

US009795604B2

(12) United States Patent

Byrd et al.

(54) METHODS OF TREATING AND PREVENTING GRAFT VERSUS HOST DISEASE

- (71) Applicant: **Pharmacyclics LLC**, Sunnyvale, CA (US)
- (72) Inventors: John C. Byrd, Columbus, OH (US);
 Jason A. Dubovsky, Columbus, OH (US); Natarajan Muthusamy,
 Galloway, OH (US); Amy Jo Johnson,
 Dublin, OH (US); David Miklos,
 Stanford, CA (US)
- (73) Assignee: **Pharmacyclics LLC**, Sunnyvale, CA (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- (21) Appl. No.: 14/523,650
- (22) Filed: Oct. 24, 2014

(65) **Prior Publication Data**

US 2015/0118209 A1 Apr. 30, 2015

Related U.S. Application Data

- (60) Provisional application No. 61/895,981, filed on Oct. 25, 2013, provisional application No. 61/910,945, filed on Dec. 2, 2013, provisional application No. 61/973,173, filed on Mar. 31, 2014, provisional application No. 61/973,176, filed on Mar. 31, 2014.
- (51) Int. Cl.

| A61K 31/519 | (2006.01) |
|--------------|-----------|
| A61K 38/13 | (2006.01) |
| A61K 35/17 | (2015.01) |
| A61K 45/06 | (2006.01) |
| A61K 31/5377 | (2006.01) |
| A61K 31/56 | (2006.01) |
| A61K 35/28 | (2015.01) |

- (52) U.S. Cl.
 CPC A61K 31/519 (2013.01); A61K 31/5377 (2013.01); A61K 31/56 (2013.01); A61K 35/17 (2013.01); A61K 38/13 (2013.01); A61K 45/06 (2013.01); A61K 35/28 (2013.01)

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

7,514,444 B2 4/2009 Honigberg et al. 7,625,880 B2 * 12/2009 Jankowski C07D 471/04

(10) Patent No.: US 9,795,604 B2

(45) **Date of Patent:** Oct. 24, 2017

| 8,067,395 | B2 * | 11/2011 | Jankowski C07D 471/04 |
|--------------|------|---------|-----------------------|
| | | | 514/252.13 |
| 8,088,781 | B2 * | 1/2012 | Honigberg A61K 31/00 |
| | | | 514/262.1 |
| 8,476,284 | B2 | 7/2013 | Honigberg et al. |
| 8,501,751 | B2 | 8/2013 | Honigberg et al. |
| 8,552,010 | B2 | 10/2013 | Honigberg et al. |
| 8,790,662 | B2 * | 7/2014 | Spellberg C12N 5/0642 |
| -,, | | | 424/93.7 |
| 8.987.421 | B2* | 3/2015 | Chang C07K 16/18 |
| 0,907,121 | 102 | 5/2015 | 424/130.1 |
| 2012/0071497 | A 1 | 3/2012 | Buggy et al. |
| | | 5/2012 | |
| 2013/0178483 | A1 | 7/2013 | Buggy et al. |
| 2015/0086507 | A1* | 3/2015 | Izumi A61K 31/519 |
| | | | 424/93.7 |
| 2015/0157634 | A1* | 6/2015 | Blazar A61K 31/519 |
| | - | | 424/93.7 |
| 2016/0256397 | A1* | 9/2016 | Chong A61K 9/2009 |
| 2010/0250557 | 111 | 2/2010 | Chong A01K 9/2009 |

FOREIGN PATENT DOCUMENTS

| CN | 101674834 A | 3/2010 |
|----|-------------------|---------|
| WO | WO-2002/080926 | 10/2002 |
| WO | WO-2011/153514 A2 | 12/2011 |
| WO | WO-2012/171007 A2 | 12/2012 |
| WO | WO-2015/061751 A1 | 4/2015 |

OTHER PUBLICATIONS

Chang-Ki Min, "The pathophysiology of chronic graft-versus-host disease: the unveiling of an enigma", Jun. 2011, The Korean Journal of Hematology, vol. 46, No. 2, pp. 80-87.*

Magenau et al., "Advances in understanding the pathogenesis of graft-versushost disease", 2016, British Journal of Haematology, vol. 173, Issue 2, pp. 190-205.*

Dubovsky et al. Ibrutinib treatment ameliorates murine chronic graft-versus-host disease, The Journal of Clinical Investigation, J Clin Invest. Oct 1, 2014. Doi:10.1172/JCI75328 (10 pgs.).

Kapur et al. B-cell involvement in chronic graft-versus-host disease. Haematologica. Nov. 2008;93(11):1702-11. (Epub Aug. 25, 2008). Jacobson et al. B-cell-directed therapy for chronic graft-versus-host disease. Haematologica. Nov. 2010;95(11):1811-3.

Srinivasan et al. Donor B-cell alloantibody deposition and germinal center formation are required for the development of murine chronic GVHD and bronchiolitis obliterans. Blood. Feb. 9, 2012; 119(6):1570-80 (Epub Nov. 9, 2011).

Treister. How we treat oral chronic graft-versus-host disease. Blood 2012 120:3407-3418.

Pharmacyclics: Study of the Bruton's Tyrosine Kinase Inhibitor in Subjects With Chronic Graft Versus Host Disease. ClinicalTrials. gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: http://clinicaltrials.gov/show/NCT02195869.

(Continued)

Primary Examiner — My-Chau T Tran (74) Attorney, Agent, or Firm — Foley Hoag LLP

(57) **ABSTRACT**

Described herein are methods for treating and preventing graft versus host disease using ACK inhibitors. The methods include administering to an individual in need thereof an ACK inhibitor such as ibrutinib for treating and preventing graft versus host disease.

(56) **References Cited**

OTHER PUBLICATIONS

Honigberg et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci USA. Jul. 20, 2010; 107(29):13075-80. (Epub Jul. 6, 2010).

Co-pending US patent application No. US201414558297, filed on Dec. 2, 2014.

PCT/US2014/062277 International Search Report and Written Opinion dated Jan. 30, 2015.

Xu et al. Oral administration of ibrutinib is ineffective at preventing scleroderma in chronic GVHD in two preclinical mouse models. Poster 56th ASH Annual Meeting and Exposition (Dec. 6-9, 2014). Miklos, Safety and Efficacy of Ibrutinib in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Who Have Undergone Prior Allogeneic Stem Cell Transplant. 2015 BMT Tandem Meetings (Feb. 11-15, San Diego, California).

PCT/US2014/068177 International Search Report and Written Opinion dated Feb. 27, 2015.

Ryan et al. Ibrutinib Treatment of Relapsed CLL Following Allogeneic Transplantation: Sustained Disease Response and Promising Donor Immune Modulation—Abstract submission to 56th ASH Annual Meeting and Exposition (Dec. 6-9, 2014).

Taiwan Search Report for TW103136912 dated Nov. 13, 2015.

The Journal of Pharmacy, 21 (2), 37-46, 2005.

DOCKE.

RM

Uckun et al. Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity. Expert Opinion Ther. Patents 20(11):1-14 (2010).

Burger et al. High-Level Expression of the T-Cell Chemokines CCL3 and CCL4 by Chronic Lymphocytic Leukemia B Cells in Nurselike Cell Cocultures and After BCR Stimulation. Blood 113(13):3050-3058 (2008).

PCT/US2014/062277 International Preliminary Report on Patentability dated Apr. 26, 2016.

Pharmacyclics, Inc. Safety and efficacy study of Bruton's tyrosine kinase inhibitor in subjects with relapsed or refractory diffuse large B-cell lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Feb. 2, 2011—[cited Nov. 22, 2013]. Available from: http://clinicaltrials.gov/ct2/show/ NCT01325701 NLM Identifier: NCT01325701.

Ponader et al. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. Blood (Epub Dec. 16, 2011), 119(5):1182-1189 (Feb. 2012).

European Search Report for European Application No. EP 14856623.5 dated Jun. 16, 2017.

Brown, "PCI-32765, the First BTK (Bruton's Tyrosine Kinase) Inhibitor in Clinical Trials," Curr Hematol Malig Rep, 8(1): 1-6 (2013).

Cetkovic-Cvrlje et al., "Dual targeting of Bruton's tyrosine kinase and Janus kinase 3 with rationally designed inhibitors prevents graft-versus-host disease (GVHD) in a murine allogeneic bone marrow transplantation model," Br J Haematol, 126(6): 821-827 (2004).

Dubovsky et al., "Ibrutinib can reverse established chronic graftversus-host disease, which is dependent upon IL-2 inducible T-cell kinase (ITK) and Bruton's tyrosine kinase (BTK)—driven lymphocyte activation," Cancer Res, 74(19): 2591 (2014).

European Search Report for European Application No. EP 14867905 dated Mar. 31, 2017.

Filipovich et al., "National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graftversus-Host Disease: I. Diagnosis and Staging Working Group Report," Biol Blood Marrow Tr, 11(12): 945-956 (2005).

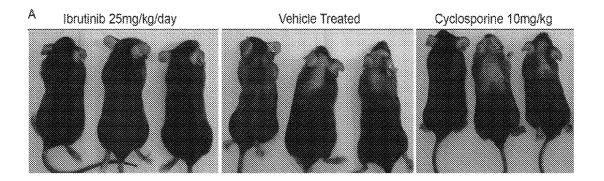
Flynn et al., "Therapeutic treatment of multi-organ system, obstructive pulmonary and scleradermatous chronic graft-versus-host disease with the BTK and ITK inhibitor Ibrutinib," J Immunol, 192(1): TRAN3P-873 (2014).

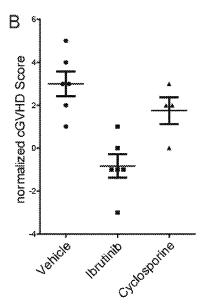
Lehmann, "Pathogenesis and treatment of immune-mediated neuropathies," Adv Neurol Disord, 2(4): 261-281 (2009). Uckun et al., "Bruton's tyrosine kinase as a molecular target in

Uckun et al., "Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity," Expert Opinion on Therapeutic Patents, 20(11): 4157-1470 (2010).

* cited by examiner

FIG. 1





DOCKET A L A R M Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

FIG. 1 (cont'd)

С

......

Chronic Graft Versus Host Disease Scoring

| | Cast | | Skin | | Weight | | Posture |
|-------|--|-------|--|------|---------------------------------------|--------|--------------------------|
| Score | Ökeniption | 5:359 | Oescription | 500R | Description | \$000¥ | Description |
| 8 | Softer los | Ş | No scienciamatosa lesam | Ŭ | No weight loss or overall weight gain | ø | No pesture defect |
| \$ | Ruffed has with a small amount of has loss | 1 | Red or initiated skin lesion | 1 | Weigh has dill | 1 | Mid hundhed posture |
| | Her bus in a single area <5cm/0 | 1 | Stan Nationg/petering single testion | 1 | Why has set by city | 1 | Moderate Nunched posture |
| 3 | Her loss in a single area vicent? | 3 | Southing or intending in a single pres | 3 | Weightion with his city | | Severely hundred posture |
| | Complete her inn os xi area instinot | Ą. | Scattering to bless ding in multiple areas | * | Waightines >15% | | 1 |

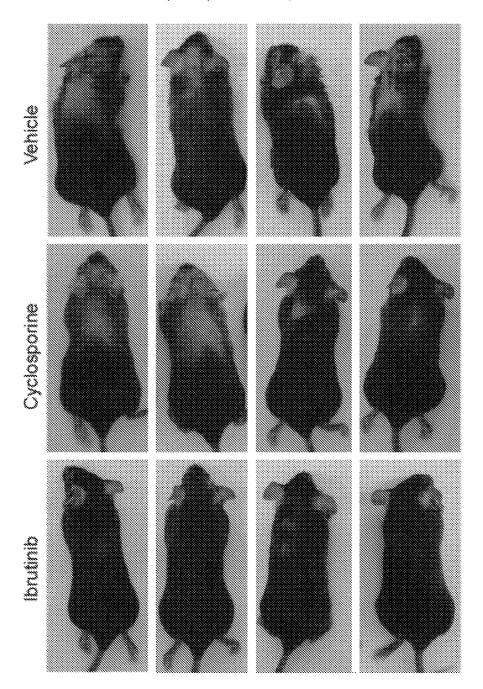
| | Posture | | Mobility | | Vitality |
|-------|--------------------------|------|---------------------------------------|------------|--|
| Score | Decorptor | 3088 | <u>Decoposi</u> | 5:278 | Desceptor |
| \$ | No pasture defect | \$ | Fall mobility | 8 | ike . |
| 1 | Mid hundred posture | 1 | Sowed poit | 8 | Qexi |
| 1 | Moximate hunched pasture | 2 | Sound get refusi to nove when pouched | instants | gg, Scone and category for each individual |
| 8 | Severely hunched posture | 3 | Instructivity when totuched | naux 1 | later score is the summation of all individual |
| | | | | scares, in | the event of a dead massa total should ~ 10 |

DOCKET ALARM Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

FIG. 1 (cont'd)

D

Day 39 post-transplant



DOCKET ALARM Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

DOCKET A L A R M



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.