IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ANDRULIS PHARMACEUTICALS CORP.,	)	
	)	
Plaintiff,	)	
	)	No. 1:13-cv-01644-RGA
v.	)	
	)	JURY TRIAL DEMANDED
CELGENE CORP.,	)	
	)	
Defendant.	)	

FIRST AMENDED COMPLAINT

This is an action for patent infringement in which Plaintiff, Andrulis Pharmaceuticals Corp., makes the following allegations against Defendant Celgene Corp. based on personal knowledge, the investigation of its counsel, and information and belief:

PARTIES

1. Plaintiff Andrulis Pharmaceuticals Corp. is a Maryland corporation with its principal place of business at 179 Rehoboth Avenue, Unit 1378, Rehoboth, Delaware 19971.

2. Defendant Celgene Corp. ("Celgene") is a Delaware corporation with its principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. Celgene is a global biopharmaceutical company with operations in more than fifty countries worldwide. Celgene regularly conducts business in Delaware, and it maintains continuous and systematic contacts with Delaware, including offering to sell, selling, and administering substantial quantities of drug products in Delaware.

4. Celgene has appointed The Corporation Trust Company, Corporation Trust Center, 1209 Orange Street, Wilmington, Delaware 19801, as its agent for service of process.

JURISDICTION AND VENUE

5. This action arises under the patent laws of the United States, Title 35, United States Code (35 U.S.C. § 1 *et seq*.). The Court has subject-matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

6. Venue is proper in this judicial district under 28 U.S.C. §§ 1391 and 1400(b).

7. The Court has personal jurisdiction over Celgene because, among other things, Celgene is a Delaware corporation and it maintains continuous and systematic contacts with Delaware.

FACTUAL BACKGROUND

Plaintiff Andrulis Pharmaceuticals Corporation

8. In 1993, Dr. Peter Andrulis, Jr. founded Andrulis Pharmaceuticals Corporation ("Andrulis Pharmaceuticals"). Andrulis Pharmaceuticals conducted extensive research in the fields of cancer and tumor treatment, and pioneered the use of thalidomide in combination therapy for cancer, neurological disorders, and other inflammatory diseases.

9. Dr. Andrulis began his career as an Assistant Professor of Chemistry at American University and then at Trinity College, both located in the District of Columbia. While at Trinity, he obtained an agreement with Catholic University to use laboratory space to produce specialty compounds for use in federal research projects. In 1971 in partnership with his wife, Marilyn W. Andrulis, Ph.D., he founded Andrulis Research Corporation with the mission of performing contracted research in the physical, social and life sciences. Within three years the business revenues grew sufficiently enough for him to join Andrulis Research on a full-time basis. He established a fully-equipped chemistry laboratory with a Good Manufacturing Practices approval by the U.S. Food and Drug Administration and was responsible for obtaining several competitively-awarded Small Business Innovation Research (SBIR) grants from the

federal government. Dr. Andrulis served as Chairman from Andrulis Research's inception to 1993 when he purchased the chemistry business from Andrulis Research, and the assets, including, without limitation, all patents, thalidomide know-how, and FDA GMP approval, were transferred to Andrulis Pharmaceuticals.

10. Andrulis Pharmaceuticals produced several platinum compounds that were proven useful in treatment of solid cancer tumors and were memorialized in patents issued to Andrulis Research by the U.S. Patent and Trademark Office and formally assigned to Andrulis Pharmaceuticals. Dr. Andrulis was an early leader in the use of clinically-pure thalidomide for use in the treatment of inflammatory diseases. His labor and ingenuity yielded six U.S. patents, including the patent-in-suit, relating to treatments using thalidomide in combination therapy for cancer, neurological disorders, and other inflammatory diseases.

11. Dr. Andrulis was diagnosed with Parkinson's Disease in 2002. On July 30, 2012, Dr. Andrulis died as a result of complications arising from Parkinson's Disease. Thereafter in accordance with the directives of his Revocable Trust and Will, his business partner and wife, Dr. Marilyn Andrulis obtained full ownership and management of Andrulis Pharmaceuticals and all other assets in his estate. The husband and wife team of Drs. Peter and Marilyn Andrulis had worked together in partnership for many years to obtain funding to sponsor clinical trials of thalidomide use for various indications. Dr. Marilyn Andrulis, now leads Andrulis Pharmaceuticals as President and CEO.

The Patent-in-Suit

12. On October 31, 2000, the United States Patent and Trademark Office ("PTO") duly and legally issued U.S. Patent No. 6,140,346 ("the '346 Patent"), entitled "Treatment of Cancer with Thalidomide Alone or in Combination with Other Anti-Cancer Agents," to

inventors Peter J. Andrulis, Jr. and Murray W. Drulak, after a full and fair examination. The '346 Patent claims priority to an application filed at the PTO on June 6, 1995. A true and correct copy of the '346 Patent is attached as Exhibit A.

13. As assignee of the '346 Patent, Andrulis Pharmaceuticals has been the only owner of the '346 Patent since its issuance. Andrulis Pharmaceuticals has the right to bring suit and recover damages for infringement of the '346 Patent.

14. The '346 Patent discloses and claims a novel method for the treatment of certain cancers, including multiple myeloma, which comprises administering therapeutically-effective amounts of the drug thalidomide in combination with an alkylating agent, such as melphalan (the "Patented Method").

15. By way of example, claim 2 of the '346 Patent recites:

> 2. A method for the treatment of neoplastic diseases in a mammal which comprises administering to said afflicted mammal enhanced therapeutically-effective amounts of thalidomide in combination with effective amounts of other alkylating agent selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin wherein said neoplastic diseases are sensitive to said enhanced combination.

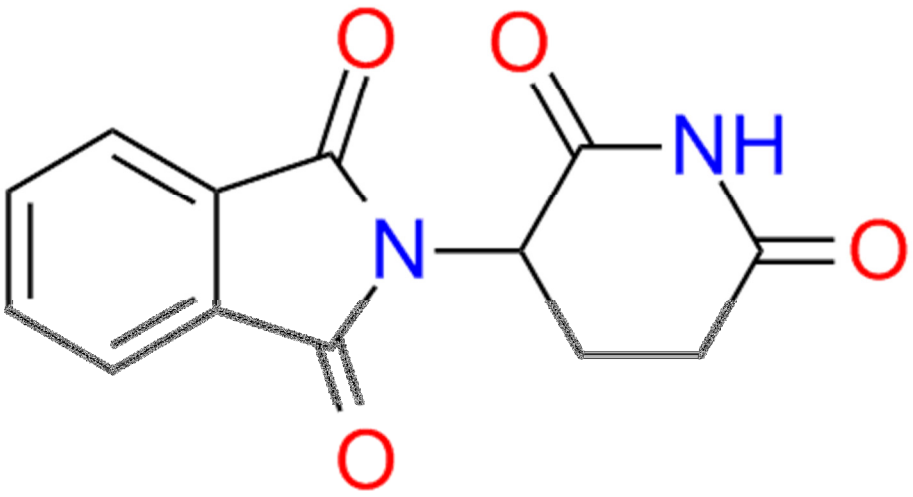
Thalidomide

16. Thalidomide was first introduced in West Germany in the 1950s as a sedative and antiemetic, but was discovered to cause tragic birth defects when ingested by pregnant women. The resulting public outcry resulted in worldwide bans of the drug, and, in the United States, led directly to amendments to the U.S. Food, Drug and Cosmetic Act.

17. Later research discovered that thalidomide can directly inhibit angiogenesis, the physiological process by which the body develops blood vessels.

18. By the 2000s, thalidomide, often in combination with melphalan, became one of the most common therapies for multiple myeloma.

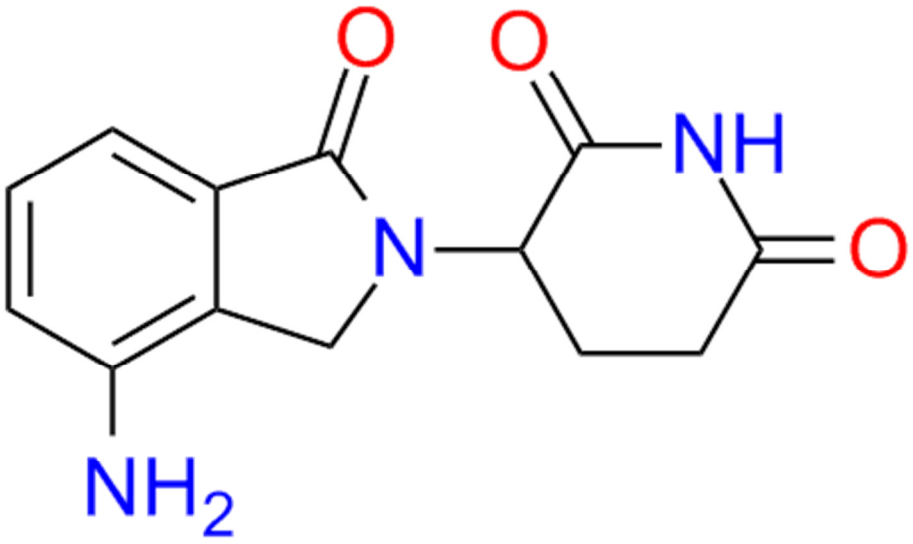
19. Thalidomide can be represented by the following chemical structure:



Lenalidomide

20. Lenalidomide is a thalidomide analogue.

21. Lenalidomide can be represented by the following chemical structure:



22. Thalidomide and lenalidomide have similar chemical structures.

23. Thalidomide and lenalidomide have similar mechanisms of action.

24. Both thalidomide and lenalidomide function to induce cancer cell death and/or impede new cancer cell formation. Both drugs achieve this function by acting on biological pathways to (1) increase biological substances that promote cancer cell death, (2) decrease biological substances that aid cancer cell survival, and/or (3) modulate the immune system. Administration of either thalidomide or lenalidomide results in a reduction in the number of cancer cells.

25. On multiple occasions, the PTO has treated thalidomide and lenalidomide as "equivalents" during Celgene's prosecution of patent applications containing claims directed to lenalidomide. For example, in a July 15, 2013 Office Action in Celgene Application No. 13/276,867, the PTO specifically stated to Celgene that thalidomide and lenalidomide are "***equivalents***" ***and effective in treating multiple myeloma*** in combination with melphalan and prednisone. And as a result of such equivalence, the PTO has repeatedly rejected claims in Celgene patent applications directed to lenalidomide substances on the basis that one skilled in the art would have found it obvious to substitute lenalidomide for thalidomide when used for treatment of multiple myeloma. In addition to the July 15, 2013 Office Action identified above, the PTO has also rejected claims on this basis in at least the following communications to Celgene:

- PTO Office Action dated May 22, 2013, in Celgene Application No. 13/276,867;
- PTO Office Action dated January 9, 2012, in Celgene Application No. 13/276,867;
- PTO Office Action dated March 7, 2012, in Celgene, Application No. 12/640,702; and

- PTO Office Action dated August 23, 2012, in Celgene Application No. 13/073,897.

26. In each of the above-listed patent applications, Celgene retained attorneys from the Jones Day law firm to represent Celgene before the PTO and/or serve as its agent in the prosecution of those patent applications.

Melphalan

27. Melphalan is an alkylating agent that is active against certain cancers, including multiple myeloma.

Multiple Myeloma

28. Multiple myeloma is a type of cancer.

29. The Multiple Myeloma Research Foundation ("MMRF") has described multiple myeloma as follows:

> Multiple myeloma (also known as myeloma or plasma cell myeloma) is a progressive hematologic (blood) disease. It is a cancer of the plasma cell, an important part of the immune system that produces immunoglobulins (antibodies) to help fight infection and disease. Multiple myeloma is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulin (IgG, IgA, IgD, or IgE) or Bence-Jones protein (free monoclonal light chains). Hypercalcemia, anemia, renal damage, increased susceptibility to bacterial infection, and impaired production of normal immunoglobulin are common clinical manifestations of multiple myeloma. It is often also characterized by diffuse osteoporosis, usually in the pelvis, spine, ribs, and skull.

http://www.themmrf.org/living-with-multiple-myeloma/newly-diagnosed-patients/what-is-multiple-myeloma/definition.html (last visited Dec. 19, 2013).

30. Multiple myeloma has also been described as follows:

> Each year in the United States, nearly 22,000 people are diagnosed with multiple myeloma, a cancer of the bone marrow. Bone marrow contains plasma cells, a type of white blood cell that is an

> important part of the immune system, which protects the body from infection.
>
> Normally, plasma cells make up less than 5 percent of the blood cells in the bone marrow. For reasons not completely understood, plasma cells can grow out of control. When they do, they are referred to as myeloma cells. These myeloma cells can fill up the bone marrow and damage the bone. Over time, they collect and form tumors in several (multiple) areas of the bones. That is why this cancer is called "multiple" myeloma.

http://www.cancercare.org/publications/12-treatment_update_multiple_myeloma (last visited Dec. 19, 2013).

Combination Therapy for Treatment of Multiple Myeloma

31. Andrulis Pharmaceuticals' patented invention for the treatment of neoplastic diseases is widely recognized and used as a primary therapy for treatment of multiple myeloma. In particular, the use of the combination of melphalan, prednisone, and thalidomide ("MPT"), as well as the combination of melphalan, prednisone, and lenalidomide ("MPL"), are widely used for the treatment of patients with multiple myeloma.

32. The FDA has not approved the use of MPT or MPL to treat patients with multiple myeloma.

33. Even though not approved by the FDA, the use of the MPT combination has become a primary therapy for many patients with multiple myeloma, and the use of the MPL combination has more recently become a primary therapy for many patients with multiple myeloma.

34. The administration of MPT and MPL practice Andrulis Pharmaceuticals' patented invention by treating multiple myeloma with a combination of melphalan and thalidomide or its analogue, lenalidomide.

Defendant Celgene Corporation

35. Celgene is a global pharmaceutical corporation that focuses on the discovery, development, and the commercialization of products for the treatment of cancer and other severe, immune, inflammatory conditions.

36. Through its research, funding, publications, and promotions, Celgene dominates all aspects of multiple myeloma research and treatments. Celgene is particularly active in the fields of MPT and MPL therapy, where Celgene is the sole manufacturer and seller of products containing thalidomide and lenalidomide.

37. Celgene promotes, offers to sell, sells, and administers a drug product containing thalidomide under the trade name Thalomid®.

38. The FDA first approved Thalomid® in 1998 for leprosy. In 2006, the FDA approved the use of Thalomid® for the treatment of multiple myeloma in combination with dexamethasone.

39. Except for Thalomid®, the FDA has not approved any drug product containing thalidomide. Thus, Celgene is the only drug manufacturer in the United States that sells a drug product containing thalidomide.

40. Celgene offers to sell, sells, and administers a drug product containing lenalidomide under the trade name Revlimid®.

41. The FDA first approved Revlimid® in 2005. Revlimid® is now FDA-approved for the treatment of multiple myeloma in combination with dexamethasone. Lenalidomide is a thalidomide analogue.

42. Celgene sought FDA approval of Revlimid® following research of thalidomide and its analogues for the purpose of treating multiple myeloma. Celgene began conducting clinical trials of Revlimid® by 2001 at latest.

43. Except for Revlimid®, the FDA has not approved any drug product containing lenalidomide. Thus, Celgene is the only drug manufacturer in the United States that sells a drug product containing lenalidomide.

44. GlaxoSmithKline offers to sell and sells a drug product containing melphalan under the trade name Alkeran®. From 2003 to 2009, Celgene distributed, promoted, and sold a drug product containing melphalan with the trade name Alkeran® under a Celgene label pursuant to a distribution agreement with GlaxoSmithKline. As stated in Celgene's 10-K filings with the SEC during this period, this agreement was "strategically valuable to us because it provides us with an approved oncology product that complements our clinical candidates, THALOMID and REVLIMID(TM), which are demonstrating potential in late stage clinical trials for the treatment of multiple myeloma[.]"

http://www.sec.gov/Archives/edgar/data/816284/000100515004000762/form10-k.txt (last visited Dec. 19, 2013).

45. Despite the foregoing, Celgene has never sought FDA approval of MPT or MPL as "on-label" indicated uses of Thalomid® or Revlimid® in the United States. Celgene did, however, obtain approval of MPT as an indicated use of Thalomid® for the treatment of multiple myeloma in other locations, including in Europe in April 2008, and in Canada in August 2010.

46. As alleged in greater detail below, Celgene has researched, promoted, advanced, and administered the off-label use of MPT and MPL treatment of multiple myeloma in the United States with great success. For the 2012 fiscal year alone, Celgene reported over $3.7 billion in net product sales of Revlimid®, and over $302 million in net product sales for

Thalomid®. A substantial driver of Celgene's sales of Revlimid® and Thalomid® is due to the use of those drugs in MPL and MPT, respectively, for the treatment of multiple myeloma.

Celgene's Knowledge of Dr. Andrulis and Andrulis Pharmaceuticals' Patented Invention

47. Celgene has had knowledge of Andrulis Pharmaceuticals' '346 Patent since at least 2004, and likely before that date as alleged below.

48. As two key players in a limited field of research, Celgene and Andrulis Pharmaceuticals have long been aware of each other's research of the treatment of multiple myeloma with thalidomide and its analogues. For example, Celgene identified Andrulis Pharmaceuticals as a competitor in a 10-K report filed with the U.S. Securities and Exchange Commission on March 31, 1997 (for the year ending 1996).

49. On May 27, 1997, the New England Journal of Medicine published an article entitled, "Thalidomide for the Treatment of Oral Aphthous Ulcers in Patients with Human Immunodeficiency Virus Infection." The article reported the results of a clinical trial conducted by the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. The publication disclosed that Andrulis Pharmaceuticals provided the thalidomide for the clinical trial.

50. After the NEJM article disclosed Andrulis Pharmaceuticals as the supplier of thalidomide for the reported clinical trial, Celgene identified Andrulis Pharmaceuticals as a competitor in a 10-K report filed with the U.S. Securities and Exchange Commission on March 31, 1998 (for the year ending 1997). Celgene likewise identified Andrulis Pharmaceuticals as a competitor in reports filed with the Securities and Exchange Commission for the years ending 1998, 1999, and 2000.

51. During the late 1990s, Celgene's then CEO, John Jackson, twice approached Dr. Andrulis to express Celgene's interest in purchasing Andrulis Pharmaceuticals. Dr. Andrulis declined each time.

52. After Celgene's overtures to purchase Andrulis Pharmaceuticals were rejected, Celgene duplicated the aphthous ulcers clinical trial disclosed in the May 1997 NEJM article, retained the same principal investigator that had used Andrulis Pharmaceuticals' thalidomide for the earlier clinical trial, and sought and obtained orphan drug status and FDA approval for the use of Celgene's thalidomide (Thalomid®) for treatment of leprosy patients.

53. Between August 2004 and April 2013, Celgene cited Andrulis Pharmaceuticals' '346 Patent no fewer than **27 times** in filings submitted to the United States Patent & Trademark Office. Celgene's submissions to the PTO identifying Andrulis Pharmaceuticals' '346 Patent were made in connection with Celgene patent applications, many of which concern cancer treatment with thalidomide or a thalidomide analogue, either alone or in combination with another anti-cancer agent. In 20 of the 27 Celgene filings that cited Andrulis Pharmaceuticals' '346 Patent, one of the named inventors on the applications was Dr. Jerome Zeldis, currently the CEO of Celgene Global Health and Chief Medical Officer of Celgene Corporation. As the Chief Medical Officer, Dr. Zeldis is responsible for the training and performance assessment of the Celgene medical affairs staff who interface with doctors at, among other sites, doctors-only admission Celgene tents at medical conferences.

54. Celgene was not only intimately aware of Andrulis Pharmaceuticals' '346 Patent as early as 2004, Celgene has also known since at least August 22, 2008, and likely well before that date, that the use of MPT for the treatment of cancers such as multiple myeloma infringed Andrulis Pharmaceuticals' '346 Patent.

55. On August 22, 2008, the PTO rejected claims in Celgene's patent application number No. 10/576,138 ("the '138 Application") identifying Dr. Jerome Zeldis as the inventor, entitled "Methods and Compositions Using Thalidomide for the Treatment and Managed of Cancers and Other Diseases," as anticipated by Andrulis Pharmaceuticals' prior art '346 Patent. In its application filed on November 4, 2004, Celgene claimed methods for treating cancer by administering thalidomide in combination with "a second active ingredient," specifically including but not limited to "melphalan." The PTO examiner rejected Celgene's asserted claims as anticipated by Andrulis Pharmaceuticals' '346 Patent, which already disclosed and claimed methods for treating cancers with thalidomide in combination with other agents such as melphalan. Celgene ultimately abandoned application number No. 10/576,138.

56. Celgene retained outside counsel to represent Celgene and/or serve as its agent to file and prosecute patent applications in the PTO with claims directed to thalidomide and lenalidomide for various treatments. For the vast majority of the 27 Celgene patent applications that cited Andrulis Pharmaceuticals' '346 Patent—including the Celgene application that had claims rejected as anticipated by the Andrulis Pharmaceuticals' '346 Patent—Celgene was represented before the PTO by attorneys from the Jones Day law firm.

57. Celgene has entered into licensing agreements with certain third parties for certain patented uses of Thalomid® and Revlimid®, which also reveal Celgene's intimate familiarity with and knowledge of not only Andrulis Pharmaceuticals itself, but also Celgene's familiarity with and knowledge of Andrulis Pharmaceuticals' patent holdings.

58. For example, in 1998 Celgene entered into a licensing agreement with a company called Entremed concerning thalidomide and its analogues. That agreement specifically cites several Andrulis Pharmaceuticals patents related to thalidomide. *See, e.g.*, Agreement between

Entremed, Inc. and Celgene,

http://www.sec.gov/Archives/edgar/data/816284/000095014699001052/0000950146-99-001052.txt (last visited Dec. 23, 2013).

The FDA's Regulation of Drug Manufacturers' Promotional Activities

59. The FDA does not regulate the practice of medicine. So doctors may prescribe approved drug products for unapproved or off-label uses, i.e., for any purpose or in any manner other than what the product's FDA-approved labeling (or package insert) specifies.

60. The FDA does regulate promotional practices for drug products, e.g., through the Office of Prescription Drug Promotion (formerly the Division of Drug Marketing, Advertising and Communications). Under the Food, Drug, and Cosmetic Act ("FDCA"), drug-product manufacturers may market drug products only for FDA-approved uses.

61. The Food and Drug Administration Modernization Act of 1997 created an exception to the prohibition against off-label marketing. Drug-product manufacturers may now provide doctors with publications concerning unapproved or off-label uses in response to unsolicited requests. But requests that are prompted in any way by manufacturers or their representatives are not unsolicited requests.

62. The FDA has identified the following examples, among others, of improper promotional activities relating to requests for information about unapproved uses:

> If a firm's sales representative mentions a use of a product that is not reflected in the product's approved labeling and invites a health care professional to request more information, resulting requests would be considered solicited requests.
>
> If a representative of a firm, such as a medical science liaison or paid speaker (e.g., key opinion leader), presents off-label use data at a company-sponsored promotional event (e.g., a dinner) and attendees then ask or submit requests for more information, these requests would be considered solicited requests.

> If a firm issues to health care professionals business reply cards that are intended for use in requesting off-label information, presents statements or contact information in promotional pieces in a manner that solicits requests for off-label medical or scientific information (e.g., "Product X continues to be evaluated in more than 50 trials in a broad range of conditions and patients" and "Call 1-800-… for more information"), or displays a commercial exhibit panel suggesting a new indication (e.g., a sign that reads "Coming Soon, a new use for Product X"), requests made in response to these types of prompts would be considered solicited requests.
>
> If a firm provides a phone number, e-mail address, uniform resource locator (URL), or username that is a word, alpha phrase, or alpha representation implying the availability of off-label information for its product, requests using this phone number, e-mail address, URL, or username would be considered solicited requests.

Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011).

Promotional Activities Influence Prescribing Decisions

63. Prescription drug sales are sensitive to promotional activities. Various studies have shown that promotional activities by drug-product manufacturers significantly affect prescribing decisions by doctors.

64. A 2000 review article states, "The present extent of physician-industry interactions appears to affect prescribing and professional behavior . . . ." A. Wazana, "Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?" 283 JOURNAL OF THE AM. MED. ASS'N No. 3, 373-380, at 373 (Jan. 2000). A 2008 article notes that the Wazana review article "found evidence of consistent and strong causality over a wide range of industry-physician interactions and a dose-response relationship in all interactions, where it was investigated, demonstrating that marketing efforts to influence prescribing do indeed work." G. Kyle et al., "Pharmaceutical Company Influences on Medication Prescribing and Their Potential Impact on Quality Use of Medicines," 33 JOURNAL OF CLINICAL PHARMACY & THERAPEUTICS

553-559, at 554 (2008). That 2008 article also notes that "many professional organizations worldwide representing doctors and pharmacists have developed professional practice guidelines for their members to increase awareness of the influence of pharmaceutical industry marketing on prescribing and other decisions." *Id*. at 558.

65. A 2005 publication states, "Increased promotion is associated with increased medicines sales, promotion influences prescribing more than doctors realise, and doctors rarely acknowledge that promotion has influenced their prescribing." P. Norris et al., "Reviews of Materials in the WHO/HAI Database on Drug Promotion: What Impact Does Pharmaceutical Promotion Have on Behavior?" at 54 (2005), available at http://apps.who.int/medicinedocs/pdf/s8109e/s8109e.pdf.

66. A 2005 article reports that "systematic reviews of the literature confirmed a direct relationship between the frequency of contact with [pharmaceutical company] reps and the likelihood that physicians will behave in ways favorable to the pharmaceutical industry." H. Brody, "The Company We Keep: Why Physicians Should Refuse to See Pharmaceutical Representatives," 3 ANNALS OF FAMILY MEDICINE No. 1, 82-85, at 83 (Jan.-Feb. 2005).

67. A 2005 review article regarding marketing in the pharmaceutical industry explains that the word "detailing" in that industry refers to marketing efforts direct toward doctors by personal selling through sales representatives. P. Manchanda et al., "The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review," 5 YALE JOURNAL OF HEALTH POLICY, LAW & ETHICS 785-822, at 785-86 (May 2005). That 2005 review article then reports that "detailing . . . affects physician prescription behavior in a positive and significant manner." *Id*. at 787. That 2005 review article also reports that detailing "has an impact on prescription behavior via both a subjective and an objective path." *Id*. at 810.

68. With regard to interactions with sales representatives, a 2010 review article reports that most of the studies considered found "an association with increased prescribing of the promoted drug" and visits by sales representatives. G. Spurling et al., "Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A Systematic Review," 7 PLoS MEDICINE No. 10, 1-22, at 4 (Oct. 2010). More generally, that 2010 review article notes that most of the studies considered "found associations between exposure [to pharmaceutical company information] and higher frequency of prescribing." *Id.* at 1.

69. A medical school has observed that the pharmaceutical industry spends billions of dollars "each year in direct marketing to physicians, including detailing by drug reps, journal ads, samples, and gifts with the ultimate goal of changing prescribing behavior. Studies have shown that even small gifts influence prescribing behavior, and that marketing leads to increased formulary requests and decreased use of generic medications." See "Industry Conflict of Interest Policy," available at http://brown.edu/academics/medical/student-affairs/policy-and-procedure/industry-conflict-interest-policy (footnotes omitted).

Celgene's Promotion and Administration of Andrulis Pharmaceuticals' Patented Invention

70. Celgene has both promoted and administered the use of Andrulis Pharmaceuticals' patented invention for the treatment of multiple myeloma.

71. Celgene sales representatives and medical affairs staff have communicated with prescribing physicians and promoted the advantages and benefits of Celgene's products, including the benefits of certain products when used in MPT and MPL therapy for the treatment of multiple myeloma.

72. At various times over the last two decades, including, without limitation, between October 2007 and to the present, Celgene sales representatives and/or medical affairs staff

communicated with prescribing physicians and promoted the use of Alkeran® to treat cancers and encouraged doctors to prescribe Alkeran® together with Thalomid® to treat multiple myeloma.

73. At various times over the last two decades, including, without limitation, between October 2007 to the present, Celgene sales representatives and/or medical affairs staff have communicated with prescribing physicians and promoted the benefits of using Thalomid® to treat multiple myeloma and have encouraged doctors to prescribe Thalomid® together with Alkeran® to treat multiple myeloma.

74. At various times over the last decade, including, without limitation, between October 2007 to the present, Celgene sales representatives and/or medical affairs staff have communicated with prescribing physicians and promoted the benefits of using Revlimid® to treat multiple myeloma and have encouraged doctors to prescribe Revlimid®, together with Alkeran® to treat multiple myeloma.

75. Celgene has employed individuals having backgrounds in science under the job title “medical liaison” or “medical science liaison” or “medical affairs representative” or something similar as part of its medical affairs division. Since at least October 2007 through the present, Celgene’s medical affairs staff have regularly communicated with prescribing physicians and promoted the use of a combination including Alkeran® and Thalomid®, and/or a combination including Alkeran® and Revlimid®, to treat multiple myeloma and have encouraged doctors to prescribe these drug products to treat multiple myeloma.

76. Revlimid® has been marketed or promoted much more than Thalomid® since 2005. Some doctors have been reluctant to prescribe Revlimid® for some patients due to the

significantly higher price of Revlimid® compared to Thalomid®, and Celgene still sells substantial quantities of Thalomid®.

77. Since 2007, Celgene has sponsored at least one study or trial in which patients with multiple myeloma were treated with a combination of melphalan, prednisone, and thalidomide.

78. Various publications from about 2005 through at least 2012 have reported favorable results from clinical trials that involved the use of melphalan and prednisone together with thalidomide and/or lenalidomide to treat patients with multiple myeloma. Those publications include:

> A. Palumbo et al., "Oral Melphalan, Prednisone, and Thalidomide for Newly Diagnosed Patients with Myeloma," 104 CANCER 1428-1433 (Oct. 2005)
>
> A. Palumbo et al., "Oral Melphalan and Prednisone Chemotherapy plus Thalidomide Compared with Melphalan and Prednisone Alone in Elderly Patients with Multiple Myeloma: Randomised Controlled Trial," 367 THE LANCET No. 9513, 825-831 (Mar. 2006)
>
> A. Palumbo et al., "Intravenous Melphalan, Thalidomide and Prednisone in Refractory and Relapsed Multiple Myeloma," 76 EUROPEAN JOURNAL OF HAEMATOLOGY 273-277 (Apr. 2006)
>
> T. Facon et al., "Melphalan and Prednisone plus Thalidomide Versus Melphalan and Prednisone Alone or Reduced-Intensity Autologous Stem Cell Transplantation in Elderly Patients with Multiple Myeloma (IFM 99-06): A Randomised Trial," 370 THE LANCET No. 9594, 1209-1218 (Oct. 2007)
>
> A. Palumbo et al., "Melphalan, Prednisone, and Lenalidomide Treatment for Newly Diagnosed Myeloma: A Report from the GIMEMA—Italian Multiple Myeloma Network," 25 JOURNAL OF CLINICAL ONCOLOGY No. 28, 4459-4465 (Oct. 2007)

C. Hulin et al., "Melphalan-Prednisone-Thalidomide (MP-T) Demonstrates a Significant Survival Advantage in Elderly Patients ≥75 Years with Multiple Myeloma Compared with Melphalan-Prednisone (MP) in a Randomized, Double-Blind, Placebo-Controlled Trial, IFM 01/01," 110 BLOOD No. 11, 31a Abstract #75 (Nov. 2007)

A. Palumbo et al., "Thalidomide for treatment of multiple myeloma: 10 years later," 111 BLOOD No. 8, 3968-3977 (Oct. 2008)

A. Palumbo et al., "Oral Melphalan, Prednisone, and Thalidomide in Elderly Patients with Multiple Myeloma: Updated Results of a Randomized Controlled Trial," 112 BLOOD No. 8, 3107-3114 (Oct. 2008)

A. Palumbo et al., "Melphalan, Prednisone, and Lenalidomide for Newly Diagnosed Myeloma: Kinetics of Neutropenia and Thrombocytopenia and Time-to-Event Results," 9 CLINICAL LYMPHOMA, MYELOMA & LEUKEMIA No. 2, 145-150 (Apr. 2009)

C. Hulin et al., "Efficacy of Melphalan and Prednisone plus Thalidomide in Patients Older than 75 Years with Newly Diagnosed Multiple Myeloma: IFM 01/01 Trial," 27 JOURNAL OF CLINICAL ONCOLOGY No. 22, 3664-3670 (Aug. 2009)

A. Palumbo et al., "Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma," 366 NEW ENGLAND JOURNAL OF MEDICINE No. 10, 1759-1769 (May 2012)

79. At least the primary, i.e., first-named, author of each of the above-identified articles, at the time the respective article was published, had received compensation from Celgene in the form of honoria, serving as a consultant to Celgene, and/or serving on Celgene's scientific advisory board and speaker's bureau. The vast majority of thought leaders in multiple myeloma, including most of the Robert A. Kyle Lifetime Achievement Award winners (one of the highest honors provided to thought leaders in multiple myeloma), have financial ties to Celgene.

80. Celgene, its representatives, and/or its agents have provided doctors with publications (e.g., in the form of reprints), including, but not limited to one or more of the

publications identified immediately above, that reported favorable results from one or more clinical trials that involved the use of melphalan and prednisone together with thalidomide or lenalidomide to treat patients with multiple myeloma. For example, Celgene, its representatives, and/or its agents purchased most or nearly all Fall 2008 reprints of A. Palumbo et al., "Oral Melphalan, Prednisone, and Thalidomide in Elderly Patients with Multiple Myeloma: Updated Results of a Randomized Controlled Trial," 112 BLOOD No. 8, 3107-3114 (Oct. 2008). Celgene, its representatives, and/or its agents distributed these reprints of the article to practicing physicians, and at least some of these practicing physicians then prescribed treatments of melphalan, prednisone, and thalidomide for their patients suffering from multiple myeloma.

81. Celgene has issued press releases about favorable results from clinical trials that involved the use of melphalan and prednisone together with thalidomide or lenalidomide to treat patients with multiple myeloma. Celgene has also issued press releases about regulatory authorities in countries outside the United States that approved the use of the combination of melphalan, prednisone, and thalidomide to treat patients with multiple myeloma. Celgene issued each of these press releases to promote and induce the use of Andrulis Pharmaceuticals' patented invention.

82. On December 6, 2004, Celgene issued a press release announcing that "data evaluating clinical results on the treatment of newly diagnosed multiple myeloma patients with an oral combination therapy consisting of melphalan, prednisone and thalidomide (MPT) were presented at the American Society of Hematology 46th Annual Meeting, one of the largest oncology meetings in the world, in San Diego, CA from December 3-7, 2004." The press release discussed the study's statistically significant difference in event free survival after a minimum of

six months of treatment with melphalan, prednisone and thalidomide (MPT) versus melphalan and prednisone (MP) alone.

83. On June 5, 2006, Celgene issued a press release that "announced results from an ongoing randomized trial evaluating the treatment of newly diagnosed, multiple myeloma patients with oral combination therapy thalidomide, melphalan and prednisone." The results were presented at the 42nd American Society of Clinical Oncology (ASCO) Meeting, on June 4, 2006, by the lead investigator of the study, Thierry Facon, M.D., of the Intergroupe Francophone du Myelome, in Lille, France. The press release reported that the combination of thalidomide plus melphalan and prednisone (MPT) compared to melphalan prednisone (MP) and autologous stem cell transplantation led to a statistically significant improvement in overall survival and progression free survival in the treatment of newly diagnosed elderly patients with multiple myeloma.

84. On or around April 7, 2008, Celgene issued a press release announcing that the Australian government authorized the use of thalidomide "in combination with melphalan and prednisone for patients with untreated multiple myeloma or ineligible for high dose chemotherapy."

85. On April 21, 2008, Celgene issued a press release announcing that the European Commission granted full marketing authorization for the use of Thalidomide "in combination with melphalan and prednisone as a treatment for patients with newly diagnosed multiple myeloma."

86. On December 7, 2009, Celgene issued a press release announcing interim results from a study involving the combination treatment of multiple myeloma using Revlimid® (lenalidomide), melphalan, and prednisone, followed by continuous Revlimid® (MPR-R). The

release stated that after ten months, elderly patients treated with MPR-R had a 50% reduction in risk of disease or death compared to those who received MP alone.

87. On December 7, 2009, Celgene also issued a press release regarding a study presented during the 51st American Society of Hematology's annual meeting in New Orleans, LA involving treating multiple myeloma with either Revlimid® (lenalidomide), melphalan and prednisone (MPR) or melphalan plus autologous stem cell transplant (MEL200) following an induction treatment of Revlimid® plus low-dose dexamethasone (Rd). The statement reported that after the Rd induction phase, 84% of patients achieved at least a partial response and 41% achieved at least a very good partial response. Patients who then received 3 cycles of MPR achieved at least a 56% very good partial response, while patients who received the first course of autologous stem cell transplant achieved at least a 62% very good partial response.

88. On December 6, 2010, Celgene issued a press release regarding a second interim analysis presented at the annual meeting of the American Society of Hematology, involving the combination treatment of multiple myeloma using Revlimid®, melphalan, and prednisone, followed by continuous Revlimid® (MPR-R). The study reported that continuous lenalidomide therapy with MPR-R compared with fixed duration MP treatment resulted in a higher overall response rate, higher rates of complete response, and a 60% reduction in the risk of disease progression.

89. On or around June 6, 2010, Celgene issued a press release announcing results of a study that included treatment of patients with multiple myeloma who received Revlimid®, melphalan and prednisone (MPR). The announcement stated that 55% of those who received at least three cycles of MPR achieved at least a very good partial response, and 13% achieved a complete response.

90. On December 12, 2011, Celgene issued a press release regarding a further interim analysis presented at the 53rd annual meeting of the American Society of Hematology, involving the combination treatment of multiple myeloma using Revlimid®, melphalan, and prednisone, followed by continuous Revlimid® (MPR-R). According to the press release, patients following the MPR-R treatment, compared to those who only melphalan and prednisone (MP), had a 70% reduction in risk of disease progression, and a trend for extended overall survival was observed with MPR-R compared with MP.

91. On June 3, 2013, Celgene issued a press release announcing a study presented during a June 3rd oral session at the American Society of Clinical Oncology Annual Meeting in Chicago, comparing melphalan, prednisone and Revlimid® (MPR) with high-dose chemotherapy and tandem autologous stem cell transplant (MEL200). The study was conducted and presented by lead investigator, Prof. Antonio Palumbo, Chief of the Myeloma Unit, Department of Oncology at the University of Torino. The press release reported that median progression-free survival was 24 months with MPR compared to 38 months with MEL200, and the five-year overall survival rate was 62% for MPR compared to 71% for MEL200.

92. Celgene, its representatives, and/or its agents have provided doctors with National Comprehensive Cancer Network ("NCCN") information or materials relating to the use of melphalan-prednisone-thalidomide therapy and/or melphalan-prednisone-lenalidomide therapy to treat patients with multiple myeloma.

93. Celgene has provided—and continues to provide—various doctors with funding or compensation, e.g., through Celgene consultancies, advisory boards/committees, or speaker bureaus and/or honoraria. Some doctors who received payments from Celgene have reported favorable results from clinical trials that involved the use of melphalan and prednisone together

with thalidomide or lenalidomide to treat patients with multiple myeloma at medical society meetings, such as meetings of the American Society of Hematology and/or the American Society of Clinical Oncology. For example, Celgene issued a press release on November 11, 2009 that reported: "More than 200 abstracts evaluating Celgene Products across a range of indications to be presented at the 51st American Society of Hematology Meeting." The abstracts referred to in this press release included studies using melphalan and prednisone together with thalidomide or lenalidomide to treat patients with multiple myeloma.

94. The 52nd Meeting of the American Society of Hematology (ASH) on December 5, 2010 in Orlando, Florida similarly included several presentations and papers regarding studies using melphalan and prednisone together with thalidomide or lenalidomide to treat patients with multiple myeloma. For example, this 52nd Meeting included a symposium on multiple myeloma, chaired by Sagar Lonial from the Winship Cancer Institute at Emory University School of Medicine, who acknowledged research funding by Celgene and spoke about combination therapies for multiple myeloma using melphalan, thalidomide, and prednisone. Upon information and belief, the ASH Education Program Book accompanying the 52nd Meeting contained at least three additional papers: one by Dr. Lonial, a consultant to Celgene, entitled "Relapsed Multiple Myeloma," which acknowledged that thalidomide with alkylating agents (i.e., melphalan) has favorable response rates; a second article by Nina Shah, a consultant to Celgene, disclosing combination regimens with significant response rates; and a third paper by Herve Avet-Loiseau, on the Board of Directors and Advisory Committees for Celgene, which acknowledged combination therapy (thalidomide and melphalan) having favorable outcomes.

95. Celgene had a booth at the 52nd Meeting of the American Society of Hematology, at which Celgene employees, representatives, and/or agents circulated literature and information

with respect to MPT and MPL treatments for multiple myeloma. The Celgene booth at the 52nd Meeting included a private tent area, in which Celgene could communicate privately with visitors. Celgene employees, representatives, and/or agents met with practicing physicians in these private tent areas to discuss and provide literature regarding the effectiveness of MPT and MPL treatments for multiple myeloma. At least some of these practicing physicians then prescribed treatments of melphalan, prednisone, and thalidomide or lenalidomide for their patients suffering from multiple myeloma.

96. From at least 2004 through the present, Celgene employees, representatives, and/or agents met privately with practicing physicians on a regular basis during professional conventions, symposia, and meetings such as the 52nd Meeting of the American Society of Hematology, and during these private meetings would similarly provide literature regarding the effectiveness of MPT and MPL treatments for multiple myeloma. Following these private meetings, these practicing physicians then prescribed treatments of melphalan, prednisone, and thalidomide or lenalidomide for their patients suffering from multiple myeloma, and these patients were subsequently treated with melphalan, prednisone, and thalidomide or lenalidomide.

97. From at least 2004 through the present, including, without limitation, from October 2007 to the present, Celgene employees, representatives, and/or agents would regularly communicate with practicing physicians (who were not necessarily previously solicited by Celgene), and such practicing physicians requested information regarding Celgene's products that could treat multiple myeloma. In response to such requests, Celgene employees, representatives, and/or agents would provide literature regarding the effectiveness of combination therapies such as MPT and MPL treatments for multiple myeloma. Following these communications, these practicing physicians then prescribed treatments of melphalan,

prednisone, and thalidomide or lenalidomide for their patients suffering from multiple myeloma, and these patients were subsequently treated with melphalan, prednisone, and thalidomide or lenalidomide.

98. After being reprimanded for off-label promotion of Thalomid® in FDA Warning Letters in 1998 and 2000, Celgene sought to continue its off-label promotion of Thalomid® (and later Revlimid®) by expanding its "medical affairs" staff in an attempt to satisfy FDA regulations governing off-label promotion. But Celgene did not stop promoting off-label use. Instead, Celgene adopted a strategy of off-label promotion that Celgene hoped would comply with FDA regulations governing off-label promotion. To date, Celgene's strategy has worked. Celgene has conducted a wide-ranging and effective promotional campaign that had induced and encouraged prescribing physicians to use Andrulis Pharmaceutical's patented invention for the treatment of multiple myeloma—even though such treatment is not approved by the FDA for such treatment.

99. Celgene's off-label promotion strategy has been effective to date, but, as the result of several ongoing investigations, it will soon be determined whether Celgene successfully created an off-label promotion strategy that stayed within the letter of FDA and state regulations governing off-label drug promotion or violated those regulations. The use of Thalomid® without dexamethasone to treat multiple myeloma constitutes an unapproved use. The use of Thalomid® in combination with melphalan and prednisone to treat multiple myeloma constitutes an unapproved use. The use of Revlimid® without dexamethasone to treat multiple myeloma constitutes an unapproved use. The use of Revlimid® in combination with melphalan and prednisone to treat multiple myeloma constitutes an unapproved use. United States Attorneys in more than one judicial district, as well as various state Attorneys General, began investigations in

2011 and 2012 into Celgene's promotion of Thalomid® and Revlimid® for uses not approved by the FDA. Those investigations are currently ongoing.

100. The investigating authorities may determine Celgene's off-label promotion of Andrulis Pharmaceuticals' patented invention for multiple myeloma treatment ran afoul of FDA and other regulations governing off-label drug promotion, or those authorities may conclude that Celgene succeeded in following the letter of those regulations by using "medical affairs" staff to communicate with prescribing physicians regarding off-label use. But in either event, Celgene's actions as alleged herein induced and encourage prescribing physicians to use Andrulis Pharmaceuticals' patented invention for the treatment of multiple myeloma.

101. In addition to Celgene's promotion and inducement of the use of Andrulis Pharmaceuticals' patented invention for the treatment of multiple myeloma, Celgene itself—either alone or together with prescribing physicians under Celgene's direction and control—has administered and continues to administer Andrulis Pharmaceuticals' patented invention for the treatment of multiple myeloma.

102. Celgene has tightly controlled, and continues to tightly control, the administration of Thalomid®. Celgene initially controlled the administration of Thalomid® pursuant to a program called the System for Thalidomide Education and Prescribing Safety ("STEPS"). Celgene subsequently changed the name of STEPS to Thalomid® Risk Evaluation and Mitigation Strategies ("Thalomid® REMS"). On August 28, 1998, Celgene applied for a United States patent on its STEPS program, and the PTO issued U.S. Patent No. 6,045,501 to Celgene covering the STEPS program on April 4, 2000.

103. Celgene has tightly controlled, and continues to tightly control, the administration of Revlimid®. Celgene initially controlled the administration of Revlimid® pursuant to a

program called "RevAssist." Celgene subsequently changed the name of RevAssist to Revlimid® Risk Evaluation and Mitigation Strategies ("Revlimid® REMS").

104. Celgene's STEPS, RevAssist, Thalomid® REMS, and Revlimid® REMS programs (together, "STEPS/REMS") administer the distribution and use of Thalomid® and Revlimid® pursuant to the following Celgene requirements:

- Only certified prescribers who have registered with Celgene's STEPS/REMS program and agreed to follow the STEPS/REMS requirements can prescribe Thalomid® and Revlimid®;
- Only patients who have enrolled in Celgene's STEPS/REMS program and have agreed to follow the STEPS/REMS requirements can receive Thalomid® and Revlimid®;
- No certified prescriber can prescribe Thalomid® or Revlimid®, and no patient can receive Thalomid® or Revlimid®, until Celgene provides an authorization number that is placed on each and every individual prescription for Thalomid® and Revlimid®;
- In order to receive a Celgene authorization number for each prescription of Thalomid® and Revlimid®, the prescribing physician and patient must each complete separate Celgene surveys every time a prescription is sought, and for each individual prescription the prescribing physician must counsel the patient on the benefits and risks of using Thalomid® and Revlimid® for the use prescribed;
- The prescribing physician must submit a form to Celgene for every prescription (the Patient Prescription Form) identifying the patient's diagnosis (such as whether the patient has been diagnosed with multiple myeloma) and other current medications the patient is taking (such as whether the patient is also taking melphalan, i.e., Alkeran®);
- Only certified pharmacies that have registered with Celgene's STEPS/REMS program and agreed to follow the STEPS/REMS requirements can dispense Thalomid® and Revlimid®, and for each prescription of Thalomid® and Revlimid® the registered pharmacy cannot dispense those drugs to the patient unless and until it receives a Celgene authorization number.

105. The mandatory Celgene-provided authorization number must be obtained for each and every individual prescription of Thalomid® and Revlimid®, the total supply of Thalomid® and Revlimid® for each authorization number cannot exceed a 28-day supply (i.e.,

the authorization number does not permit refills—a new authorization number is required for each and every new prescription), and the Celgene-provided authorization number is only valid for 7 days. If the prescription is not filled within 7 days, the Celgene-required physician and patient surveys must be completed again before Celgene will issue a new authorization number.

COUNT I

Infringement of U.S. Patent No. 6,140,346

106. Andrulis Pharmaceuticals restates and realleges the preceding paragraphs in this First Amended Complaint.

107. Celgene has directly infringed, and continues to directly infringe, one or more claims of the ’346 Patent, both literally and under the doctrine of equivalents, by making, using, selling, offering for sale, and/or administering thalidomide (Thalomid®) and lenalidomide (Revlimid®) with an alkylating agent, e.g., melphalan (Alkeran®), to treat certain cancers, e.g., multiple myeloma, including by administering itself and/or together with prescribing physicians under the direction and control of Celgene, Andrulis Pharmaceuticals’ patented combination therapy for the treatment of multiple myeloma. By doing so, Celgene has violated 35 U.S.C. § 271(a).

108. Celgene has actively induced, and continues to actively induce, others, e.g., prescribing physicians, to directly infringe, both literally and under the doctrine of equivalents, one or more claims of the ’346 Patent. Since at least August 2008, and likely before that date, Celgene has acted with knowledge, or at least with willful blindness, of the fact that the induced acts constitute infringement of one or more claims of the ’346 Patent. Celgene has intended to cause direct infringement by others, e.g., prescribing physicians. Celgene has taken affirmative steps to induce infringement by, among other things, communicating (orally and/or in writing) the advantages or benefits of using thalidomide (Thalomid®) and lenalidomide (Revlimid®) in

combination with melphalan (Alkeran®) to treat certain cancers, such as multiple myeloma. Thus, Celgene has aided, abetted, urged, or encouraged others, e.g., prescribing physicians, to directly infringe one or more claims of the '346 Patent, and Celgene has affirmatively and specifically intended to cause such direct infringement. By doing so, Celgene has violated 35 U.S.C. § 271(b).

109. Celgene has contributed, and continues to contribute, to the direct infringement, both literally and under the doctrine of equivalents, of one or more claims of the '346 Patent. Celgene offers to sell or sells components or materials, including thalidomide (Thalomid®) and lenalidomide (Revlimid®), that are specially designed for use in combination with melphalan (Alkeran®) to treat certain cancers, such as multiple myeloma, as claimed in the '346 Patent. These components or materials constitute a material part of the patented invention and, since at least after October 2007, have had no other substantial non-infringing uses. Since at least August 2008, and likely before that date, Celgene has known, or has been willfully blind to the fact, that others, e.g., prescribing physicians, infringe the '346 Patent by using (Thalomid®) and lenalidomide (Revlimid®) in combination with melphalan (Alkeran®) to treat certain cancers, such as multiple myeloma. By doing so, Celgene has violated 35 U.S.C. § 271(c).

110. Celgene's acts of infringement of the '346 Patent have been willful and deliberate. Since at least August 2008, and likely before that date, Celgene has acted with an objectively high likelihood that its actions constituted infringement of the '346 Patent by refusing to seek or take a license and continuing to make, sell, use, and/or promote thalidomide (Thalomid®) and lenalidomide (Revlimid®) in combination with melphalan (Alkeran®) to treat cancers. The objectively defined risk was either known to Celgene or so obvious that it should have been known to Celgene.

111. Andrulis Pharmaceuticals has suffered and continues to suffer damages as a result of Celgene's infringement of the '346 Patent. Pursuant to 35 U.S.C. § 284, Andrulis Pharmaceuticals is entitled to recover damages in an amount that is no less than a reasonable royalty from Celgene for its infringing acts. Andrulis Pharmaceuticals is further entitled to recover enhanced damages for Celgene's willful infringement of the '346 Patent.

112. Celgene's infringement of the '346 Patent has caused Andrulis Pharmaceuticals to suffer irreparable harm. Celgene's infringement will continue unless enjoined by the Court. Andrulis Pharmaceuticals has no adequate remedy at law and is entitled to preliminary and permanent injunctions prohibiting Celgene from infringing the '346 Patent.

Prayer for Relief

WHEREFORE, Andrulis Pharmaceuticals requests a judgment:

(a) declaring that Celgene has infringed the '346 Patent under 35 U.S.C. § 271;

(b) declaring that Celgene's infringement has been willful and deliberate;

(c) awarding damages adequate to compensate for Celgene's infringement of the '346 Patent, but in no event less than a reasonable royalty, and awarding increased damages due to Celgene's willful and deliberate infringement;

(d) awarding interest on all damages;

(e) preliminarily and permanently enjoining Celgene, its officers, agents, servants, employees, attorneys, and any person who acts in concert or participation with Celgene from infringing the '346 Patent;

(f) declaring this an exceptional case under 35 U.S.C. § 285 and awarding Andrulis Pharmaceuticals its attorneys' fees;

(g) awarding Andrulis Pharmaceuticals its costs and expenses; and

(h) granting such other and further relief as the Court deems just and proper.

Jury Demand

Andrulis Pharmaceuticals demands a jury trial on all issues so triable by right.

Dated: December 23, 2013

/s/ Kenneth L. Dorsney

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EXHIBIT A

US006140346A

United States Patent [19]

Andrulis, Jr. et al.

[11] Patent Number: 6,140,346

[45] Date of Patent: Oct. 31, 2000

[54] **TREATMENT OF CANCER WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-CANCER AGENTS**

[75] Inventors: **Peter J. Andrulis, Jr.**, Bethesda; **Murray W. Drulak**, Gaithersburg, both of Md.

[73] Assignee: **Andrulis Pharmaceuticals Corp.**, Bethesda, Md.

[21] Appl. No.: **09/071,813**

[22] Filed: **May 4, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/471,353, Jun. 6, 1995, abandoned.

[51] **Int. Cl.**[7] **A61K 31/445**; A61K 31/66; A61K 31/28; A61K 31/195; A61K 31/13; A61K 33/24

[52] **U.S. Cl.** **514/323**; 514/105; 514/492; 514/561; 514/564; 514/672; 424/649

[58] **Field of Search** 514/323, 105, 514/492, 561, 564, 672; 424/649

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,399,363 3/1995 Liversidge et al. 424/490

OTHER PUBLICATIONS

Nguyen et al., Int. J. Oncol., 10(5), 965–969 Abstract Only, 1997.

Primary Examiner—Jerome D. Goldberg
Attorney, Agent, or Firm—Isaac Angres

[57] **ABSTRACT**

A method is provided for the treatment of neoplastic diseases in a mammal which comprises administering to said mammal a therapeutically effective amount of thalidomide. The method also uses a combination of thalidomide with other anti-neoplastic agents. Additionally, pharmaceutical compositions containing thalidomide and other anti-cancer agents are also provided.

3 Claims, No Drawings

TREATMENT OF CANCER WITH THALIDOMIDE ALONE OR IN COMBINATION WITH OTHER ANTI-CANCER AGENTS

This application is a continuation of Ser. No. 08/471,353, filed Jun. 6, 1995, now abandoned.

The present invention relates to a novel method for treating cancers with thalidomide alone or in combination with other antiangiogenic and anti-cancer agents. The present invention also relates to methods of treating cancers with cytokine/growth factor inhibitors such as those agents inhibitory to basic fibroblast growth factor (bFGF), Tumor Necrosis Factor alpha (TNF-alpha), and interleukin 1 beta (IL-1 beta) and other antiangiogenic agents as well as pharmaceutical compositions containing thalidomide and/or other antiangiogenesis agents and/or anticancer drugs.

The present invention further relates to a method for ameliorating the symptoms of neoplastic diseases by administering thalidomide alone or in combination with other anti-neoplastic drugs.

The instant invention also relates to a method for inhibiting establishment of neoplastic metastasis by administering thalidomide alone or in combination with other anti-neoplastic drugs.

BACKGROUND OF THE INVENTION

Cancer is second only to cardiovascular disease as a cause of death in the United States. One third of all individuals in the United States will develop cancer and 20% of Americans will die of the disease. In the United States in 1992 there were 26,000 deaths due to malignancies and, of these, half of the deaths were due to the three most common types of cancer lung, breast and colon.

Further, cancer is defined as an abnormal growth of tissue characterized by a loss of cellular differentiation. This term encompasses a large group of diseases in which there is an invasive spread of such undifferentiated cells from a primary site to other parts of the body where further undifferentiated cellular replication occurs, which eventually interferes with the normal functioning of tissues and organs. According to Harrison's *Principles of Internal Medicine,* 13th Edition (McGraw Hill NY, Chap. 317–318, 1994), the terms cancer, neoplasia and malignancy are often used interchangeably in both lay and professional publications.

Cancer is defined by four characteristics which differentiate neoplastic cells from normal ones:

(1) Clonality—Cancer starts from genetic changes in a single cell which multiplies to form a clone of neoplastic cells;

(2) Autonomy—Biochemical and physical factors that normally regulate cell growth, do not do so in the case of neoplastic cells;

(3) Anaplasia—Neoplastic cells lack normal differentiation which occurs in nonmalignant cells of that tissue type;

(4) Metastasis—Neoplastic cells grow in an unregulated fashion and spread to other parts of the body.

Each cancer is characterized by the site, nature and clinical cause of undifferentiated cellular proliferation. The underlying mechanism for the initiation of cancer is incompletely understood; however, 80% of cancers are believed to be triggered by external stimuli such as exposure to certain chemicals, tobacco smoke, UV rays, ionizing radiation and viruses. Development of cancer in immunosuppressed individuals indicates the immune system is an important factor

controlling the replication and spread of cancerous cells throughout the body.

The high incidence of cancer in certain families, though, suggests a genetic disposition towards development of cancer. The molecular mechanisms involved in such genetic dispositions fall into a number of classes including those that involve oncogenes and suppressor genes (Vogelstein, et al., *Cell,* 70:523, 1992).

Proto-oncogenes are genes that code for growth promoting factors necessary for normal cellular replication. Due to mutation, such proto-oncogenes are inappropriately expressed—and are then termed oncogenes. Oncogenes can be involved in malignant transformation of the cell by stimulating uncontrolled multiplication.

Suppressor genes normally act by controlling cellular proliferation through a number of mechanisms including binding transcription factors important to this process. Mutations or deletions in such genes contribute to malignant transformation of a cell. Examples of suppressor genes include p53 on chromosome 17, which enables a cell to repair damaged DNA, and DCC on chromosome 18, which normally appears on colon cells enabling them to stick together but is deleted in cancerous colon cells (Cavenee and White, *Scientific American,* 272:72–9, 1995).

Malignant transformation develops and cancer results because cells of a single lineage accumulate defects in certain genes such as proto-oncogenes and suppressor genes responsible for regulating cellular proliferation. A number of such specific mutations and/or deletions must occur in a given cell for initiation of uncontrolled replication. It is believed that genetic predisposition to a certain type of cancer results from inheritance of genes that already have a number of mutations in such key regulatory genes and subsequent exposure to environmental carcinogens causes enough additional key mutations or deletions in these genes in a given cell to result in malignant transformation (Nowell et al., *Science,* 194:23–8, 1976). Changes in other types of genes could further the ability of tumors to grow, invade local tissue and establish metastases at distant body sites.

Cancers can produce clinical symptoms in three general ways:

1) Obliteration of normal tissues with concomitant interference with normal tissue function, as cancerous cells proliferate. This local expansion of cancerous tissue can result in pain due to pressure on or stretching of nerve fibers;

2) Excessive or inappropriate production of biologically active agents by cancerous cells such as cytokines or hormones. This can result in clinical illness. Such agents are important because they may serve as markers for a certain tumor type, may produce symptoms themselves and may serve to promote direct tumor growth;

3) Psychological effects upon the patient.

Early detection of cancer by the clinician depends on his awareness of the patient's family history with respect to different types of cancer, possible exposure of the patient to environmental factors that cause cancer combined with manifestation of any of the seven common warning signs of cancer:

1) change in bowel or bladder habits;

2) a sore that does not heal;

3) unusual bleeding or discharge;

4) thickening or lumps in the breast or elsewhere;

5) obvious change in a wart or mole;

6) nagging cough or hoarseness;

7) indigestion or difficulty in swallowing.

The diagnosis of cancer is primarily made by histologic and cytologic examination of tumor specimens to exclude benign tumors, hyperplasia and inflammatory processes. After a diagnosis of cancer is made, the description of the malignancy should include three characteristics that classify the neoplasm, yield information important to prognosis and, together with determining the anatomic extent of tumors (staging), help select optimal therapy:

1) Tissue of origin of the cancer;

2) Anatomic origin of the cancer;

3) Degree of cellular differentiation of the tumor.

With most solid tumors, it is the metastatic encroachment of the tumor on ohter vital function that causes the demise of the patient. Approximately 30–40% of patients at initial diagnois have metastatic disease; once this occurs, there is a relentless progression of the disease. Invasion is a prerequisite for migrationof tumor cells in connective tissue stroma and baseement membranes form the major physical barriers to the migration process.

This local extracellular matrix (ECM) invasion is the initial event in the development of metastasis although the rate limiting step in the often prolonged natural history of tumor metastasis is unknown. The sequential biochemical mechanism first invovles cell attachment to specific components of ECM followed by progressive protolytic dissolution.

The signaling pathways that intiate tumor cell migdration are mong the least understood aspects of invasion and metastasis, but are believed to result from specific ligand-receptor interactions. Phospholipase A_2 (PLA_2) is akey membrane signaling enzyme that modulates the level of available arachidonic acid, the substrate required for the production of eicosanoids (e.g., prostaglandin's leukotrienes, and thromboxanes). These pro-inflammatory mediators have been implicated as initiators of metastasis in primary neoplastic tissue. Inhibition of PLA_2 has been suggested as a novel means to control chronic inflammation associated with tumor progression.

Cancer therapy is currently divided into five subspecialties: (1) surgery, (2) radiation therapy, (3) chemotherapy, (4) immunotherapy, and (5) anti-angiogenic therapy.

Surgery was the first and, in a number of cases, still the only effective therapy in many of the common solid tumors. However, surgery alone has been proven to be effective in treating only 25% of tumors. Most often surgery is used as a means of reducing the size of a tumor and is used in combination with other therapeutic approaches.

Radiation therapy acts by delivering ionizing electromagnetic radiation to a tumor site. Electromagnetic radiation, termed external beam radiation, is delivered externally to a body site from an outside source, while in bradytherapy radiation is delivered by insertion of radioactive materials within the body at the site of the tumor.

In radiation-induced cell death, reactive oxygen intermediates and free radicals are produced by exposure to the radiation. The utility of radiation depends on the inherent radiosensitivity of a given tumor versus adjacent normal tissue with the presence of oxygen in the tumor being an important determinant of radiosensitivity. Oxygen free radicals produced from the oxygen in the tumor by exposure to radiation damages cellular components, especially DNA. Radiation therapy has both short and long-term sequelae. Acute sequelae are self limited and include erythema and desquamation of skin; anemia, myelosuppression and gastrointestinal upset. Long-term sequelae can be progressive and include myelitis, pericarditis, stenoses, hepatitis, and nephropathy.

At the moment, chemotherapy is the primary treatment used for disseminated malignant disease. Often the tumor burden is initially reduced by surgery followed by chemotherapy whose goal it is to eliminate the undetectable micrometastasis which remain. Death of malignant cells by chemotherapy is dependent on the exposure time to the chemotherapeutic agent and its concentration, both of which are limited due to toxicity. In combination therapy, agents should have different mechanisms of action on tumor cells to complement each other and prevent resistance from developing. The following are a number of different groups of chemotherapeutic agents which are used alone or in combination to treat various cancers:

1) Antimetabolites: compounds that induce cytotoxicity in tumor cells by being false substrates in biochemical pathways which results in interference with important cellular functions. Examples include aminopterin, hydroxyurea, methotrexate, pyrimidine analogue antimetabolites such as fluorouracil and cytarabine, and purine analogue antimetabolites such as six-mercaptopurine, fludarabine, pentostatin and chlorodeoxyadenosine. High dosages of these drugs may be associated with acute renal damage, hepatotoxicity and gastrointestinal toxicity.

2) Plant alkaloids: vinca alkaloids such as vincristine and vinbiastine; the taxanes such as taxol; and the epipodophyllotoxins such as etoposide and teniposide. These substances may induce neurotoxicity, bone marrow hyperplasia and hypersensitivity reactions.

3) Anti-tumor antibiotics: anthracyclines such as doxorubicin, daunorubicin, idarubicin, and epirubicin; anthracenediones such as mitoxantone; cytotoxic glycopeptides such as bleomycin, mitomycin and dactinomycin. This group of compounds has been demonstrated to induce cardiomyopathy, tissue extravasation, chronic interstitial pneumonitis, renal failure, gastrointestinal toxicity and myelosuppression.

4) Alkylating agents: compounds that inhibit DNA synthesis by forming covalent bonds with nucleic acids. This group includes mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, and thiotepa as well as nitrosurea alkylating agents such as carmustine and lomustine and platinum compound alkylating agents such as cisplatin and carboplatin. The most common dose-limiting toxicity of these compounds is myelosuppression. Alkylating agents have also been known to induce secondary leukemias, neurotoxicity, myocardial necrosis and nephrotoxicity;

5) Endocrine therapy: adrenocorticosteroids such as prednisone, methylprednisone and dexamethasone; androgens such as fluoxymesterone; anti-androgens such as flutamide; estrogens such as diethylstilbestrol and ethinyl estradiol; anti-estrogens such as tamoxifen; progestins such as medroxyprogesterone and megastrol acetate; aromatase inhibitors such as aminoglutethimide; gonadotropin-releasing hormone agonists such as leuprolide and somatostatin analogues such as octreotide. Endocrine therapy maybe accompanied by neurotoxicity, metabolic derangements such as hyperglycemia, hypokalemia, fluid retention, hepatotoxicity, impotence, amenorrhea, nausea and maculopapular rash;

6) Other agents: dacarbazine, procarbazine and L-asparaginase.

Drug resistance exhibited by tumors is the most important cause of treatment failures. Such resistance is either de novo

in nature where tumors are inherently resistant to chemotherapy, or acquired, upon exposure to a chemotherapeutic agent. In the later instance, a tumor undergoes further spontaneous mutations resulting in a population of genetically heterogeneous cells as it grows from a single malignantly transformed cell. This heterogeneity applies to the extent individual cells in the tumor are susceptible to the chemotherapeutic agent as well. Treatment with a given agent will eliminate all the susceptible cells from the tumor and select for those cells that are resistant to the agent. To maximize success in treating such tumors it is important to initially reduce the tumor size by surgery and then use combination chemotherapy involving agents with distinctly different mechanisms of action.

Another facet of this combination approach to cancer therapy that may produce an answer to this issue of drug resistance is immunotherapy. The basic assumption here is that since tumor cells have antigens unique to the tumor on their surface, it may be possible to assist the host's immune system to more effectively respond to them and thereby destroy the cancer. A number of approaches have been used. For example, attempts have been made by a number of investigators to increase the antigen-specific immune response to the tumor by immunizing the host with cells originally taken from his tumor along with BCG. Hoover and Hanna (*Semin. Surg. Oncol.,* 5:436–440, 1989) reported that such a vaccine had a therapeutic effect in the treatment of colon cancer.

Cytokines such as interferon or interleukin 2 (IL-2) alone or with lymphokine-activated killer cells have been used as cancer therapeutics. Interferon-alpha has proven to be effective in treating hairy cell leukemia (Golomb et al., *Hematology,* 4thd ed., NY McGraw Hill, pgs. 1025–30, 1990, Quesada et al., *N. E. J. M.,* 310:15–18, 1984) and for AIDS-associated Kaposi's Sarcoma (Real et al., *J. Clin. Oncol.,* 4:544–551, 1986). IL-2 has been used in vitro to stimulate and develop natural killer cells taken from a cancer patient. Such cells are then reinfused back into the patient and have acted as an effective cancer therapy in renal cell carcinoma and melanoma (Greenberg, *Adv. Immunol,* 49:281–355, 1991; Yabro, *Semin. Surg. Oncol.,* 7:183–191, 1991). It is believed that IL-2 stimulates interferon gamma production, which in turn, induces genes that code for major histocompatibility class I and class II antigens that are essential for tumor antigen presentation leading to an adequate immune response (Janik, from *Clinical Applications of Cytokines* J. J. Oppenheim et al Editors, Oxford Univ. Press, NY, 1993). Another approach employing cytokines as anticancer therapeutics involves delivering cytokines continuously to the tumor by transfecting tumor cells in vitro with genes that code for cytokines so they can produce these cytokines when reinfused back into the patient. Tepper et al. (*Cell,* 57:503–12, 1989) studied the introduction of the IL-4 gene into several tumor cell types. The problem encountered, however, was that many cytokine-producing cells failed to grow when infused into animals. However, Golumbek et al. (*Science,* 254:713–6, 1991) showed that tumor cells expressing IL-4 were able to cause tumor regression in animals, thereby validating this approach. Kedar and Klein (*Adv. Cancer Res.,* 59:245–322, 1992) modified this approach by obtaining T cells that had infiltrated a tumor, exposing them to IL-2 in vitro, and reinfusing them into the same patient. Although this approach has shown promise, it is limited by difficulties in obtaining and expanding the cytotoxic T cell populations needed. Cytokine therapy in general has not been as effective as hoped for in the treatment of cancer because under natural conditions cytokines are produced and act in synchrony with one another; to administer one cytokine in high doses upsets the natural balance and can result in many unforeseen effects on other cytokines and more generally the host (Janik, from *Clinical Applications of Cytokines* J. J. Oppenheim et al Editors Oxford Univ. Press, NY, 1993).

The difficulty in working with cytokines is that they can facilitate cancer as well as treat it. It is well known that in order for tumors to grow and spread, they must have an adequate blood supply, so angiogenesis is a necessary part of a cancer's progression (Folkman, *J. Natl. Cancer Inst.,* 82:4–6, 1990). Further, the continuous stimulation of neovascularization is also a prerequisite for metastasis (Weidner et al., *N.E.J.M.,* 324:1–8, 1991). Tumor angiogenesis may be mediated by dysregulation of certain cytokines which play a role in the normal angiogenic process (Rosen, *EXS,* 65:301–10, 1993). Angiogenesis involves a series of discrete steps commencing with the formation of new capillaries derived from the existing microvasculature (Folkman, *Adv. Cancer Res.,* 43:175–203, 1985). Initially, protease degradation of the basement membrane of the parent blood vessel enables endothelial cell migration into the tissue in response to an angiogenic stimulus. These migrating endothelial cells differentiate into a lumen or sprout which increases in length with time as endothelial cells proliferate. Since there are a series of discrete steps involved in angiogenesis, this has presented a opportunity for development of a number of therapies each with a markedly different mechanism of action. Optimal anti-angiogenic therapy, therefore, may involve multiple therapeutic interventions at the different steps of angiogenesis.

The following are examples of some of these cytokine-based approaches to anti-angiogenic and/or cancer therapy:

1) Agents such as lisofylline (CT1501R) and CT2584 inhibit tumor angiogenesis by interfering with the lipid second messenger phosphatidic acid which is common to both angiogenic growth factors and autocrine tumor growth factor production;

2) Antibodies against the transmembrane glycosylated 185 KD tyrosine kinase of erbB2 oncogene neu. Amplification of erbB2 has an adverse effect in patients with breast cancer (Slamon et al., *Science,* 235:177–82, 1987). An antibody against p185 causes transformed neu cells to revert to a nontransformed phenotype. Growth of tumor xenografts were inhibited by a monoclonal antibody to p185 in a dose dependent manner (Drebin et al., *Proc. Natl. Acad. Sci. (USA),* 83:9129–33, 1986). An antibody to the product of erbB2 can inhibit proliferation of breast adenocarcinoma cells which express elevated levels of p185 (Kumar et al., *Mol. Cell Biol.* 11:979–86, 1991);

3) Protease inhibitors such as Batismastat (BB94), an anti-metalloprotease, as well as cartilage and eye-derived protease inhibitors. Each inhibits proteases involved in a number of steps of angiogenesis including degradation of the basement membrane of parent venules to facilitate endothelial cell escape during capillary sprouting and migration (Moses and Langer, *Biotechnology,* 9:630–34, 1991);

4) Antibodies against the tumor vasculature itself, such as antibody to vitronectin (integrin avB3) which blocks interaction between this receptor and matrix proteins resulting in apoptosis of dividing immature endothelial cells;

5) Inhibitors to such heparin binding growth factors as the fibroblast growth factors (FGF), which are involved in

tumor growth and/or angiogenesis. The affinity of FGF for heparin regulates their function in vivo. Heparin produced by vascular endothelial cells (Nader et al., *Proc. Natl. Acad. Sci.* (*USA*), 84:3565–9, 1987) can break down into low molecular weight degradation products (Vannucchi et al, *Biochem. Biophys. Res. Commun.,* 140:294–301, 1986). It is believed that such degradation products act as a heparin transport system for FGF's into endothelial cells (Folkman and Ingber, In *Angiogenesis: Regulatory Role of Heparin and Related Molecules,* Lane, Lindahl Editors London: Edward Arnold, 317–333, 1989). Agents such as pentosan polysulfate, platelet factor 4 (PF_4) and protamine act as inhibitors of such heparin-binding growth factors, such as FGF's by binding to heparin and thus preventing it from growth factor binding (Folkman and Shing, *Adv. Exp. Med. Biol.,* 313:355–64, 1992). Chick embryo and rabbit cornea animal models have demonstrated that such agents inhibit angiogenesis (Taylor et al., *Nature,* 297:307–12, 1982) and tumor growth in animals (Maione, *Science,* 247:77–9, 1990; *Cancer Res.,* 51:2077–2083, 1991);

6) Angiostatic steroids are combinations of heparin derivatives and glucocorticosteroids which inhibit capillary endothelial cell proliferation (Sakamoto et al., *Cancer J.,* 1:55–58, 1986); and tumor extracts from animals treated with the two substances can inhibit endothelial cell migration (Rong et al., *Cancer,* 57:586–90, 1986). One mechanism of action for these angiostatic steroids maybe by influencing endothelial cell migration and proliferation or by dissolving the basement membrane resulting in a loss in capillary viability (Ingber et al., *Endocrinology,* 119:1768–75, 1986);

7) Thrombospondin is a 140 KD protein that inhibits angiogenesis in vivo in the the corneal pocket assay and capillary endothelial cell migration in vitro (Good et al., *Proc. Natl. Acad. Sci.* (*USA*), 87:6624–8, 1990). Thrombospondin has a high affinity for heparin derivatives (Folkman and Shing, *Adv. Exp. Med. Biol.,* 313:355–64, 1992).

8) Cytokines such as IL-12 which exhibit preliminary evidence of an inhibitory effect on angiogenesis.

In addition to the previously cited angiogenic interventions used to treat cancer, applicants have developed a novel approach to antiangiogenic therapy which is based on the role of IL-1 beta, TNF alpha and basic FGF (bFGF) play in tumor development and angiogenesis.

IL-1 beta and TNF-alpha can stimulate tumor cell mobility and invasiveness by eliciting the expression of plasminogen activators in tumor cells. Such plasminogen activators convert latent proenzyme plasminogen into plasmin, a serine protease that degrades the basement membrane of the microvasculature and facilitates tumor cell spread from the blood into adjacent tissues (Rosen et al., *EXS,* 65:301–10, 1993). Further TNF-alpha also stimulates endothelial cell motility in vitro (Leibovich, *Nature,* 329:630–632, 1987; Rosen et al., from *Cell Motility Factors,* Goldberg and Rosen, Editors Verlag, Basel, pg. 194–205, 1991) and demonstrates strong angiogenic activity in vivo (Leibovich et al., *Nature,* 329:630–632, 1987; Frater-Schroder et al., *Proc. Natl. Acad. Sci.* (*USA*), 84:5277–5281, 1987). IL-1 beta and TNF-alpha are important factors in in vitro induction of the endothelial cell-leukocyte receptor E-selectin (Bevilacqua et al., *Science,* 243:1160–65, 1989), VCAM1 (Elices et al., *Cell* 60:577–84, 1990) and ICAM (Rothein et al., *J. Immunol,* 137:1270–4, 1986); and of dermal vasculature in vivo. It is believed that expression of macrophage receptors on the surface of endothelial cells facilitates the binding of these cells that is the precondition to transendothelial migration. Once in the tissues, macrophages are believed to act as an angiogenic stimulus by secreting angiogenic substances such as bFGF (Frater Schroder et al., *Proc. Natl. Acad. Sci.* (*USA*), 84:5277–5281, 1987). Gross et al. (*J. Natl. Cancer Inst.,* 85:121–131, 1993) showed that bFGF stimulates proliferation in some tumor cells and facilitates tumor vascularization.

Thalidomide has been shown to inhibit TNF-alpha production in erythema nodosum leprosum patients (Sarno et al., 1991) and in vitro stimulated monocytes (Sampaio et al., *J. Exp. Med.,* 173:699–703, 1991). Shannon et al. (*Amer. Soc. for Microbiology Ann. Meeting,* Abst. U-53, 1990) indicated thalidomide inhibited IL-1 beta production in vitro. Furthermore, D'Amato et al. (*Proc. Natl. Acad. Sci.* (USA), 91:4082–5, 1994) demonstrated that thalidomide was an effective inhibitor of angiogenesis induced by bFGF in the rabbit cornea micropocket assay. In light of thalidomide inhibitory activity on IL-1 beta, TNF-alpha and bFGF and the role these cytokines to play in angiogenesis, the purpose of this invention is to use thalidomide alone or in combination with other anti-cancer and/or anti-angiogenic therapies to treat cancer. An example of such combination therapy could involve thalidomide given with pentoxifylline and a glucocorticoid such as dexamethasone. The activity of each of these agents would be expected to enhance that of the other two in inhibiting TNF-alpha synthesis since each of these agents acts as a inhibitor at a different point in this synthesis. Pentoxifylline inhibits TNF-alpha gene transcription (Doherty et al., *Surgery,* 110:192, 1991), while thalidomide enhances TNF-alpha m-RNA degradation (Moreira et al., *J. Exp. Med.,* 177:1675–80, 1993) and glucocorticoids such as dexamethasone inhibit TNF-alpha m-RNA translation (Han et al. *J. Exp. Med.,* 172:391, 1990).

Thalidomide was first synthesized and marketed in the 1950's as a sedative. The toxicity of the compound was so low that a dose killing 50% of animals (LD_{50}) could not be established. Thalidomide was therefore thought to be a safer alternative to barbiturates. In 1961 thalidomide administered to pregnant women resulted in an epidemic of congenial malformations. The incidence of malformed babies paralleled the sales of thalidomide and quickly dropped off when thalidomide was removed from the market.

Oral administration of thalidomide in the range of 100–200 mg in adult humans results in a peak blood level of 0.9–1.5 mg/liter after 4–6 hours. Hydrolytic cleavage of thalidomide occurs in vitro, the rate of which increases as the pH increases. However, hydrolytic cleavage of thalidomide in serum is much slower than in vitro at pH 7.4. This may be due to thalidomide being highly bound to plasma proteins. Studies in animals demonstrated high thalidomide concentrations in the gastrointestinal tract, liver and kidneys with lower concentrations in muscle, brain and adipose tissue. In pregnant animals, thalidomide can pass across the placenta. Although a complete study of thalidomide metabolism in humans has not been performed, in animals the main pathway for thalidomide breakdown appears to be nonenzymatic hydrolytic cleavage.

Even though immunodulatory effects of thalidomide have not been clearly defined at the molecular level, thalidomide has been used to treat a number of immunologically based diseases such as: aphthous ulcers (Jenkins et at., *Lancet,* 2:1424–6, 1984; Grinspan, *J. Amer. Acad. Dermatol,* 12:85–90, 1985; Revuz et al., *Arch. Dermatol,* 126:923–7, 1990), Graft vs Host Disease (Lim et al., *Lancet,* 1:117,

1988; McCarthy et al., *Lancet,* 2:1135, 1988; Henley et al., *Lancet,* 2:1317, 1988), erythema nodosum leprosum (Sheskin, *Lepr. Rev.,* 36:183–7, 1965; Sheskin and Convit, *Int. J. Lepr.,* 37:135–46, 1969; Pearson and Vedagiri, *Lepr. Rev.,* 40:111–6, 1969), Behcet's syndrome (Saylan and Saltik, *Arch. Dermatol* 118: 536, 1982; Jorizzo et al., *Arch. Int. Med.,* 146:878–81, 1986), actinic prurigo (Londono, *Int. J. Dermatol,* 12:326–8, 1973; Lovell et al., *Brit. J. Dermatol,* 108:467–71, 1983), ulcerative colitis (Waters et al., *Brit. Med. J.,* 1:792, 1979) and discoid lupus erythematosus (Knop et al., *Arch. Dermatol Res.,* 271:165–70, 1981). In these studies, dosages of thalidomide ranging from 100 mg/day to 800 mg/day were administered without serious side effects.

SUMMARY OF THE INVENTION

The primary objective of the present invention is to provide a method for the treatment of angiogenesis accompanying cancer with antiangiogenic agents, including inhibitors of cytokines and growth factors.

A further objective of the present invention is the treatment of cancers with thalidomide alone or in combination with other agents that inhibit angiogenesis, including cytokines and growth factors, and/or with other classes of anticancer therapeutics.

Another objective of the current invention is to provide a method for treating cancer with thalidomide at a given regimen.

An additional objective of the current invention is to provide compositions of matter comprising one or more antiangiogenic agents and/or cytokine and/or growth factor inhibitors with one or more anticancer therapeutics.

A further objective of the present invention is a method for the treatment of cancers which comprises therapy with thalidomide and other drugs on alternative days by diverse schedules.

An additional objective of the current invention is to utilize thalidomide alone or in combination with other antiangiogenic agents, including cytokine and growth factor inhibitors and/or other cancer treatments as a maintenance therapy to prevent the relapse of cancer.

A still further objective of this invention is to use thalidomide alone or in combination with other angiogenesis and/or cytokine or growth factor inhibitors and/or other cancer treatments as prophylactic therapy for individuals believed to be susceptible to developing a certain type of cancer.

Another objective of the present invention is to provide a method for inhibiting the establishment of cancer metastases by administering thalidomide alone or in combination with other chemotherapeutic agents.

Another further objective of the present invention is to provide a method for treating Kaposi's Sarcoma by administering thalidomide either orally or topically.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Within the context of the present specification, applicant will use the terms cancer and neoplasms interchangeably and their meaning is intended to be the same. Accordingly, the present invention is directed to a method for the treatment of neoplastic diseases in a mammal which comprises administering to said mammal a therapeutically effective amount of thalidomide.

The instant invention is more particularly directed to a method for the treatment of solid neoplasms in a mammal which comprises administering to said mammal a therapeutically-effective amount of an inhibitor selected from the group consisting of basic fibroblast growth factor (bFGF) inhibitors, tumor necrosis factor alpha (TNF-alpha) inhibitors and Interleukin-1 beta (IL-1 beta) inhibitors.

In another aspect of the invention, a method is provided for the inhibiting the establishment of neoplastic metastasis in a mammal afflicted with a neoplastic condition which comprises administering to said mammal a therapeutically-effective amount of thalidomide to inhibit said tumor development.

The invention also provides a method for the treatment of Kaposi's sarcoma in a patient which comprises administering to said afflicted patient a therapeutically-effective amount of thalidomide.

The therapeutic treatment with thalidomide can utilize any type of administration including oral administration, topical application, intramuscular injection and intravenous infusion. The effective dose per kg of body weight may be determined for example by chemosensitive assays utilizing cells derived from the patient neoplasms. A typical therapeutic dose is about 100 mg to 1200 mg/kg of thalidomide for a typical body weight of 70 kg.

In another embodiment, applicants provide a pharmaceutical composition of matter suitable for treating and inhibiting the spread of cancer comprising: (a) a therapeutically effective amount of thalidomide; (b) a effective amount of an anticancer drug selected from the group consisting of antimetabolites, plant alkaloids, anti-tumor antibiotics, alkylating agents, endocrinologic drugs and miscellaneous anticancer agents and (c) effective amounts of another TNF alpha, IL-1 beta and bFGF inhibitors.

Suitable antimetabolites are compounds that induce cytotoxicity in tumor cells by being false substrates in biochemical pathways which results in interference with important cellular functions. Examples of antimetabolites are aminopterin, hydroxyurea, methotrexate, pyrimidine analogue antimetabolites such as fluorouracil and cytarabine, and purine analogue antimetabolites such as six-mercaptopurine, fludarabine, pentostatin, and chlorodeoxyadenosine.

The preferred plant alkaloids consist of vinca alkaloids such as vincristine and vinblastine; the taxanes such as taxol; and the epipodophyllotoxins such as etoposide and teniposide.

Suitable anti-tumor antibiotics include the anthracyclines such as doxorubicin, daunorubicin, idarubicin, and epirubicin; antracenediones such as mitoxantone; cytotoxic glycopeptides such as bleomycin, mitomycin and dactinomycin.

Alkylating agents which can be used are compounds that inhibit DNA synthesis by forming covalent bonds with nucleic acids. This group includes mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, and thiotepa as well as nitrosurea alkylating agent such as carmustine and lomustine and plantinum compound alkylating agents such as cisplatin and carboplatin.

Compounds suitable for endocrine therapy includes adrenocorticosteroids such as prednisone, methylprednisone and dexamethasone; androgens such as fluoxymesterone; anti-androgens such as flutamide; estrogens such as diethylstilbestrol and ethinyl estradiol; anti-estrogens such as tamoxifen; progestins such as medroxyprogesterone and megastrol acetate; aromatase inhibitors such as aminoglutethimide; gonadotropin-releasing hormone agonists such as leuprolide and somatostatin analogues. Endocrine therapy may be accompanied by neutrotoxicity or metabolic

derangements such as hyperglycemia, hypokalemia, fluid retention, hepatotoxicity, impotence, amenorrhea, nausea and maculopapula rash.

Other miscellaneous agents which include dacarbazine, procarbazine and L-asparaginase.

The instant invention is also directed to a method for inhibiting the spread of malignant neoplasms selected from the group consisting of lung and breast neoplasms, prostatic carcinoma, brain cancer, as well as other cancers in a mammal in need thereof which comprises administering to said mammal an effective amount of thalidomide alone or in combination with other anti cancer agents. Other cancers contemplated within the scope of the invention include colonic, GI, pancreatic, uterine, ovarian, endometrial, bone or any other cancer of epithelial or connective tissue cell origin.

When used alone, the therapeutically effective amounts of thalidomide are typically 50 mg to 1000 mg and preferably 100 mg to 750 mg one to three times a day for a sufficient period of time to induce shrinkage or remission of the cancer.

Under certain circumstances, it is desirable to administer thalidomide therapy simultaneously with other anti-cancer drugs. For example, 500 mg of thalidomide can be administered three times a day while the patient is being given a chemotherapeutic treatment with carmustine, i.e., 150–200 mg/m^2 every six weeks.

If Lomustine is given orally, typically 130 mg/m^2 in a single oral dose is given every six weeks while the patient is in thalidomide therapy. When bleomycin is the drug of choice, 10 to 20 units/m^2 IV is given daily for five days every three weeks. The therapy with all of the above chemotherapeutic compounds is given concurrently or separately with thalidomide. In an alternate embodiment, thalidomide is administered every other day.

The precise amount of thalidomide alone or in combination With other chemotherapeutic agents mentioned above will vary depending, for example, on the condition for which the drug is administered and the size and kind of the mammal. Generally speaking the thalidomide can be employed in any amount effective in the treatment of cancers.

For humans, typically effective amounts of thalidomide for use in the unit dose compositions of the present invention range form 50 mg to 1200 mg per 24 hours; however, greater amounts may be employed if desired. This range is based on administration to a 70 Kg human. A preferred amount is 100 to 1500 mg per 24 hour period. Of course, the amounts of each compound selected will depend on the weight of the mammal and the disease state. One skilled in the art can adjust the dosage forms to achieve the desired therapeutic levels.

The compound of the present invention can be prepared and administered in a wide variety of oral, topical and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the component, either thalidomide alone or in combination with other compounds.

Preferably the compounds of the present invention are administered orally, cutaneously, intramuscularly, subcutaneously, or intravenously.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutical acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders, capsules and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills cachets, and lozenges can be used as solid dosage forms suitable for oral administration. Lotions, ointments, or suspensions can be used as dosage forms for topical application.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid for preparations include solutions, suspension, emulsions, for example, water or water propylene glycol solutions or DMSO solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution or DMSO-water solutions.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid for preparation for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, lotions, ointments and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, lotion, ointment, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

It is also possible to administer thalidomide in a time-release formulation. A wide variety of methods are now available in the art for preparing time-release or long-acting compositions. Any of these time-release or long-acting formulations are suitable in the practice of the present invention as long as it does not adversely affect the effec-

tiveness of the thalidomide in the treatment of the cancer. Advantages of time-release formulations include a lower concentration of peak serum absorption which substantially reduces the adverse side effects and toxicity of the compound administered. In addition, a reduced frequency of administration results, which substantially improves patient compliance. A frequency of administration of every 12 to 24 hours would be preferred. In addition, more constant serum concentration of thalidomide would result thereby allowing a more consistent relief of symptoms.

The following examples, not to be construed as limiting, illustrate formulations which can be made according to the invention.

EXAMPLE 1

500 mg of thalidomide are mixed with 130 mg of lomustine. The active ingredients are triturated and q.s. with lactose to selected capsules size.

EXAMPLE 2

500 mg of thalidomide are mixed with 375 mg of cyclophosphamide. The active ingredients are triturated and q.s. with lactose to selected capsule size.

EXAMPLE 3

250 mg of thalidomide are mixed with 100 mg of taxol. The active ingredients are triturated and q.s. with lactose to selected capsule size.

The following Examples further illustrate the usefulness of the invention.

EXAMPLE 4

750 mg of thalidomide are mixed with 100 mg of tamoxifen. The active ingredients are triturated and q.s. with lactose into selected capsule size.

EXAMPLE 5

Hard gelatin capsules are prepared using the following ingredients

Thalidomide	250
Starch dried	200
Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

EXAMPLE 6

A tablet formula is prepared using the ingredients below

Thalidomide	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5

The components are blended and compressed to form tablets each weighing 665 mg.

EXAMPLE 7

Tablets each containing 60 mg of active ingredient are made up as follows:

Thalidomide	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50–60° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed by a tablet machine to yield tablets each weighing 150 mg.

EXAMPLE 8

Capsule each containing 80 mg of medicament are made as follows:

Thalidomide	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

EXAMPLE 9

Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

Thalidomide	50 mg
Sodium carboxymethylcellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v
Color	q.v
Purified water to	5 ml

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

EXAMPLE 10

Capsules each containing 150 mg of medicament are made as follows:

Thalidomide	150 mg
Starch	164 mg
Microcrystalline cellulose	164 mg
Magnesium stearate	22 mg
Total	500 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 500 mg quantities.

The thalidomide alone or in combination with other therapeutic agents can also be formulated in liposomal form. The liposomal-encapsulated thalidomide composition of the present invention also represents a novel approach in cancer therapy.

The liposome-encapsulated material can be obtained by dissolving thalidomide in a solvent. The solvent used is preferably a polar organic solvent, e.g., methanol or ethanol. When the thalidomide is completely dissolved in the solvent, the dissolved thalidomide is complexed with cardiolipin by adding a solution of cardiolipin to the solvated chemotherapeutic agent. The solvent used to dissolve the cardiolipin can be methanol or ethanol.

The mixture obtained is then stirred gently and evaporated under an inert atmosphere to dryness. The inert atmosphere can be nitrogen, argon, or combination of these two.

To this dried mixture, one then adds phosphatidylcholine, cholesterol, and either phosphatidylserine or dicetylphosphate (DCP). The mixture obtained is then stirred gently to achieve a homogeneous solution and evaporated to dryness under an inert atmosphere to produce lipids and drug films.

The dried lipids are then resuspended in a solution where they are hydrated and then sonicated. The solution used can be a saline solution, a phosphate buffered saline, a lactose solution, a glucose solution, a mannitol solution, or any other known physiologic buffered solution. Non-entrapped thalidomide is separated from the liposome-encapsulated thalidomide by dialysis and/or high speed centrifugation.

If desired, the liposome encapsulated thalidomide can then be lyophilized to permit storage. If the liposome-encapsulated thalidomide is stable in solution, however, it can be stored in a saline or lactose medium.

In the above preparation, the relative amounts of the components used to prepare the liposome-encapsulated thalidomide are as follows. The thalidomide is used in an amount of from 6.8 parts by weight to 9.2 parts by weight. The cardiolipin is used in an amount of from 30.6 parts by weight to 41.4 parts by weight. The phosphtidylcholine is used in an amount of form 102 parts by weight to 138 parts by weight. The cholesterol is used in an amount of from 34 parts by weight to 46 parts by weight. And the phosphatidylserine or dicetyphosphate is used in an amount of from 6.8 parts by weight to 9.2 parts by weight.

Those liposome-encapsulated chemotherapeutic compositions are useful in the treatment of solid cancers such as lung, breast prostate, colon, GI and others. In the treatment of these tumors, the liposome-encapsulated chemotherapeutic agent dissolved in an appropriate pharmaceutical carrier or excipient is administered intravenously either as a bolus or continuously over a period of from 5 minutes to 30 minutes. In continuous administration, the liposome-encapsulated therapeutic agent suspended in an appropriate pharmaceutical carrier or excipient can be delivered by osmotic pump.

Carriers which can be used in the present invention include suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Suitable formulations for intravenous administration of the active compound may include suspensions of the active ingredients.

Solutions for administration intravenously contain from about 0.1 to about 99.5% by weight, and preferably from about 25 to 85% by weight of active ingredients, together with the excipient.

The dose and the route of administration and the carrier and/or adjuvants used may vary based on the tumor type being treated and in view of known procedures for treatment of such tumors.

EXAMPLE 11

Liposomal Encapsulation

To encapsulate thalidomide in liposome, various lipid constituents were investigated and percent efficiency of the drug entrapped in liposomes was determined. The best combination of lipids which is developed in our laboratories is as follow:

Thalidomide 8 mg, was dissolved in methanol and stirred gently to achieve a clear solution, and was complexed with 36 mg of cardiolipin in ethanol. The mixture was stirred gently and evaporated under N_2 to dryness. To this dried mixture were then added 120 mg of phosphatidycholine, 40 mg of cholesterol and 8 mg of phosphatidylserine. The mixture was stirred gently to achieve a homogeneous solution and evaporated to dryness under N_2. The dried lipids were resuspended in 0.9% NaCl solution, hydrated for 112 hour in the dark and then sonicated in a cup-horn sonicator at 37° C. for 30 minutes. The non-entrapped was separated from liposomal encapsulated drug by extensive dialysis against 0.9% NaCl at 4° C. for 24 hours with at least 3 changes of saline solution. The percentage of entrapment of thalidomide in liposomes is determined spectrophometrically after the completion of dialysis.

EXAMPLE 12

Clinical Applications of the Invention

For patients who initially present without metastatic disease, thalidomide is used as an immediate initial therapy prior to surgery and radiation therapy, and as a continuous post-treatment therapy in patients at risk for recurrence or metastasis. The goal in these patients is to decrease the potential for metastatic cells from the primary tumor to develop into secondary tumors at other body sites.

For patients who initially present with metastatic disease, thalidomide is used as a continuous supplement to, or possible as a replacement for chemotherapy. The goal in these patients is to reduce or eliminate the possibility of metastases from primary tumors developing into secondary tumors at other body sites.

Thalidomide may be administered to a patient having prostate carcinoma at a dosage level of 750 mg once a day for a period of 10 days. The patient is monitored by observing the following parameters:

1. Tumor growth: x-rays and MRI and PET scans are used to determined if regression has occurred after one 10 day cycle of therapy.
2. Blood: the leukocyte count is observed between the 3rd and 5th days to see if there is an increase.
3. Liver function: urinalysis, serum creatinine and uric acid levels are monitored to determine toxicity.
4. The levels of the enzymes SGOT, SGPT, serum alkaline phosphatase are also determined.
5. Neurological side effects are also monitored during therapy.

It is to be understood that the forms of the invention herein are to be taken as preferred examples of the same and that various changes may be made without departing from the spirit of the invention or scope of the subjoined claims:

1. An enhanced pharmaceutical composition suitable for treating neoplastic diseases sensitive to said enhanced composition comprising:

(a) an enhanced effective amount of thalidomide;

(b) an effective amount of an alkylating agent selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin; and

(c) a pharmaceutically acceptable inert carrier.

2. A method for the treatment of neoplastic diseases in a mammal which comprises administering to said afflicted mammal enhanced therapeutically-effective amounts of thalidomide in combination with effective amounts of other alkylating agent selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin wherein said neoplastic diseases are sensitive to said enhanced combination.

3. An enhanced pharmaceutical composition suitable for treating neoplastic diseases sensitive to said enhanced composition comprising:

(a) an enhanced effective amount of thalidomide; and

(b) an effective amount of an alkylating agent selected from the group consisting of mechlorethamine, cyclophosphamide, ifosamide, melphalan, chlorambucil, busulfan, thiotepa, carmustine, lomustin, cisplatin, and carboplatin.

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