Current Clinical Trials of R115777 (Zarnestra)

Review Article  [1]  July 01, 2002
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R115777 (Zarnestra) is an orally available methylquinolone derivative from Johnson & Johnson Pharmaceutical Research and Development L.L.C. that is a potent and selective nonpeptidomimetic farnesyltransferase inhibitor (FTI).[1] FTIs represent a new class of agents that were originally developed to inhibit tumors by interfering with posttranslational processing of oncogenic Ras protein. The anticancer activity of FTIs might stem from their ability to effect various proteins other than Ras that can also mediate signal transduction, apoptosis, angiogenesis, and growth.[2]

“115777 (Zarnestra) is an orally available methylquinolone derivative from Johnson & Johnson Pharmaceutical Research and Development L.L.C. that is a potent and selective nonpeptidomimetic farnesyltransferase inhibitor (FTI).[1] FTIs represent a new class of agents that were originally developed to inhibit tumors by interfering with posttranslational processing of oncogenic Ras protein. The anticancer activity of FTIs might stem from their ability to effect various proteins other than Ras that can also mediate signal transduction, apoptosis, angiogenesis, and growth.[2]

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community. It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).* We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study. This month's installment of Clinical Trials Referral Resource is devoted to current clinical trials of R115777 (Zarnestra). For patient entry information, see the individual trials.

In vitro experiments, using isolated human farnesyl protein transferase, demonstrated that R115777 competitively inhibited farnesylation of substrates with IC\textsubscript{50} values of 0.86 nM (lamin B) to 7.9 nM (K-ras). The majority of the FTI-sensitive cell lines had a wild-type ras gene.[3] R115777 has been shown to inhibit in vitro the metabolism of specific CYP3A4, CYP2D6, and CYP2C8/9/10 isoenzymes, possibly indicating a potential interaction with comedicated drugs that are primarily metabolized by cytochrome P450.[1]

Antitumor Effects

R115777 was tested using human xenograft mouse models with twice daily oral dosing for 15 to 32 days. Xenograft model data revealed that this compound inhibited growth of tumors derived from T24 (mutant H-ras), LoVo (mutant K-ras) and CAPAN-2 (mutant K-ras) at doses of 25 to 100 mg/kg.[4] Upon examination of the tumors treated with this FTI compound, the antiangiogenesis, apoptotic, and antiproliferative effects of treatment were evident.[5] In preclinical models, combinations of R115777 and several cytotoxic agents (eg, paclitaxel, cisplatin) produced an additive cytotoxic and cell-cycle effect.[6] Pharmacokinetic data from phase I studies revealed that R115777 is best consumed after a meal.
because bioavailability increases following food ingestion. Results demonstrated that under fasting conditions the bioavailability was less than that of the oral solution, although after a meal it equaled that of the oral solution.[1]

R115777 was the first farnesyltransferase inhibitor to enter clinical trials. The National Cancer Institute (NCI) is currently sponsoring phase I and II trials of R115777 in several different tumor types with additional studies to be activated. From phase I dose-escalation studies, the recommended phase II dose of R115777 for several tumor types (breast, pancreas, and glioma) has been determined to be 300 mg twice daily on a schedule of 21 days every 28 days.[7-9]

**Phase I and II Trials**

In a phase I trial conducted by the University of Maryland Cancer Center (UMCC), R115777 in patients with refractory and relapsed acute leukemias produced clinical responses in 10 of 34 evaluable patients (29%), including two complete remissions.[10] R115777 was shown to inhibit farnesyltransferase activity at the 300 and 600 mg twice daily dose levels (in vitro inhibition of substrates lamin A and HDJ-2).[10] Approximately 10% to 15% of patients with refractory malignancies have achieved disease stabilization or an objective response in single-agent R115777 trials.[11]

A company-sponsored phase II study was initiated to confirm the results of the UMCC phase I trial in patients with relapsed and refractory acute myelogenous leukemia (AML). The regimen entailed a dose of 600 mg twice daily for 21 days every 28 days. To date, 151 patients have been enrolled in the trial, with 42 evaluable AML patients. A reduction in bone marrow leukemic blasts to less than 5% was seen in seven relapsed patients.[12]

R115777 in combination with other standard cytotoxic chemotherapy agents is currently under clinical investigation. Phase II NCI-sponsored and phase II and III company-sponsored clinical trials are ongoing.

Preliminary data from another phase II company-sponsored trial investigating the efficacy and tolerability of two dosing regimens of R115777 in patients with advanced breast cancer, was presented at the 38th annual meeting of the American Society of Clinical Oncology (ASCO). Two cohorts of patients were sequentially recruited. The first cohort received continuous dosing at 400 or 300 mg twice daily, while the second cohort received 300 mg twice daily for 21 days every 28 days (intermittent dosing). Trial results concluded that the two regimens showed similar clinical efficacy, but the intermittent-dosing regimen was associated with a significantly improved tolerability profile over the continuous-dosing regimen.[8]

**Phase III Trials**

Data from a phase III company-sponsored trial comparing gemcitabine (Gemzar) and R115777 vs gemcitabine and placebo in pancreatic cancer patients was also presented at the 2002 ASCO meeting. The 688 previously untreated patients with locally advanced or metastatic pancreatic cancer were randomized to one of two treatment arms. Patients randomized to the R115777-plus-gemcitabine arm received 200 mg of oral R115777 twice daily and gemcitabine at 1,000 mg/m2 IV weekly for 7 weeks every 8 weeks, then weekly for 3 weeks every 4 weeks. Compared with single-agent gemcitabine, no statistically significant differences in overall survival were observed. The median overall survival for gemcitabine plus R115777 was 193 days, compared to 182 days for the control group.[13]

Additional phase III colorectal data presented at the ASCO meeting compared R115777 and placebo in 368 previously treated metastatic colorectal patients. The primary end point was overall survival. The median survival was 5.7 months in patients receiving R115777, compared to 6.1 months for those receiving placebo. R115777 in combination with chemotherapy could still be investigated in earlier stages of colorectal cancer.[14]

The most common patient hematologic toxicities include anemia, leukopenia, neutropenia, granulocytopenia, and thrombocytopenia. Nonhematologic toxicities include skin rash, motor and sensory neuropathy, nausea, vomiting, fatigue, and dizziness.

The list below includes approved, active, in review, or temporarily closed R115777 protocols, sponsored by the Division of Cancer Treatment and Diagnosis of the NCI.

**Breast**

**Title:** A Phase I/II Study of R115777 (Zarnestra) Plus Doxorubicin and Cyclophosphamide in Patients
with Locally Advanced and Metastatic Breast Cancer

**Protocol Number:** 5598  
**Participating Institution:** Montefiore Medical Center  
**Contact:** Joseph Sparano, MD, (212) 746-2844  
**Title:** Phase IB/II Neoadjuvant Trial of the Farnesyltransferase Inhibitor, R115777 With Docetaxel and Capecitabine for Patients With Stage IIIA or IIIB Breast Cancer

**Protocol Number:** 5599  
**Participating Institution:** Mayo Clinic  
**Contact:** Bennett Yu, (313) 966-7198  
**Title:** A Phase II Evaluation of the Efficacy and Safety of R115777, a Nonpeptidomimetic Farnesyltransferase Inhibitor, and Trastuzumab in Patients With Advanced Breast Cancer

**Protocol Number:** 5330  
**Participating Institution:** University of Texas Health Science Center  
**Contact:** Garry Schwartz, MD, (210) 916-1057

### Central Nervous System

**Title:** Phase I Trial With Radiation Therapy in Patients With Newly Diagnosed Glioblastoma Multiforme  
**Protocol Number:** NABTC-02-02  
**Participating Institution:** North American Brain Tumor Consortium  
**Contact:** Timothy F. Cloughesy, MD, (310) 825-5321  
**Title:** Phase II Study of R115777 in Patients With Recurrent or Progressive Malignant Glioma  
**Protocol Number:** NABTC-9901  
**Participating Institutions:** Dana Farber Cancer Center, M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, National Institutes of Health, North American Brain Tumor Consortium, University of California at Los Angeles, University of California San Francisco, University of Michigan Medical Center, University of Pittsburgh, University of Texas Health Science Center, University of Texas Southwestern Medical Center, University of Wisconsin  
**Contact:** Timothy Cloughesy, MD, (310) 825-5321; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

### Gastrointestinal

**Title:** Phase II Randomized Study of Gemcitabine, Paclitaxel, and Radiotherapy With or Without R115777 in Patients With Locally Advanced Pancreatic Cancer  
**Protocol Number:** RTOG-PA-0020  
**Participating Institution:** Radiation Therapy Oncology Group  
**Contact:** Tyvin Rich, MD, (804) 924-5191; for a complete listing of study contacts, click [here](http://www.cancer.gov/clinical_trials/)

### Genitourinary

**Title:** A Phase II Study of R115777 (Zarnestra) in Patients With Superficial Transitional Cell Carcinoma of the Bladder  
**Protocol Number:** 5612  
**Participating Institution:** Princess Margaret Hospital  
**Contact:** Joseph L. Chin, MD, (519) 685-8451

### Lung

**Title:** Phase I Study of Paclitaxel and Carboplatin Followed By R115777 Concurrently With Radiotherapy Followed By Maintenance Therapy With R115777 in Patients With Stage IIIA or IIIB Non-Small Cell Lung Cancer  
**Protocol Number:** NCI-5150, UPCC-NCI-5150  
**Participating Institution:** University of Pennsylvania Cancer Center  
**Contact:** Stephen Hahn, MD, (215) 662-7296  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

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Page 3 of 6
Phase I Solid Tumors

**Title:** Phase I Study of R115777 in Patients With Advanced Malignant Solid Tumors  
**Protocol Number:** NCI-4751  
**Participating Institutions:** University of California at Davis, Veteran’s Administration Medical Center  
**Contact:** Primo Lara, MD, (916) 734-3772  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of R115777 and Topotecan in Patients With Advanced Solid Tumors  
**Protocol Number:** NCI-T99-0110, NYU-9932  
**Participating Institutions:** Albert Einstein College of Medicine, New York University Medical Center  
**Contact:** Howard Hochster, MD, (212) 263-8210  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

Hematologic Malignancies

**Title:** Phase I Randomized Study of R115777 in Patients With Advanced Hematologic Malignancies  
**Protocol Number:** NCI-42, UCCRC-10294  
**Participating Institution:** University of Chicago  
**Contact:** Todd Zimmerman, MD, (773) 702-4159  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I Study of R115777 in Patients With Myelodysplastic Syndrome  
**Protocol Number:** MDA-DM-01582, MDA-DM-99169, NCI-5625, NCI-T99-0101  
**Participating Institution:** M. D. Anderson Cancer Center  
**Contact:** Razelle Kurzrock, MD, (713) 794-1226  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase I/II Study of R115777 in Patients With Myeloproliferative Disorders  
**Protocol Number:** NCI-38, SUMC-NCI-38  
**Participating Institutions:** Stanford University, University of California San Francisco Medical Center  
**Contact:** Peter Greenberg, MD, (650) 725-8355  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase II Study of R115777 in Patients With Previously Untreated Poor-Risk Acute Myeloid Leukemia, Myelodysplastic Syndrome, or Chronic Myelomonocytic Leukemia  
**Protocol Number:** MSGC-0116, MSGCC-U5400, NCI-1754  
**Participating Institutions:** University of Maryland Cancer Center, Stanford University, University of Rochester  
**Contact:** Judith Karp, MD, (410) 328-7394  
**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase II Evaluation of FTI R115777 in the Treatment of Advanced Multiple Myeloma  
**Protocol Number:** 2030  
**Participating Institutions:** Mayo Clinic, Moffitt Cancer Center, University of Wisconsin, Washington University  
**Contact:** Melissa Alsina, MD, (813) 903-6886  
**Title:** A Phase II Trial of R115777 in Myelofibrosis With Myeloid Metaplasia (MMM)  
**Protocol Number:** 5576  
**Participating Institution:** Mayo Clinic  
**Contact:** Ayalew Tefferi, MD, (507) 284-2511  
**Title:** A Phase II Study of the Farnesyltransferase Inhibitor Zarnestra (R115777, NSC 702818, IND 58,359) in Complete Remission Following Induction and/or Consolidation Chemotherapy in Adults With Poor-Risk Acute Myelogenous Leukemia (AML) and High-Risk Myelodysplasia (MDS)  
**Protocol Number:** 5689  
**Participating Institution:** University of Maryland Cancer Center  
**Contact:** Judith Karp, MD, (410) 328-7394

Pediatric

**Title:** Phase I Study of R115777 in Pediatric Patients With Refractory Leukemia  
**Protocol Number:** COG-ADVLO116, NCI-01-C-0196, NCI-1930  
**Participating Institutions:** Children’s Hospital and Regional Medical Center, Children’s Oncology
Group Phase 1 Consortium, Columbia-Presbyterian Medical Center, Johns Hopkins University, National Cancer Institute Pediatric Oncology Branch, Packard Children's Hospital-Stanford, Saint-Justine, University of California at San Francisco, University of Texas Southwestern Medical Center

**Contact:** Brigitte Widemann, MD, (301) 496-7387; for a complete listing of study contacts, click here

**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**Title:** Phase II Study of R115777, Isotretinoin, Cytarabine, and Fludarabine Followed By Allogeneic Bone Marrow or Umbilical Cord Blood Transplantation in Children With Newly Diagnosed Juvenile Myelomonocytic Leukemia

**Protocol Number:** COG-AAML0122

**Participating Institution:** Children's Oncology Group

**Contact:** Robert Castleberry, MD, (205) 939-9285; for a complete listing of study contacts, click here

**Latest Information:** [http://www.cancer.gov/clinical_trials/](http://www.cancer.gov/clinical_trials/)

**References:**


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