, which was generally a secondary phenomenon.

Strengths and Limitations
An important strength of our study was the inclusion of a large number of sipuleucel-T reports, thereby providing the first broad perspective of AEs in the postmarketing period, to our knowledge. However, our study also has limitations, including those inherent to passive surveillance reporting systems, such as voluntary (underreporting) and duplicate reporting (despite efforts to exclude duplicate reports), varying report quality, reporting bias, and absence of denominator data. In addition, data mining analyses do not implicate an association between reported AEs and use of sipuleucel-T but identify potential signals that may need further assessment.

Conclusions
In summary, the present analysis—the largest postmarketing study to our knowledge to assess the safety profile of sipuleucel-T after its availability in the general population—did not raise new safety concerns. We found disproportionate reporting for labeled events, including infusion-associated reactions, infections, catheter-associated complications, and thromboembolic events, including TIA. Although the US FDA continues to monitor reports of AEs following sipuleucel-T administration, this overview of postapproval experience provides reassurance to health care professionals that the current USPI is consistent with the safety profile and serves as a resource for clinicians and patients as they consider the potential risks and benefits of treatment in the context of all available therapeutic options for CRPC.

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