Ridaforolimus (AP23573; MK 8669) is an analog of sirolimus and a small molecule inhibitor of the mammalian target of rapamycin for the treatment of cancer. Both intravenous and oral formulations of the compound are being tested in clinical trials for the treatment of soft-tissue and bone sarcomas. It is in phase III development for sarcoma in the EU and US, and phase II for breast cancer, endometrial cancer, non-small cell lung cancer, and prostate cancer in the US and other markets in the world. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Merck & Co. are developing ridaforolimus, an analog of sirolimus and a small molecule inhibitor of the mammalian target of rapamycin (mTOR), for the treatment of cancer. mTOR is a protein kinase that controls cell growth by regulating many cellular processes, including protein synthesis and autophagy. Compared with other mTOR inhibitors, ridaforolimus is not a prodrug and has shown in vivo stability. Both intravenous and oral formulations of the compound are being tested in clinical trials for the treatment of various solid tumors and hematologic malignancies. The initial indication is soft-tissue and bone sarcomas.

ARIAD Pharmaceuticals, the compound’s originator, considered developing ridaforolimus for use in drug-eluting stents to prevent restenosis, in conjunction with balloon angioplasty.

1.1 Company Agreements

In May 2010, ARIAD and Merck restructured their July 2007 collaboration agreement for ridaforolimus, so that Merck has the exclusive license to develop, manufacture, and commercialize the compound in oncology. Merck will assume responsibility and costs for all ridaforolimus activities, including clinical trials and regulatory filings. Merck will make an upfront cash payment of $US50 million to ARIAD and will reimburse ARIAD for its ridaforolimus expenses incurred since 1 January 2010, estimated at approximately $US19 million. The transfer of all ridaforolimus activities to Merck is expected to take 6 months, and Merck will reimburse ARIAD for all its ridaforolimus costs incurred until the transfer is completed. ARIAD will be eligible to receive up to $US514 million in regulatory and sales milestones, based on successful commercialization in multiple indications. This includes $US65 million in milestones associated with the potential sarcoma indication ($US25 million for acceptance of a new drug application [NDA] by the US FDA, $US25 million for US registration, $US10 million for European registration and $US5 million for Japanese registration), and $US200 million in milestones based on
achievement of significant sales thresholds. Merck will book global sales and pay ARIAD tiered double-digit royalties on global net sales. In addition to now receiving royalties on US sales in lieu of a profit split, these global royalty rates are approximately one-third greater than the rates ARIAD would have received for ex-US sales under the original collaboration agreement. ARIAD will have an option to co-promote ridaforolimus with up to 20% of the sales effort for the product in all indications in the US, and Merck will compensate ARIAD for its sales efforts. Milestones associated with the start of four phase III trials (US$74.5 million) in indications other than sarcoma and the development-cost advance contemplated by the original collaboration agreement are not included in the revised agreement. The terms for development and commercialization of ridaforolimus in potential non-oncology indications remain subject to future agreement between the companies[1,2]

In July 2007, ARIAD entered into a global collaboration agreement with Merck, to jointly develop and commercialize ridaforolimus for the treatment of cancer. Each party would fund 50% of the cost of global development of ridaforolimus, except that Merck would fund 100% of the cost of ex-US development specific to the development or commercialization of the drug outside the US. In certain circumstances, either party could opt-out of conducting and funding certain late-stage clinical development, which would result in changes in development and commercialization responsibilities and compensation arrangements. Both companies would share overall responsibility for global commercialization and development of ridaforolimus. In the US, ARIAD would distribute and sell ridaforolimus for all cancer indications and book all sales, and ARIAD and Merck would co-promote and would each receive 50% of the income from such sales. Outside the US, Merck would distribute, sell, and promote ridaforolimus and book all sales; Merck would pay ARIAD tiered double-digit royalties on such end-market sales of ridaforolimus. On a global basis, ARIAD would be responsible for manufacturing the active pharmaceutical ingredient used in the product, and Merck would be responsible for the formulation of the finished tablets. In the US, ARIAD would have primary responsibility for development of ridaforolimus for metastatic sarcoma. Merck and ARIAD would have joint responsibility in the US for development of all other cancer indications being pursued. Outside the US, Merck would have primary responsibility for development in all cancer indications being pursued[3]

ARIAD entered into two licensing agreements for ridaforolimus for potential cardiovascular indications with Medinol (January 2005) and ICON Medical Corporation (October 2007) to develop and commercialize stents and other medical devices to deliver ridaforolimus for use in vascular disease. Under the terms of the agreements, ARIAD granted these companies non-exclusive, worldwide, royalty-bearing licenses under its patents and technology related to ridaforolimus to develop, commercialize, and sell stents and other medical devices to deliver ridaforolimus. ARIAD would supply ridaforolimus for use in development, manufacture, and sale of the stents and other medical devices. It also retained the right to enter into one additional non-exclusive licensing agreement in this area.

1.2 Key Development Milestones

1.2.1 Breast Cancer

A phase II trial (NCT00736970) is being conducted to evaluate the safety and efficacy of ridaforolimus in combination with trastuzumab (Herceptin®) in patients with metastatic, HER2-positive breast cancer who have developed resistance to trastuzumab. The study has enrolled 37 patients in Chile, the US, and the EU, and initial data showed that the trial met its primary endpoint of objective response rate.[4-6]

1.2.2 Endometrial Cancer

In August 2008, ARIAD initiated a phase II clinical trial (NCT00739830) assessing the safety and efficacy of oral ridaforolimus in patients with metastatic or recurrent endometrial cancer following first-line chemotherapy, comparing ridaforolimus with progestin. The primary endpoint will be progression-free survival (PFS). ARIAD will receive a US$2.5 million milestone payment from Merck upon the treatment of the first patient.[7] Enrollment of 150 patients from the US,
EU, Asia, and Australia is ongoing as of June 2010.

ARIAD Pharmaceuticals has presented results from its phase II study (NCT00122343) of ridaforolimus monotherapy (12.5 mg, 30 minute intravenous infusion for 5 consecutive days every other week for 28-day cycles) in 45 patients with progressive metastatic endometrial cancer despite prior chemotherapy; the trial met its primary endpoint, and achieved single-agent activity in the treatment of endometrial cancer. The study was conducted in the US and Europe. Subjects were monitored for at least 6 months after enrollment, and could continue on ridaforolimus if they had clinical benefit.[8,9]

1.2.3 Non-Small Cell Lung Cancer

A phase II trial (NCT00818675) of ridaforolimus in patients with advanced non-small cell lung cancer (NSCLC) who have not responded to two prior treatment regimens was initiated by Merck and ARIAD in February 2009. The randomized, double-blind trial will compare ridaforolimus against placebo in patients with a KRAS mutation, a mutation in lung tumors that is recognized as a predictor of poor response to endothelial growth factor receptor inhibitors. All patients will receive four 10 mg tablets of ridaforolimus once daily for 5 consecutive days each week during an 8-week lead-in treatment period. Patients with partial response will continue on ridaforolimus until disease progression. Any patients with stable disease will be randomized to receive ridaforolimus or placebo until disease progression. The primary endpoint is PFS in the randomized population. The trial will enroll 150 patients at approximately 38 sites including medical centers in the US and Europe.[10] Enrollment of patients is ongoing as of June 2010.

Ridaforolimus has demonstrated potent single-agent, anti-tumor activity in preclinical models of NSCLC with a KRAS mutation.[11]

1.2.4 Prostate Cancer

Merck has initiated a double-blind, randomized, phase II trial (NCT00777959) in the US and other countries, to compare oral ridaforolimus in combination with bicalutamide versus placebo and bicalutamide in patients with asymptomatic, metastatic, androgen-independent prostate cancer. The primary endpoint is a 30% decrease in prostate specific antigen compared to baseline within 12 weeks of treatment.[12] The study enrolled 156 patients.

A phase II trial (NCT00110188) of ridaforolimus monotherapy has been completed in patients with advanced refractory prostate cancer. The trial is being conducted at multiple US centers in approximately 38 patients. Patient enrollment was completed in the first quarter of 2006. The agent was administered using a weekly intravenous dosing regimen.[13,14]

Positive preclinical data on ridaforolimus in combination with bicalutamide in prostate cancer models have been reported.[15,16]

1.2.5 Sarcoma

ARIAD has completed enrollment in its multinational, phase III trial of oral ridaforolimus in patients with metastatic soft-tissue and bone sarcomas. The pivotal SUCCEED (Sarcoma mUlti-Center Clinical Evaluation of the Efficacy of Deforolimus; NCT00538239) trial is assessing PFS as the primary endpoint and overall survival as a secondary endpoint, in patients with metastatic sarcomas following a favorable response to chemotherapy. Approximately 650 patients worldwide were randomized to ridaforolimus or placebo. An independent Data Monitoring Committee has now completed the final second interim analysis, and has recommended that the trial continue to its final analysis without modification. This second interim analysis was triggered by the achievement of two-thirds of the prescribed PFS events, and final data analysis is expected in the fourth quarter of 2010. ARIAD has reached an agreement on a Special Protocol Assessment with the US FDA for the SUCCEED trial, and the European Medicines Agency (EMA) has provided protocol advice consistent with that of the FDA, as part of its Protocol Assistance programme.[1,17-21]

Merck plans to file for approval of ridaforolimus for the treatment of sarcoma in the US in 2010.[22]

In March 2010, Merck and ARIAD commenced a phase II study (NCT01010672) evaluating
maintenance therapy with ridaforolimus in patients with metastatic or soft-tissue sarcoma. This non-randomized, open-label study is expected to enroll approximately 50 patients in Japan.

ARIAD has conducted a phase II trial (NCT00093080) of intravenously administered ridaforolimus as a single agent among patients with relapsed and/or refractory sarcomas. The non-randomized, multicenter trial recruited 212 patients from the US and Europe, who were divided into four well defined subgroups, characterized by tumor type. Clinical benefit response (CBR) rate, the primary endpoint, was achieved in patients with the three most prevalent types of sarcoma (bone sarcoma, leiomyosarcoma, and liposarcoma). Additional positive efficacy data from a phase II trial in 61 evaluated patients with advanced sarcoma were presented in November 2006.[23-25]

Ridaforolimus was designated fast-track status by the FDA for the treatment of soft-tissue and bone sarcomas in April 2005. ARIAD will pursue treatment of soft-tissue and bone sarcomas as the initial registration path for ridaforolimus. The compound also received orphan drug status for the same indications from the FDA and EMA in August and November 2005, respectively.[26-28]

1.2.6 Various Advanced Cancers

In March 2010, Merck and ARIAD initiated a phase I study (NCT01071304) to evaluate the effect of multiple oral doses of ridaforolimus 40 mg, on the single-dose pharmacokinetics of midazolam. The trial will enroll approximately 16 patients with advanced solid tumors, lymphoma, or hematologic malignancies that have failed to respond to standard therapy, have progressed despite standard therapy, or for which standard therapy does not exist.

Merck and ARIAD have initiated a phase I clinical trial (NCT00781846) to combine oral ridaforolimus with intravenous bevacizumab in patients with advanced cancers. This trial will assess the safety, tolerability, and recommended phase II dose in approximately 17 patients from the US. Patient recruitment has been completed, with results presented in September 2009.[5,29-31]

Merck has completed a phase I trial (NCT00874731) to assess the effect of ridaforolimus on corrected QT interval in patients with advanced cancer. A total of 23 patients participated in this study conducted in the US.

A phase Ib trial (NCT00288431) has been completed, evaluating an oral formulation of ridaforolimus plus doxorubicin in patients with advanced cancer, particularly those with soft-tissue sarcomas as well as breast, ovarian, and endometrial cancers. The trial was initiated in February 2006 at three US sites enrolled 37 patients.[32] ARIAD initiated a phase I/IIa trial (AP23573-05-106; NCT00112372) in May 2005, to investigate seven different dosage regimens of oral ridaforolimus in approximately 150 patients with relapsed or refractory cancers. This study was completed in March 2009. Pharmacokinetic and pharmacodynamic results have been reported.[33,34]

Intravenous ridaforolimus (as a single agent) is in a phase I/II clinical trial (SUNSHINE; NCT00704054) in pediatric patients (aged 1–17 years) with advanced solid tumors. The US-based trial is being sponsored by the Pediatric Cancer Foundation. Approximately 36 subjects are expected to be recruited into the study.[31,35]

A phase I combination trial (MK8669-004; NCT00730379) of ridaforolimus and dalotuzumab in patients with advanced cancer is ongoing in the US. The study has completed enrollment of 87 patients and is designed to determine the toxicity profile, maximum tolerated dose and recommended phase II dose.

Ridaforolimus plus dalotuzumab (an anti-insulin-like growth factor [IGF]-1R monoclonal antibody) synergistically enhanced anti-tumor activity, in vivo and in vitro. The results serve to confirm the ‘vertical-pathway synergy’ and blocking of feedback signaling between IGF-1R and mTOR.[11]

1.3 Patent Information

ARIAD Pharmaceuticals was issued US Patent No. 7 091 213 in August 2006, which provides coverage for ridaforolimus and family of structurally related compounds, as well as their medical uses through to the year 2023. Related patents are pending in the US and major markets outside the US.[36]
2. Scientific Summary

2.1 Pharmacokinetics

In 129 evaluable patients receiving oral ridaforolimus, maximum plasma concentration (C_max) occurred at 2–3 hours and the median terminal elimination half-life (t½) was 35–70 hours. Ridaforolimus showed a rapid exponential decline followed by a slower linear phase of elimination. Mean estimated area under the concentration-time curve (AUC) and C_max increased in a less than dose-proportional manner. Absolute bioavailability derived from data for intravenous ridaforolimus estimates it to be 20%.[34]

Combined phase I data showed that daily and weekly dosing regimens of ridaforolimus displayed a highly predictable and reproducible blood-clearance profile with a median t½ of 49 hours for all evaluable patients with various types of advanced solid tumors.[37]

In a phase I dose-escalation trial involving 24 patients with refractory or advanced malignancies, preliminary pharmacokinetic analyses showed a median C_max for ridaforolimus of 98.5 ng/mL (range 77–163 ng/mL) on three schedules at doses ranging from 10–30 mg/day.[38]

2.2 Adverse Events

2.2.1 Breast Cancer

Updated preliminary clinical data from a phase II study with oral ridaforolimus (40 mg/day, once daily for 5 days) in combination with trastuzumab in 34 patients with resistant, metastatic HER2-positive breast cancer showed that 26 patients were discontinued from the trial, 13 due to progressive disease, 7 due to adverse events, and two patients died (one death was from an intestinal perforation and was possibly drug related). The safety profile of the combination was consistent with previous single-agent data and there were no new safety signals.[4,5]

2.2.2 Endometrial Cancer

Preliminary phase II results indicated that ridaforolimus monotherapy was well tolerated with
predictable and manageable adverse events in 45 treatment-experienced patients with advanced, progressive endometrial cancer. The most common grade 1–2 adverse events were oral mucositis (or mouth sores), fatigue, anemia, diarrhea, nausea, asthenia, vomiting, and anorexia.\[9\]

### 2.2.3 Hematologic Malignancies

**Phase II:** Preliminary results from a phase II, open-label, non-randomized, fixed-dose study of intravenous ridaforolimus (once daily for 5 days) in a total of 51 patients with refractory or relapsed hematologic malignancies showed that the drug had an acceptable adverse effect profile. Patients were stratified into five disease-specific groups and administered ridaforolimus (12.5 mg intravenously daily for 5 days every 2 weeks). The most common treatment-related adverse events were mucositis (total incidence of 32.1%), nausea (21.4%), hypokalemia and hyponatremia (both 17.9%), and pruritus (14.3%). Other events occurring in approximately 10% of patients included diarrhea, hypertriglyceridermia, rash, and hypocalcemia. Serious treatment-related adverse effects included mucositis (three patients), diarrhea (two patients), syncope, neutropenic sepsis, pulmonary infiltrates, and hypertriglyceridermia (all one patient each). Patient enrollment and treatment continues in this study.\[39\]

**Phase I:** No dose-limiting toxicities or serious adverse events associated with ridaforolimus (12.5 or 15 mg/day) occurred in a phase I trial involving nine patients with recurrent malignant glioma. Related adverse events observed during pre-surgery and cycle 1 dosing included hypertriglyceridermia/ hyperlipidemia (n = 3 patients), thrombocytopenia (2), hypercholesterolemia (2), hyperglycemia (2), diarrhea (2), and mucositis (1). Patients in this study received ridaforolimus as a 30-minute intravenous infusion daily for 4 days prior to tumor resection, followed by daily dosing for 5 days every 2 weeks on a 4-week cycle post-surgery recovery.\[40\]

### 2.2.4 Sarcoma

**Phase II:** Patients with advanced sarcoma who were treated with intravenous ridaforolimus experienced adverse events that were generally mild or moderate and reversible. The most common adverse events were mouth sores, fatigue, increased triglycerides, low red blood cell count, and nausea. The patients in this phase II, open-label, non-randomized, fixed-dose study received ridaforolimus 12.5 mg/day in a 5 days on, 9 days off dosing schedule for ≥4 months.\[25\]

In a phase II study of ridaforolimus in patients with advanced sarcoma, the main dose-related adverse events were mucositis, anemia, thrombocytopenia, and maculopapular rash. Most of these events were mild or moderate in severity.\[41\]

**Phase I:** Ridaforolimus in combination with paclitaxel was well tolerated with predictable and manageable adverse events in a phase I b study in patients with progressive solid tumors.\[8\]

In a phase I trial of the oral formulation of ridaforolimus in 58 patients with solid tumors, the maximum tolerated dose was 10 mg/day with daily administration. The maximum tolerated dose was 15 mg/day with daily dosing for 3 out of every 4 weeks. The dose-limiting toxicity was oral mucositis. The maximum tolerated dose had not been reached at 40 mg/day in the dosing group who received daily doses for 4 consecutive days with 3 days off. Initial data showed that the three dosing regimens were well tolerated and resulted in similar treatment-related adverse events. The adverse events experienced with the oral formulation were the same as those of the intravenous formulation.\[42\]

### 2.2.5 Solid Tumors

In a phase I study involving 17 patients receiving ridaforolimus and bevacizumab for the treatment of solid tumors, the combination was well tolerated at standard dose, with no dose-limiting toxicity observed.\[5\] In further results, 6 of 17 patients experienced non-fatal bowel ulcers, perforations, and abscesses, thought to be related to bevacizumab and/or ridaforolimus treatment. No new or unexpected safety signals were observed.\[29\]

Ridaforolimus administered under a daily and weekly dosing regimens have been well tolerated by patients with various types of advanced solid tumors in phase I trials. Overall, adverse events were mild to moderate and easily managed. The dose-limiting toxicity was severe oral mucositis.\[37\]
In a phase I dose-escalation trial of ridaforolimus in 24 patients with refractory or advanced malignancies, frequent adverse events related to the study drug—mucositis, fatigue, rash, diarrhea, anorexia, and nausea—were mild to moderate in severity and reversible. Patients received ridaforolimus on three schedules at doses ranging from 10 to 30 mg/day.\[38\]

2.3 Pharmacodynamics

2.3.1 Cancer

Clinical

Pharmacodynamic assays on samples collected from patients with various types of advanced solid tumors showed a good correlation of ridaforolimus blood levels with inhibition of mTOR protein. Combined phase I data demonstrated >90% mTOR inhibition within 1 hour after dosing among all patients administered ridaforolimus under a daily and weekly dosing regimen. With the daily dosing schedule, ridaforolimus maintained inhibition of mTOR activity for up to 10 days among the majority of subjects.\[37\]

In a phase I dose-escalation trial involving 24 patients with refractory or advanced malignancies, ridaforolimus (10–30 mg/day) reduced phosphorylated 4E-BP1 (P-4E-BP1) levels by >80% 1 day after dosing; levels remained reduced during the 28-day dosing period. Of three patients who had completed two cycles, anti-tumor activity associated with the study drug was observed in two patients while one had stable disease.\[38\]

In the phase I/IIa dose escalation AP23573-05-106 trial, oral ridaforolimus dosing resulted in rapid, potent, and prolonged mTOR inhibition in peripheral blood mononuclear cells, in 141 evaluable adults with refractory or advanced solid tumors. Patients were randomized to one of seven dosing regimens (10–100 mg) in a 28-day cycle. P-4E-BP1 levels decreased by 83–93% in 24 hours at all dose levels. With the exception of the one daily for 21 days regimen, >70% mTOR inhibition was seen at most timepoints through the cycle. In the 24 patients receiving 40 mg once daily for 5 days, mTOR was inhibited by >90% within 24 hours after the first dose, and inhibition was maintained at >75% throughout the cycle. This dosing regimen was selected for the phase III SUCCEED trial. These results are comparable with those obtained with intravenous ridaforolimus dosing.\[33\]

In a phase I trial involving nine patients with recurrent malignant glioma, treatment with ridaforolimus (12.5 or 15 mg/day) was associated with marked reduction in levels of phospho-S6 in six of eight patients analyzed, with ≥95% reduction in three patients (range 50–100% reduction). The authors suggested that this finding indicates the study drug is reaching its target in the brain. Patients received ridaforolimus as a 30-minute intravenous infusion daily for 4 days prior to tumor resection, followed by daily dosing for 5 days every 2 weeks on a 4-week cycle post-surgery recovery.\[40\]

Preclinical

In a mouse model of breast cancer, the anti-tumor effect of ridaforolimus was enhanced by combination with an agent that reduced the level of hypoxia-inducible factor (HIF) in tumors. In vitro, in cancer cell lines, mTOR pathway activity was detected in normoxic regions and HIF pathway activity was present only in hypoxic regions; this indicated that targeting both pathways simultaneously should achieve a greater anti-tumor effect than separate targeting. Addition of HIF-1β knockdown treatment to ridaforolimus administration in a mouse model of breast cancer led to a 4-fold decrease in tumor growth, whereas either treatment alone resulted in a 2-fold reduction in tumor growth.\[43\]

Ridaforolimus potently inhibited the growth of erlotinib-resistant, KRAS-mutant NSCLC tumors in three different mouse models. In a panel of >100 lung-cancer cell lines, ridaforolimus showed greater inhibition of tumor growth than erlotinib in 79% of cell lines and 84% of KRAS mutant cell lines.\[11\]

The combination of ridaforolimus and bicalutamide inhibited the growth of prostate cancer cells in both cell culture and mouse models. The combination also inhibited mTOR, androgen signaling pathways in prostate cancer cells, evidenced by a decrease in prostate specific antigen levels.\[16\] Further in vitro data showed that ridaforolimus alone inhibited the growth of seven...
prostate cell lines, with sensitivity associated with the loss of PTEN. Ridaforolimus plus bicalutamide was strongly synergistic in both LNCaP (androgen dependent) and C4-2 (androgen independent) cell lines, but only additive in RWPE-1 (normal prostate epithelium) cells. Synergism was demonstrated by the fact that p-S6 (Ser235/236) levels in LNCaP and C4-2 were reduced more by the combination, than by ridaforolimus alone. Colony formation of C4-2 in anchorage-independent conditions was inhibited by ~75% with combination treatment, compared with control. Ridaforolimus did not interfere with the inhibition of androgen receptor expression by bicalutamide.\[15\]

Ridaforolimus reduced tumor size in mice bearing solid tumors by 46% compared with a 150% increase for animals not treated. Following retreatment with ridaforolimus, further tumor regression was observed.\[44\]

In animal models, ridaforolimus treatment at an early stage caused the regression of persistent human tumors by up to 90%. When treatment was initiated at a later more aggressive stage, there were still significant reductions in the rate of growth of all six tumor types studied (brain, prostate, breast, pancreas, lung, and colon cancers). Molecular analysis of the tumors after removal showed that the mTOR protein signaling was completely abolished after a single low dose. This suppression was found to last for 2–3 days. Researchers also discovered that the anti-cancer activity of three widely used chemotherapy agents was markedly enhanced by combining ridaforolimus to the regimen.\[45\]

2.4 Therapeutic Trials

2.4.1 Cancer

Breast Cancer

Updated preliminary clinical data from a phase II study with oral ridaforolimus (40 mg/day, once daily for 5 days) in combination with trastuzumab in 34 patients with resistant, metastatic, HER2-positive breast cancer showed an objective response rate of 15%, with five partial responses. The clinical benefit response (objective responses and durable stable disease) rate was 21% (median duration of 4 months). Thirteen patients demonstrated progressive disease.\[4\]

Earlier results from the phase II trial in 28 enrolled patients showed a preliminary CBR rate of 35%.\[5\]

Endometrial Cancer

Ridaforolimus monotherapy (12.5 mg, 30-minute intravenous infusion for 5 consecutive days every other week for 28-day cycles) was effective in the treatment of endometrial cancer in a phase II study. The non-randomized study enrolled 45 patients with metastatic endometrial cancer, who had received a median of two prior cytotoxic chemotherapy regimens. Overall, 13 of 45 patients (29%) had a CBR defined as tumor regression or disease stabilization; 10% of patients had a partial response.\[8,9\]

Glioblastoma

In a phase I study in patients with glioblastoma, low doses of ridaforolimus reduced the growth of brain tumor cells by 40%. The reduction of tumor cell growth was achieved in brain cancer cells both expressing and not expressing epidermal growth factor receptor.\[46\]

Hematological Malignancies

Preliminary results from a phase II, open-label, non-randomized, fixed-dose study of intravenous ridaforolimus were promising. Data have been presented for a total of 51 patients with refractory or relapsed hematological malignancies who were stratified into five disease-specific groups and administered intravenous ridaforolimus (12.5 mg daily for 5 days for every 2 weeks). Indications of anti-cancer activity were seen in four of five disease cohorts, with 20 of 50 evaluable patients (40%) showing a partial response, minor response or stable disease. Patient enrollment and treatment continues in this study.\[39\]

Sarcoma

Phase II: In a phase II study, ridaforolimus exhibited single-agent activity in 212 patients with advanced sarcomas. Patients were enrolled into four cohorts based on histologic subtypes; there were no enrollment restrictions based on prior therapies. Ridaforolimus (12.5 mg, intravenous) was administered daily for 5 days every 2 weeks.
| Date               | Comment                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 26 May 2010        | Independent Data Monitoring Committee completes second interim efficacy analysis of the phase III SUCCEED trial in metastatic sarcoma and recommends trial continue without modification to its final analysis[17] |
| 5 May 2010         | Merck and ARIAD restructure their collaboration agreement, granting Merck full rights to ridaforolimus in Cancer[1,2]                                                                                      |
| 25 March 2010      | Merck and Ariad Pharmaceuticals initiate enrollment in a phase I trial in the US                                                                                                                                                                                                         |
| 25 March 2010      | Phase I clinical trials in cancer in the US (PO)                                                                                                                                                                                                                  |
| 5 March 2010       | Phase II clinical trials in sarcoma in Japan (PO)                                                                                                                                                                                                                  |
| 18 December 2009   | ARIAD Pharmaceuticals completes enrollment in the phase III SUCCEED trial for metastatic soft-tissue and bone sarcomas (809108162)                                                                               |
| 15 December 2009   | Efficacy and adverse events data from a phase II trial in breast cancer presented at the 32nd Annual San Antonio Breast Cancer Symposium (SABCS-2009)[4]                                                      |
| 19 November 2009   | Pharmacodynamics data from a preclinical trial in cancer presented at the 21st AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2009)[43]     |
| 21 September 2009  | Interim efficacy and adverse events data from a phase I trial in solid tumors released by ARIAD Pharmaceuticals[29]                                                                                           |
| 14 September 2009  | Independent Data Monitoring Committee recommends that the phase III SUCCEED trial in sarcoma continue to full patient enrollment                                                                              |
| 9 September 2009   | Phase II clinical trials in non-small cell lung cancer in the EU (PO)                                                                                                                                         |
| 28 July 2009       | Interim efficacy and adverse events data from a phase I trial in solid tumors released by ARIAD Pharmaceuticals[5]                                                                                            |
| 28 July 2009       | Interim efficacy and adverse events data from a phase II trial in breast cancer released by ARIAD Pharmaceuticals[5]                                                                                          |
| 7 May 2009         | Merck and ARIAD complete enrollment in their phase I trial with ridaforolimus in combination with bevacizumab for cancer in the US                                                                            |
| 21 April 2009      | Pharmacodynamics data from preclinical trials in non-small cell lung cancer presented at the 100th Annual Meeting of the American Association for Cancer Research (AACR-2009)[11]                           |
| 28 February 2009   | Phase II clinical trials in non-small cell lung cancer in the US (PO)                                                                                                                                       |
| 24 October 2008    | Pharmacodynamics data from a preclinical trial in prostate cancer presented at the 20th-EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)[16]               |
| 24 October 2008    | Pharmacodynamics data from an in vitro study in Prostate cancer presented at the 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)[15]          |
| 24 October 2008    | Pharmacodynamics data from the phase I/IIa AP23573-05-106 trial in solid tumors presented at the 20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2008)[33] |
| 21 October 2008    | Phase II clinical trials in combination with bicalutamide in prostate cancer in the US (PO)                                                                                                                      |
| 31 August 2008     | Phase I clinical trial in combination with MK 0646 in cancer in Spain (PO)                                                                                                                                   |
| 6 August 2008      | Phase II clinical trials in endometrial cancer in Asia (PO)                                                                                                                                                   |
| 6 August 2008      | Phase II clinical trials in endometrial cancer in Australia (PO)                                                                                                                                               |
| 6 August 2008      | Phase II clinical trials in endometrial cancer in the EU (PO)                                                                                                                                               |
| 30 July 2008       | Phase II clinical trials in breast cancer in Chile (PO)                                                                                                                                                      |
| 30 July 2008       | Phase II clinical trials in breast cancer in the EU (PO)                                                                                                                                                      |
| 30 July 2008       | Phase II clinical trials in breast cancer in the US (PO)                                                                                                                                                     |
| 30 June 2008       | Phase I/II clinical trials in solid tumors in pediatric patients in the US (IV)                                                                                                                             |
| 19 June 2008       | Interim efficacy data from a phase I trial in sarcoma presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[47]                                                      |
| 3 June 2008        | Pharmacokinetics data from a phase I trial in solid tumors presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO-2008)[34]                                                     |
| 24 September 2007  | Phase III clinical trials in sarcoma in the EU (PO)                                                                                                                                                         |
| 24 September 2007  | Phase III clinical trials in sarcoma in the US (PO)                                                                                                                                                         |

(Continued next page)
| Date               | Comment                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10 September 2007  | ARIAD Pharmaceuticals receives special protocol assessment from the US FDA for a pivotal trial of deforolimus for metastatic sarcomas                                                                      |
| 12 July 2007       | ARIAD and Merck & Co. agree to jointly develop and commercialize deforolimus worldwide for cancer                                                                                                         |
| 11 June 2007       | Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events and cancer therapeutic trials sections[8,9,24]                                          |
| 6 November 2006    | Additional results from a phase II clinical trial in patients with advanced sarcoma have been added to the cancer therapeutic trials section[23]                                                            |
| 21 August 2006     | ARIAD Pharmaceuticals has completed enrollment in the first stage of the two-stage, phase II trial for endometrial cancer in the US and Europe                                                              |
| 9 August 2006      | Deforolimus is available for licensing outside of North America (http://www.ariad.com)                                                                                                                 |
| 15 June 2006       | Data presented at the 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO-2006) have been added to the adverse events and cancer therapeutic trials sections[25]                             |
| 4 May 2006         | ARIAD Pharmaceuticals has completed enrollment in a phase II trial for sarcoma in the US and Europe                                                                                            |
| 14 February 2006   | ARIAD Pharmaceuticals has initiated enrollment in a phase Ib trial evaluating oral deforolimus plus doxorubicin for advanced solid tumors, particularly certain sarcomas as well as breast, ovarian, and endometrial cancers in the US |
| 14 February 2006   | Phase I clinical trials in breast cancer in the US (PO)                                                                                                                                               |
| 14 February 2006   | Phase I clinical trials in endometrial cancer in the US (PO)                                                                                                                                          |
| 14 February 2006   | Phase I clinical trials in ovarian cancer in the US (PO)                                                                                                                                              |
| 14 February 2006   | Phase II clinical trials in sarcoma in the US (PO)                                                                                                                                                   |
| 11 January 2006    | Data presented at the 47th Annual Meeting and Exposition of the American Society of Hematology (ASH-2005) have been added to the adverse events and cancer therapeutic trials sections[39]       |
| 22 November 2005   | Clinical data from a media release have been added to the adverse events section[42]                                                                                                                 |
| 18 November 2005   | Data presented at the 17th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2005) have been added to the adverse events, pharmacokinetics, and cancer pharmacodynamics sections[38,40] |
| 15 November 2005   | Deforolimus has received orphan drug status for soft-tissue and bone sarcomas in Europe                                                                                                             |
| 22 August 2005     | Deforolimus has received orphan drug status for soft-tissue and bone sarcomas in the US                                                                                                               |
| 30 June 2005       | Phase II clinical trials in endometrial cancer in Europe (IV infusion)                                                                                                                                |
| 30 June 2005       | Phase II clinical trials in endometrial cancer in the US (IV infusion)                                                                                                                                |
| 27 May 2005        | Phase II clinical trials in hematologic malignancies in the US (IV infusion)                                                                                                                          |
| 20 May 2005        | Data presented at the 41st Annual Meeting of the American Society of Clinical Oncology (ASCO-2005) have been added to the adverse events and cancer therapeutic trials section[41,48] |
| 6 May 2005         | ARIAD has filed an IND with the FDA for an oral formulation for cancer                                                                                                                                |
| 6 May 2005         | Preclinical trials in solid tumors in the US (PO)                                                                                                                                                     |
| 5 May 2005         | Phase II clinical trials in prostate cancer in the US (IV infusion)                                                                                                                                     |
| 22 April 2005      | Deforolimus has received fast track status for the treatment of soft-tissue and bone sarcomas in the US                                                                                                 |
| 5 October 2004     | Data presented at the 16th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2004) have been added to the adverse events, pharmacokinetics, cancer pharmacodynamics and cancer therapeutic trials sections[57] |
| 30 September 2004  | Phase II clinical trials in sarcoma in Europe (IV infusion)                                                                                                                                              |
| 30 September 2004  | Phase II clinical trials in sarcoma in the US (IV infusion)                                                                                                                                               |
| 25 August 2004     | A study has been added to the cancer therapeutic trials section[49]                                                                                                                                     |
| 22 July 2004       | ARIAD has initiated enrollment in two phase II trials for solid tumors in the US                                                                                                                        |
| 30 June 2004       | Phase I clinical trials in glioblastoma in the US (IV infusion)                                                                                                                                         |
| 30 June 2004       | Phase II clinical trials in solid tumors in the US (IV infusion)                                                                                                                                      |
| 18 November 2003   | Data from a media release have been added to the cancer therapeutic trials section[46]                                                                                                                 |
At the time of enrollment, 79% of patients had received two prior treatments, and over 90% had disease progression. The overall CBR rate was 29%, which included five partial responses (four bone sarcoma, one malignant fibrous histiocytoma). The median overall survival was 40.1 weeks for the entire study population. In the subset of patients who achieved CBR, the median overall survival was 67.6 weeks.[24]

**Phase I**: Preliminary data from an ongoing open-label, single ascending dose study evaluating 7 regimens of oral ridaforolimus showed that the dose of 40 mg daily for 5 days each week provided clinical benefit response in 3 of 13 (23%) patients with sarcomas and partial response in two (15.4%) patients with liposarcoma or dendritic cells sarcoma. In 145 patients (85 with sarcomas) receiving ridaforolimus, clinical benefit response was classified as stable disease or better lasting for at least 4 cycles of 28 days, and was seen in all regimens in patients with several types of sarcomas and a variety of carcinomas. The 40 mg daily for 5 days dose of ridaforolimus was selected for a phase III study (SUCCEED) in patients with metastatic soft-tissue and bone sarcoma in the maintenance setting.[47]

**Solid Tumors**

**Phase II**: Final results from a non-randomized phase II trial of ridaforolimus in patients (n=212) with advanced sarcoma demonstrated that the drug produces clinical benefit and symptomatic improvement. Patients with either bone sarcoma, leiomyosarcoma, liposarcoma, or other soft-tissue sarcomas, received intravenous ridaforolimus 12.5 mg/day in a 5 days on, 9 days off

### Table II. Contd

| Date            | Comment                                                                 |
|-----------------|-------------------------------------------------------------------------|
| 24 June 2003    | Preclinical data from a media release have been added to the cancer pharmacodynamics section[45] |
| 2 May 2003      | Phase I clinical trials in cancer in the US (IV infusion)               |
| 20 January 2003 | Deforolimus is available for licensing (http://www.ariad.com)           |
| 14 January 2003 | ARIAD has filed an IND with the FDA in the US                            |
| 18 April 2002   | Preliminary data from a preclinical study has been added to the cancer pharmacodynamics section[44] |
| 11 December 2001| New profile                                                             |
| 11 December 2001| Preclinical development for cancer in the US (IV infusion)               |

### Table III. Forecasts

| Indication                | Approval Date | inThought Approvability Index | Last Update |
|---------------------------|---------------|-------------------------------|-------------|
| Breast cancer             | NE            | 31% (NYR)                     | 21 Jul 2009 |
| Endometrial cancer        | NE            | 31% (NYR)                     | 21 Jul 2009 |
| Non-small cell lung cancer| NE            | 31% (NYR)                     | 21 Jul 2009 |
| Prostate cancer           | NE            | 31% (NYR)                     | 21 Jul 2009 |
| Sarcoma                   | NE            | 66% (NYR)                     | 21 Jul 2009 |
| Solid tumors              | NE            | 25% (NYR)                     | 21 Jul 2009 |

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with ‘A’ indicating significantly above average/likely to progress, ‘C’ indicating average, and ‘F’ indicating significantly below average/unlikely to progress. ‘NYR’ stands for ‘Not Yet Rated,’ indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

**NE** = no estimate.
dosing schedule for ≥4 months. CBRs, consisting of sustained anti-tumor activity as defined by RECIST (Response Evaluation Criteria in Solid Tumours) guidelines, occurred in 29% of all patients. CBR rates were not statistically significant among the four subgroups (bone sarcoma 30%; leiomyosarcoma 33%; liposarcoma 30%, and other 23%). At 6 months, 24% of all patients had survived with progression-free disease, which was more than double that of historic control data (8%) published by EORTC. The median PFS time for all patients in the study was 15 weeks, compared with 7 weeks for EORTC historical control patients. It was also noted that results from one major center showed that 23 of 32 patients who had tumor-related symptoms, such as pain, shortness of breath, and cough on entry to the trial, showed clinically beneficial symptom improvement during treatment with AP 23573.[25,41,48]

Additional positive efficacy data from a phase II trial in 61 (n=212) evaluated patients with advanced sarcoma showed that patients with CBRs had PFS rate at 6 months of 70% and a median PFS of 36 weeks. In comparison, the overall trial population had PFS rate of around 24% at 6 months and the median PFS of 15 weeks. The CBR therefore can be used as a clinically useful surrogate endpoint for PFS rate in patients with advanced sarcoma.[23]

**Phase I:** In a phase I study involving 17 patients receiving ridaforolimus and bevacizumab for the treatment of solid tumors, five patients remain on study without disease progression.[5] In further results, disease stabilization for at least four cycles of treatment was demonstrated in 6 of 17 patients, giving a CBR rate of 35%. Tumor stability for more than 8 months was observed in four patients; two of whom remained on study with stable disease.[29]

Ridaforolimus in combination with paclitaxel had anti-tumor activity in patients with advanced pharyngeal, pancreatic, ovarian, thyroid, and breast cancers. The phase 1b dose-escalation trial evaluated the optimal dosing regimen for the combination therapy.[8]

According to updated data from two phase I trials, patients with various types of relapsed and/or refractory solid tumors demonstrated anti-tumor responses with daily and weekly dosing regimens of ridaforolimus. Among 49 evaluable patients, tumor regression was evident in nine patients (four partial responses with ≥30% tumor shrinkage and five minor responses with 15–29% shrinkage). Disease stabilization was achieved in another 15 patients. Overall, 24 of 49 (49%) of subjects attained anti-tumor responses (including partial and minor responses as well as stable disease) with a median response duration of 5 months that was extended to >18 months. Anti-tumor responses were demonstrated in nine different refractory and/or relapsed cancers, including evaluable patients with sarcoma (5 of 5; 100%), kidney cancer (7 of 7; 100%), lymphoma (1 of 1; 100%), and non-small cell lung cancer (2 of 3; 67%).[37]

Previously, in the phase I trials among patients with various solid tumors, ridaforolimus produced stable disease for at least 3 months in 50% of evaluable patients in the daily dosing regimen and in 17% of the evaluable patients in the weekly dosing regimen. Median duration of activity in those patients was 5 months, extending >12 months.[49]

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Ridaforolimus

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