



US007968569B2

(12) **United States Patent**
Zeldis

(10) **Patent No.:** **US 7,968,569 B2**
(45) **Date of Patent:** **Jun. 28, 2011**

(54) **METHODS FOR TREATMENT OF MULTIPLE MYELOMA USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE**

(75) Inventor: **Jerome B. Zeldis**, Princeton, NJ (US)

(73) Assignee: **Celgene Corporation**, Summit, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 145 days.

(21) Appl. No.: **10/438,213**

(22) Filed: **May 15, 2003**

(65) **Prior Publication Data**

US 2004/0029832 A1 Feb. 12, 2004

Related U.S. Application Data

(60) Provisional application No. 60/380,842, filed on May 17, 2002, provisional application No. 60/424,600, filed on Nov. 6, 2002.

(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/323**

(58) **Field of Classification Search** 514/321,
514/323

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,536,809	A	10/1970	Applezweig	
3,598,123	A	8/1971	Zaffaroni et al.	
3,845,770	A	11/1974	Theeuwes et al.	
3,916,899	A	11/1975	Theeuwes et al.	
4,008,719	A	2/1977	Theeuwes et al.	
4,810,643	A	3/1989	Souza	
4,999,291	A	3/1991	Souza	
5,059,595	A	10/1991	Le Grazie	
5,073,543	A	12/1991	Marshall et al.	
5,120,548	A	6/1992	McClelland et al.	
5,134,127	A	7/1992	Stella et al.	
5,229,496	A	7/1993	Deeley et al.	
5,354,556	A	10/1994	Sparks et al.	
5,385,901	A	1/1995	Kaplan et al.	
5,391,485	A	2/1995	Deeley et al.	
5,393,870	A	2/1995	Deeley et al.	
5,528,823	A	6/1996	Rudy, Jr. et al.	
5,580,755	A	12/1996	Souza	
5,591,767	A	1/1997	Mohr et al.	
5,593,990	A	1/1997	D'Amato	
5,629,327	A	5/1997	D'Amato	
5,635,517	A *	6/1997	Muller et al.	514/323
5,639,476	A	6/1997	Oshlack et al.	
5,674,533	A	10/1997	Santus et al.	
5,698,579	A	12/1997	Muller	
5,712,291	A	1/1998	D'Amato	
5,731,325	A	3/1998	Andrulis, Jr. et al.	
5,733,566	A	3/1998	Lewis	
5,798,368	A	8/1998	Muller et al.	
5,874,448	A	2/1999	Muller et al.	
5,877,200	A	3/1999	Muller	

6,020,358	A	2/2000	Muller et al.	
6,071,948	A	6/2000	D'Amato	
6,077,822	A *	6/2000	Dyrsting et al.	514/8
6,114,355	A	9/2000	D'Amato	
6,140,346	A	10/2000	Andrulis, Jr. et al.	
6,228,879	B1	5/2001	Green et al.	
6,235,756	B1	5/2001	D'Amato	
6,281,230	B1 *	8/2001	Muller et al.	514/323
6,316,471	B1	11/2001	Muller et al.	
6,326,388	B1	12/2001	Man et al.	
6,335,349	B1	1/2002	Muller et al.	
6,380,239	B1	4/2002	Muller et al.	
6,395,754	B1	5/2002	Muller et al.	
6,403,613	B1	6/2002	Man et al.	
6,420,414	B1	7/2002	D'Amato	
6,458,810	B1	10/2002	Muller et al.	
6,469,045	B1	10/2002	D'Amato	
6,476,052	B1	11/2002	Muller et al.	
6,518,298	B2	2/2003	Green et al.	
6,555,554	B2 *	4/2003	Muller et al.	514/323
6,673,828	B1	1/2004	Green et al.	
7,119,106	B2 *	10/2006	Muller et al.	514/323
7,189,740	B2 *	3/2007	Zeldis	514/323
7,393,862	B2 *	7/2008	Zeldis	514/320
7,435,745	B2	10/2008	D'Amato	

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO 92/14455 9/1992

(Continued)

OTHER PUBLICATIONS

Corral et al. Immunomodulation by thalidomide and thalidomide analogues . . . Ann. Rheum. 1999; 58; 107-13.*
 Kyle et al. ("The Application of Thalidomide in Multiple Myeloma", Semin Oncol. Dec. 2001; 28(6):583-7).
 Davies et al. ("Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma", Blood. Jul. 1, 2001;98(1):210-6).
 Broder et al. ("Dideoxycytidine: current clinical experience and future prospects. A summary.", Am J Med. May 21, 1990;88(5B):31S-33S).
 Filella et al. (Cancer Detect Prey. 1996;20(1):52-6).
 Raza et al., 2001, "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes," Blood 98(4):958-965.

(Continued)

Primary Examiner — Frederick Krass
Assistant Examiner — Chris E Simmons
(74) *Attorney, Agent, or Firm* — Jones Day

(57) **ABSTRACT**

Methods of treating, preventing and/or managing cancer as well as and diseases and disorders associated with, or characterized by, undesired angiogenesis are disclosed. Specific methods encompass the administration of an immunomodulatory compound alone or in combination with a second active ingredient. The invention further relates to methods of reducing or avoiding adverse side effects associated with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy which comprise the administration of an immunomodulatory compound. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

U.S. PATENT DOCUMENTS

2001/0018445	A1	8/2001	Huang et al.	
2001/0022973	A1*	9/2001	Ortyl et al.	424/452
2001/0056114	A1	12/2001	D'Amato	
2002/0035090	A1	3/2002	Zeldis et al.	
2002/0045643	A1	4/2002	Muller et al.	
2002/0052398	A1	5/2002	D'Amato	
2002/0054899	A1	5/2002	Zeldis	
2002/0061923	A1	5/2002	D'Amato	
2002/0128228	A1	9/2002	Hwu	
2002/0161023	A1	10/2002	D'Amato	
2002/0173658	A1	11/2002	Muller et al.	
2002/0183360	A1	12/2002	Muller et al.	
2003/0013739	A1	1/2003	Masferrer et al.	
2003/0028028	A1	2/2003	Man et al.	
2003/0045552	A1	3/2003	Robarge et al.	
2003/0069428	A1	4/2003	Muller et al.	
2003/0096841	A1	5/2003	Robarge et al.	
2003/0139451	A1	7/2003	Shah et al.	
2003/0144325	A1	7/2003	Muller et al.	
2003/0181428	A1	9/2003	Green et al.	
2003/0187024	A1	10/2003	D'Amato	
2003/0191098	A1	10/2003	D'Amato	
2003/0235909	A1	12/2003	Hariri et al.	
2004/0029832	A1	2/2004	Zeldis	
2004/0067953	A1*	4/2004	Stein et al.	514/251
2004/0077685	A1	4/2004	Figg et al.	
2004/0077686	A1	4/2004	Dannenberg et al.	
2004/0087546	A1	5/2004	Zeldis	
2004/0091455	A1	5/2004	Zeldis	
2004/0122052	A1	6/2004	Muller et al.	
2004/0147558	A1*	7/2004	Treston et al.	514/323
2004/0266809	A1	12/2004	Emanuel et al.	
2005/0049265	A1*	3/2005	Adams	514/267

FOREIGN PATENT DOCUMENTS

WO	WO 94/20085	9/1994
WO	WO 98/03502	1/1998
WO	WO 98/54170	12/1998
WO	WO 01/70275	9/2001
WO	WO 01/87307	11/2001
WO	WO 02/015926	2/2002
WO	WO 02/059106	8/2002
WO	WO 02/064083	8/2002
WO	WO03086373	10/2003

OTHER PUBLICATIONS

Shah et al., 1999, "Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis," *J. Med. Chem.* 42:3014-3017.

Shibata et al., 1995, "N-alkylphthalimides: structural requirement of thalidomidial action on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor production by human leukemia HL-60 cells," *Chem. Pharm. Bull.* 43(1):177-179.

Shimazawa et al., 1999, "Antiangiogenic activity of tumor necrosis factor-alpha production regulators derived from thalidomide," *Biol. Pharm. Bull.* 22(2):224-226.

Rubin et al., "Principles of Cancer Treatment-I", 12 ONCO IV I, May 2003.

Wilen et al., 1977, *Tetrahedron* 33:2725.

Wilen, 1972, *Tables of Resolving Agents and Optical Resolutions*, E.L. Eliel, ed., Univ. of Notre Dame Press, Notre Dame, IN pp. 268.

Wolff ed., 1995, *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., pp. 172-178, 949-982.

Bach, 1963, "Thalidomide in Cancer Chemotherapy," *The Lancet*, No. 1271, p. 71.

Bach, 1963, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide," *Acta Pathologica Et Microbiologica Scandinavica* 59:491-499.

Chandhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1):1884-86.

DiPaolo, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors," *Cancer Chemotherapy Reports* No. 29, p. 99-102.

in vivo Inhibition of Ehrlich Ascites Tumor," *Proceedings of the Society for Experimental Biology & Medicine*, 114:384-387.

DiPaolo, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells in vitro" *Science* 144:1583.

Mauad, 1963, "Clinical Improvements Obtained in Advanced Cancer Patients with Treatment with Thalidomide Associated with Hormones," *Anais Paulistas de Medicina e Cirurgia* 86:13-40.

Roe and Mitchley, 1963, "Thalidomide and Neoplasia" *Nature* 200:1016-1017.

Alexanian et al., 2004, "VTD (Velcade, thalidomide, dexamethasone) as primary therapy for newly-diagnosed multiple myeloma," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #210.

Anderson, 2000, "Thalidomide: Therapeutic potential in hematologic malignancies," *Seminars in Hematology* 37(1 Supp 3): 1-4.

Attal et al., 2004, "Maintenance treatment with thalidomide after autologous transplantation for myeloma: First analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM99 02)," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #535.

Bemardeschi et al., 2003, *J. Exp. Clin. Cancer Res.* 22(4):129-133.

Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," *J. Immunol.* 163(1):380-386.

Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood* 98(1):210-216.

Dimopoulos et al., 2004, "Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≥ 75 years of age," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #1482.

Eisen et al., 2000, "Continuous low dose Thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer," *Br. J. Cancer* 82(4):812-817.

Fakhouri et al., 2004, "Thalidomide in patients with multiple myeloma and renal failure," *Br. J. Haematol.* 125:90-102.

Fenk et al., 2005, "Single-agent thalidomide for treatment of first relapse following high-dose chemotherapy in patients with multiple myeloma," *Leukemia* 19(1):156-159.

Gupta et al., 2001, "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia* 15(12):1950-1961.

Haslett et al., 2003, "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro," *J. Infect. Dis.* 187(6):946-955.

Hideshima et al., 2000, "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood* 96(9):2943-2950.

Offidani et al., 2003, Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study. *Haematologica*. Dec. 2003;88(12):1432-1433.

Palumbo et al., 2004, "A prospective randomized trial of oral melphalan prednisone, thalidomide (MPT) vs. oral melphalan, prednisone (MP): An interim analysis," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #207.

Raje et al., 1999, "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609.

Rajkumar et al., 2004, "Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma (E1A00): Results of a phase III trial coordinated by the Eastern Cooperative Oncology Group," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #205.

Rajkumar et al., 2000, "Prognostic value of bone marrow angiogenesis in multiple myeloma," *Clin. Cancer Res.* 6(8):3111-3116.

Ribatti et al., 1999, "Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma," *Br. J. Cancer* 79(3-4):451-455.

Singhal et al., 1999, Antitumor activity of thalidomide in refractory multiple myeloma, *N. Engl. J. Med.* 341(21):1565-1571.

- Vacca et al., 1999, "Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma," *Blood* 93(9):3064-3073.
- Wohrer et al., 2004, "Effective treatment of primary plasma cell leukemia with thalidomide and dexamethasone—a case report," *Hematol. J.* 5(4):361-363.
- N. Ake Jonnson, 1972, "Chemical Structure and Teratogenic Properties," *Acta Pharm.*, pp. 521-542.
- Anderson, "Moving disease biology from the laboratory to the clinic," *Seminars in Oncology*, 2002 29:17-20.
- Barlogie et al., "Total Therapy II (TII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial total therapy I (TTI) (N=231)," *Blood, Abstract # 2857*, Dec. 7-11, 2001, *American Society of Hematology*.
- Barlogie et al., "High-dose therapy immunomodulatory drugs in multiple myeloma," *Seminars in Oncology*, 2002, 29 (6):26-33.
- Barlogie et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2.
- Barlogie, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38.
- Bartlett et al., "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9.
- Bartlett et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961.
- Battagay, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346.
- Baz et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (Dvd-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559*, *American Society of Hematology*, Dec. 10-13, 2005.
- Brennen et al., "Thalidomide and analogues: current proposed mechanisms and therapeutic usage," *Clinical Prostate Cancer*, 2004, 3 (1):54-61.
- Celgene Corporation, "Celgene advances immunomodulatory drug (IMiD™) clinical program," Press Release, Feb. 2000.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead ImiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," Press Release, Oct. 2001.
- Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) sales increase 24%. Prescriptions up 50%. Enhanced S.T.E.P.S.® launched. Pilot d-MPH data presented," Press Release, Oct. 2001.
- Celgene Corporation, "Celgene expands clinical development program for Revimid™—Five additional trials of Revimid initiated in hematological and solid tumor cancers," Press Release, Jun. 2002.
- Celgene Corporation, "Celgene Corporation announces third quarter results. THALOMID® (thalidomide) revenue increases 41% to \$30.5 million. Pivotal programs for THALOMID and REVIMID™ finalized. Peer-reviewed publications of THALOMID and REVIMID data. First JNK inhibitor advanced to Phase I clinical trial," Press Release, Oct. 2002.
- Celgene Corporation, "Blood reports Revimid™ has anti-tumor activity in patients with relapsed and refractory multiple myeloma," Press Release, Nov. 1, 2002.
- Celgene Corporation, "Celgene provides update on clinical pipeline. Celgene Announces first target indication for ACTIMID™, CC-8490. SelCID™ program to advance based on results from Phase I/II trial of CC-1088. First JNK inhibitor successfully completes phase I trial," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene Corporation announces fourth quarter and full year results for 2002," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic syndromes," Press Release, Apr. 2003.
- Celgene Corporation, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," Press Release, May 2003.
- Celgene Corporation, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," Press Release, Jul. 2003.
- Celgene Corporation, "Celgene corporation reports record operating performance in third quarter as total revenue increases 117% and profits rise," Press Release, Oct. 2003.
- Celgene Corporation, "Celgene corporation advances ACTIMID™ (CC-4047) into phase II trial for prostate cancer," Press Release, Oct. 2003.
- Celgene Corporation, "Additional clinical data presented on Revimid™ in myelodysplastic syndromes at the American Society of Hematology 45th annual meeting," Press Release, Dec. 2003.
- Celgene Corporation, "Celgene corporation reviews 2003 achievements and announces 2004 financial outlook," Press Release, Jan. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for multiple myeloma," Press Release, Feb. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for myelodysplastic syndromes," Press Release, Mar. 2004.
- Celgene Corporation, "Celgene corporation reports record operating performance in first quarter with strong revenue growth and profits," Press Release, Apr. 2004.
- Celgene Corporation, "Celgene announces plans to stop phase III trials in melanoma due to lack of efficacy," Press Release, Apr. 2004.
- Dalgleish, et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 2001, 85 (1)25.
- Dalgleish et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl 1), S25-S54.
- Database Pharmaml XP002369094 retrieved from STN. Database accession No. 1659300, & Marketletter, Oct. 9, 2001.
- Database NLDB XP002369095 retrieved from STN. Database accession No. 2002:35280, & Marketletter, Jun. 18, 2001.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma (MM)," Abstract # 3617, *American Society of Hematology*, Dec. 1-5, 2000.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma (MM)," Abstract # P222, *VIIIth International Myeloma Workshop*, May 4-8, 2001.
- Dibbs et al., "Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes," Abstract # 1284, *Circulation*, 1998.
- Dimopoulos et al., "Results of thalidomide and IMiDs in multiple myeloma," Abstract # P12.1.4, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Dimopoulos et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23)4444-4454.
- Dimopoulos et al., "Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 Study (MM-010)," Abstract # 6, *American Society of Hematology*, Dec. 10-13, 2005.
- Dredge et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer," Abstract # 491, *American Association for Cancer Research*, Apr. 6-10, 2002.
- Dredge et al., "Adjuvants and the promotion of Th1-type cytokines in tumour immunotherapy," *Cancer Immunol. Immunother.*, 2002, 51:521-531.
- Dredge et al., "Immunological effects of thalidomide and its chemi-

- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1 -type immunity¹," *The Journal of Immunology*, 2002, 168:4914-4919.
- Dredge et al., "Recent developments in antiangiogenic therapy," *Expert Opin. Biol. Ther.*, 2002, 2 (8):953-966.
- Dredge et al., "Angiogenesis inhibitors in cancer therapy," *Current Opinion in Investigational Drugs*, 2003, 4 (6):667-674.
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335.
- Fickentscher et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141.
- Figg et al., "Inhibition of angiogenesis: treatment options for patients with metastatic prostate cancer," *Investigational New Drugs*, 2002, 20(2):183-194.
- Galustian et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol. Ther.*, 2004, 4 (12):1-8.
- Glaspay et al., "The potential role of thalidomide and thalidomide analogs in melanoma," *Clinical Advances in Hematology & Oncology*, 2004, 1-7.
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 2001, 15:1950-1961.
- Hayashi et al., "Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity," *Blood Abstract #3219*, Dec. 6-10, 2002, *American Society of Hematology*.
- He, W., et al., 1993, Abstract of papers, 206th American Chemical Society, Chicago, IL; Med. Chem., paper 216.
- Helm et al., "Comparative teratological investigation of compounds of structurally and pharmacologically related to thalidomide," *Arzneimittel Forschung/Drug Research*, 1981, 31 (I)941-949.
- Hernandez-Illizaliturri et al., "Addition of immunomodulatory drugs CC5013 or CC4047 to rituximab enhances anti-tumor activity in a severe combined immunodeficiency (SCID) mouse lymphoma model," Abstract # 235, *American Society of Hematology*, Dec. 6-9, 2003.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood*, 2000, 96:2943-2950, *American Society of Hematology*.
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," Abstract 1313, *American Society of Hematology*, Dec. 1-5, 2000.
- Hunt et al., "Markers of endothelial and haemostatic activation in the use of CC-4047, a structural analogue of thalidamide, in relapsed myeloma," *Blood Abstract # 3216*, Dec. 6-10, 2002, *American Society of Hematology*.
- Hussein et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208*, *American Society of Hematology*, Dec. 4-7, 2004.
- Hwu et al., "Thalidomide and its analogues in the treatment of metastatic melanoma," *Chemotherapy Foundation Symposium*, Abstract #44, 2002.
- Kyle, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3)175-180.
- Kyle et al., "Multiple myeloma," *New England Journal of Medicine*, 2004, 351:1860-1873.
- LeBlanc et al., "Immunomodulatory drug costimulates T cells via the B7-CD28 pathway," *Blood*, 2004, 103:1787-1790, *American Society of Hematology*.
- Lentzsch et al., "In vivo activity of thalidomide and immunomodulatory drugs against multiple myeloma," *VIIIth International Myeloma Workshop. Abstract #P225*, May 4-8, 2001.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) determine the lineage commitment of hematopoietic progenitors by down regulation of GATA-1 and modu-
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) down regulates CAAT/enhancer-binding protein β (C/EBP β) in multiple myeloma (MM)," Abstract # 3456, *American Society of Hematology*, Dec. 6-9, 2003.
- Luzzio et al., "Thalidomide analogues: derivatives of an orphan drug with diverse biological activity," *Expert Opin. Ther. Patents*, 2004, 14 (2):215-229.
- Man et al., " α - Fluoro-substituted thalidomide analogues," *Bioorganic & Medicinal Chemistry Letters* 13, 2003, 3415-3417.
- Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 2001, 1 (4):1-8.
- Marriott et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 85:25, Jul. 6, 2001.
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF- α and TNFR2 during co-stimulation of both CD4⁺ and CD8⁺ T cells," *Clin. Exp. Immunol.*, 2002, 130:75-84.
- Marriott et al., "A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins¹," *Cancer Research*, 2003, 63:593-599.
- Marriott et al., "Thalidomide derived immunomodulatory drugs (IMiDs) as potential therapeutic agents," *Current Drug Targets—Immune, Endocrine & Metabolic Disorders*, 2003, 3:181-186.
- Masellis et al., "Changes in gene expression in bone marrow mesenchymal progenitor cells as a consequence of IMiD therapy in multiple myeloma patients," *Blood, Abstract #1548*, Dec. 7-11, 2001, *American Society of Hematology*.
- McCarty, "Thalidomide may impede cell migration in primates by down-regulating integrin β -chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis," *Medical Hypotheses*, 1997, 49:123-131.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs (Imids) in human multiple myeloma cells: therapeutic implications," Abstract # 3224, Dec. 7-11, 2001, *American Society of Hematology*.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Mitsiades et al., "CC-5013 Celgene," *Current Opinion in Investigational Drugs*, 2004, 5 (6):635-647.
- Moutouh et al., "Novel immunomodulatory drugs (IMiD®): A potential, new therapy for β - hemoglobinopathies," Abstract # 3740, *American Society of Hematology*, Dec. 4-7, 2004.
- Patten et al., "The early use of the serum free light chain assay in patients with relapsed refractory myeloma receiving treatment with a thalidomide analogue (CC-4047)," Abstract # 1640, *American Society of Hematology*, Dec. 6-9, 2003.
- Payvandi et al., "Effects of a thalidomide analog on binding activity of transcription factors and cell cycle progression of multiple myeloma cell lines," *Blood Abstract #2487*, Dec. 1-5, 200, *American Society of Hematology*.
- Payvandi et al., "The thalidomide analogs IMiDs enhance expression of CD69 stimulatory receptor on natural killer cells," Abstract # 1793, *American Association for Cancer Research*, Mar. 24-28, 2001.
- Payvandi et al., "Thalidomide analogs IMiDs inhibit expression of cyclooxygenase-2 in multiple myeloma cell line and LPS stimulated PBMCs," *Blood, Abstract # 2689*, Dec. 7-11, 2001, *American Society of Hematology*.
- Payvandi et al., "Thalidomide and IMiDs inhibit microvessel formation from human arterial rings in the absence of human liver microsomes," *Blood, Abstract # 5046*, Dec. 6-10, 2002, *American Society of Hematology*.
- Payvandi et al., "CC-5013 inhibits the expression of adhesion molecules ICAM-1 and CD44 and prevents metastasis of B16 F10 mouse melanoma cells in an animal model," *American Society of Clinical Oncology, Abstract # 992*, 2003.
- Payvandi et al., "Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF- α , IL-1 β , and LPS-stimulated stimu-

- Raje et al., "Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma," *Blood*, Dec. 15, 2004, 104 (13)4188-4193.
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13)4050-4053.
- Richardson et al., "A Phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood Abstract #3225*, Dec. 7-11, 2001, *American Society of Hematology*.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood*, 2002 100:3063-3067, *American Society of Hematology*.
- Richardson et al., "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood, Abstract # 825*, *American Society of Hematology*, Dec. 6-9, 2003.
- Richardson et al., "Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma," *Journal of Clinical Oncology*, 2004, 22(16) 3212-3214.
- Richardson et al., "A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; preliminary results," *10th International Myeloma Workshop*, Apr. 10-14, 2005.
- Richardson et al., "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634.
- Richardson et al., "A phase I trial of lenalidomide (REVLIMID®) with bortezomib (VELCADE®) in relapsed and refractory multiple myeloma," *Blood, Abstract # 365*, *American Society of Hematology*, Dec. 10-13, 2005.
- Rubin et al., "Principles of cancer treatment-1," 2003, 12 ONCO IV 1.
- Schafer et al., "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs," *Journal of Pharmacology and Experimental Therapeutics*, 2003, 305(3)1222-1232.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma," *Journal of Clinical Oncology*, 2004, 22 (16):1-8.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology, Abstract #248*, 2002.
- Shaughnessy et al., "Global gene expression analysis shows loss of C-MYC and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," Abstract # 2485, *The American Society of Hematology*, Dec. 1-5, 2000.
- Shire et al., "TNF- α inhibitors and rheumatoid arthritis," *Exp. Opin. Ther. Patents*, 1998, 8 (5):531-544.
- Sorbbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- α production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431.
- Streety et al., "Thalidomide analogue CC-4047 is effective in the treatment of patients with relapsed and refractory multiple myeloma (MM) and induces T-cell activation and IL-12 production," Abstract # 367, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Streety et al., "Changes in neutrophil phenotype following the administration of CC-4047 (Actimid) to patients with multiple myeloma," Abstract # 2543, *American Society of Hematology*, Dec. 6-9, 2003.
- Streety et al., "An update of the use and outcomes of the new immunomodulatory agent CC-4047 (Actimid) in patients with relapsed/refractory myeloma," Abstract #829, *American Society of Hematology*, Dec. 6-9, 2003.
- Teo et al., "A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory—oncologic agent, in healthy Teo et al., "Chiral inversion of the second generation IMiD™ CC-4047 (ACTIMID™) in human plasma and phosphate-buffered saline," *Chirality*, 2003, 15:348-351.
- Thertulien et al., "Hybrid MEL/DT PACE autotransplant regimen for Multiple Myeloma (MM)—safety and efficacy data in pilot study of 15 patients," *Blood Abstract # 2869*, *American Society of Hematology*, Dec. 7-11, 2001.
- Tohnya et al., "A phase I study of oral CC-5013 (lenalidomide, Revlimid™), a thalidomide derivative, in patients with refractory metastatic cancer," *Clinical Prostate Cancer*, 2004, 2:241-243.
- Tricot et al., "Angiochemotherapy (ACT) for multiple myeloma (MM) with DT-PACE results in a high response rate, but in contrast to tandem transplants with melphalan does not affect durable disease control," *Blood, Abstract # 3531*, *American Society of Hematology*, Dec. 7-11, 2001.
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrobial Agents and Chemotherapy*, 2002, 46 (6)1887-1895.
- Weber, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," Abstract # PL5.02, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Weber et al., "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," Abstract # PO.738, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Ye et al., "Novel IMiD drugs enhance expansion and regulate differentiation of human cord blood CD34+ cells with cytokines," *Blood, Abstract #4099*, *American Society of Hematology*, Dec. 6-10, 2002.
- Zangari et al., "Risk factors for deep vein thrombosis (DVT) in a large group of myeloma patients (Pts) treated with thalidomide (Thal): The Arkansas Experience," *Blood, Abstract # 681*, *American Society of Hematology*, Dec. 7-11, 2001.
- Zangari et al., "Revimid 25 mg (REV 25) \times 20 versus 50 mg (REV 50) \times 10 q 28 days with bridging of 5 mg \times 10 versus 10 mg \times 5 as post-transplant salvage therapy for multiple myeloma (MM)," *Blood, Abstract # 1642*, *American Society of Hematology*, Dec. 6-9, 2003.
- Zeldis et al., "Potential new therapeutics for Waldenstrom's macroglobulinemia," *Seminars in Oncology*, 2003, 30 (2):275-281.
- Zhang et al., "CC-5079, a novel microtubule and TNF- α inhibitor with anti-angiogenic and antimetastasis activity," Abstract # B012, *International Conference on Molecular Targets and Cancer Therapeutics*, Nov. 17-21, 2003.
- Anderson, "The Role of Immunomodulatory Drugs in Multiple Myeloma," *Seminars in Hematology*, vol. 40, No. 4, Suppl 4, 2003: pp. 23-32.
- Weber, "Thalidomide and Its Derivatives: New Promise for Multiple Myeloma," *Cancer Control*, vol. 10, No. 5, 375-383, 2003.
- U.S. Appl. No. 60/499,723, filed Sep. 4, 2003, Markian.
- U.S. Appl. No. 60/372,348, filed Apr. 12, 2002, Hariri et al.
- U.S. Appl. No. 10/732,867, filed Dec. 9, 2003, D'Amato et al.
- U.S. Appl. No. 09/545,654, filed Apr. 10, 2000, D'Amato.
- U.S. Appl. No. 09/287,377, filed Apr. 7, 1999, D'Amato.
- Carstensen, 1995, *Drug Stability: Principles & Practice*, 2nd. ed., Marcel Dekker, New York, NY pp. 379-380.
- Corral et al., 1999, "Immunomodulation by thalidomide and thalidomide analogues," *Ann. Rheum. Dis.* 58(Suppl 1):1107-1113.
- Craig et al., 1967, "Potential anticancer agents. III. 2-phthalimidoaldehydes and derivatives," *Potential Anticancer Agents III* 10:1071-1073.
- D'Amato et al., 2001, "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.* 28:597-601.
- D'Amato et al., 1994, "Thalidomide is an Inhibitor of Angiogenesis", *Proc. Natl. Acad. Sci.* 91:4082-4085.
- De et al., 1976, "Hansch analysis for some antineoplastic glutarimides," *J. Indian Chem. Soc.* I.III: 825-826.
- De et al., 1976, "Possible antineoplastic agents: III. Synthesis of 6-alkyl-2-[4'-methoxyphthalimido] and 6-alkyl-3-[3'-4'-

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.