AGIOS PHARMACEUTICALS INC
Form 10-K
March 18, 2014
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

(Mark One)

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2013

OR

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
Commission File Number:

001-36014

AGIOS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**26-0662915**
(State or other jurisdiction of incorporation or organization)	*(IRS Employer Identification No.)*
38 Sidney Street, 2nd Floor	**02139**
Cambridge, MA	
(Address of principal executive offices)	*(Zip Code)*

Registrant s telephone number, including area code:

(617) 649-8600

Securities registered pursuant to Section 12(b) of the Act:

Title of Class	Name of Exchange on Which Registered
Common Stock, Par Value $0.001 per share	**NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ¨ No þ

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes þ No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨	Non-accelerated filer þ	Smaller reporting company ¨
			(Do not check if a smaller reporting company)

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No þ

As of June 28, 2013, the last business day of the registrant s most recently completed second fiscal quarter, there was no established public market for the registrant s Common Stock. The registrant s Common Stock began trading on the NASDAQ Global Select Market on July 24, 2013. The aggregate market value of Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant s Common Stock as of July 24, 2013 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was $314,467,443.

As of March 14, 2014, there were 31,589,860 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement for its 2014 Annual Meeting of Stockholders to be filed pursuant to Regulation 14A within 120 days of the end of the registrant s fiscal year ended December 31, 2013 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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References to Agios

Throughout this Annual Report on Form 10-K, the Company, Agios, we, us, and our, except where the context requires otherwise, refer to Agios Pharmaceuticals, Inc. and its consolidated subsidiary, and our board of directors refers to the board of directors of Agios Pharmaceuticals, Inc.

Forward Looking Information

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- the initiation, timing, progress and results of future preclinical studies and clinical trials, and our research and development programs;
- our plans to develop and commercialize our product candidates;
- our collaboration with Celgene Corporation;
- our ability to establish and maintain additional collaborations or obtain additional funding;
- the timing or likelihood of regulatory filings and approvals;
- the implementation of our business model, strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the rate and degree of market acceptance and clinical utility of our products;
- our competitive position;

our intellectual property position;

developments and projections relating to our competitors and our industry;

our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and

our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the Risk Factors section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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Item 1. Business

We are a biopharmaceutical company committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and inborn errors of metabolism, or IEMs, which are a subset of orphan genetic metabolic diseases. Metabolism is a complex biological process involving the uptake and assimilation of nutrients in cells to produce energy and facilitate many of the processes required for cellular division and growth. We believe that dysregulation of normal cellular metabolism plays a crucial role in many diseases, including certain cancers and IEMs. We singularly focus our efforts on using cellular metabolism, an unexploited area of biological research with disruptive potential, as a platform for developing potentially transformative small molecule medicines for cancer and IEMs. The lead product candidates in our most advanced programs are aimed at druggable targets which have undergone rigorous validation processes. Our most advanced cancer product candidates, AG-221 and AG-120, which target mutant isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, have demonstrated strong proof of concept in preclinical models. In September 2013, we initiated a phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation and expect to report initial clinical data at the 2014 American Association for Cancer Research Annual Meeting in April 2014. In March 2014, we initiated a phase 1 study for AG-120 in patients with advanced hematologic malignancies with an IDH1 mutation. We expect to initiate a second phase 1 clinical trial for AG-120 in early 2014. The lead candidate in our IEM program, AG-348, targets pyruvate kinase for the treatment of pyruvate kinase deficiency. We have completed IND-enabling studies and expect to initiate Phase 1 clinical trials for AG-348 in mid-2014.

Our ability to identify, validate and drug novel targets is enabled by a set of core capabilities. Key proprietary aspects of our core capabilities in cellular metabolism include the ability to measure the activities of numerous metabolic pathways in cells or tissues in a high throughput fashion and expertise in flux biochemistry. This refers to the dynamic analysis of how metabolites, which are intermediates or small molecule products of metabolism, accumulate or diminish as they are created or chemically altered by multiple networks of metabolic enzymes. Complex mathematical modeling of metabolic pathways, enzymatic activity and the flux of metabolites through metabolic enzymatic reactions within diseased tissues allow us to identify novel biological parameters that can be measured to characterize a disease state or the effect of therapy, or biomarkers, and targets for drug discovery.

Our understanding of metabolism within diseased tissues enables the development of methods to measure the effect of a drug on the target of interest and the patient, or pharmacodynamic markers, and patient selection strategies for clinical development. Utilizing our approach we identify altered metabolic pathways within abnormal cells. Altered metabolic pathways generate disease-specific metabolic fingerprints, comprising patterns of metabolite levels, which are the amounts of particular metabolites, that can be exploited in both discovery and development of novel therapeutics. Metabolites make ideal biomarkers because they are readily measured in the target tissues and blood. Metabolic biomarkers can identify appropriate patients for clinical trials, serve as pharmacodynamic markers to characterize medicine/target engagement in patients, and permit the monitoring of patient response to therapy. The clinical development strategy for all of our product candidates will always include initial study designs that allow for genetically or biomarker defined patient populations, enabling the potential for proof of concept early in clinical development, along with the potential for accelerated approval.

We have assembled a set of core capabilities at the intersection of cellular biology and metabolism, centered on the expertise of our founding scientists who are widely considered to be the thought leaders in cancer metabolism Lewis Cantley, Ph.D. (Director of the Cancer Center at Weill Cornell Medical College and New York Presbyterian Hospital), Tak Mak, Ph.D. (Professor of Medical Biophysics, University of Toronto) and Craig Thompson, M.D. (President and CEO of Memorial Sloan-Kettering Cancer Center) as well as on the strength of our management team, including our CEO, David Schenkein, M.D., and a group of world class scientists. We have built an exceptional team of cancer biologists, enzymologists and a core group of metabolomic experts that interrogate cellular metabolism to

identify key metabolic targets and biomarkers in cancer and IEMs. Our scientists have published numerous scientific papers since 2009, including several in both

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Nature and *Science*. We have also established an intellectual property portfolio consisting of over 100 patent applications worldwide, including multiple patent applications directed to our lead product candidates, together with trade secrets, know-how and continuing technological innovation.

Our initial therapeutic area of focus is cancer. We are leveraging our expertise in metabolic pathways to discover, validate, develop and commercialize a pipeline of novel drug candidates. In April 2010, and subsequently amended in October 2011, we entered into a collaboration agreement with Celgene Corporation, or Celgene, focused on cancer metabolism. Under the collaboration, we are leading discovery, preclinical and early clinical development for all cancer metabolism programs. The discovery phase of the collaboration expires in April 2014, subject to Celgene s option to extend the discovery phase for up to two additional years. In December 2013, Celgene notified us of its intent to extend the discovery phase for an additional year through April 2015. Celgene has the option to obtain exclusive rights for the further development and commercialization of certain of these programs, and we will retain rights to the others. For the programs that Celgene chooses to license, we may elect to participate in a portion of sales activities for the medicines from such programs in the United States. In addition, for certain of these programs, we may elect to retain full rights to develop and commercialize medicines from these programs in the United States. Through December 31, 2013, we have received approximately $141.2 million in payments from Celgene and $50.3 million in equity investments and are entitled to a $20.0 million payment in 2014 as a result of the discovery term extension exercised in December 2013. We are also eligible to receive an additional extension payment, payments upon the successful achievement of specified milestones, reimbursements for certain development expenses and royalties on any product sales.

We believe that our competitive advantage and singular focus in understanding cellular metabolism has created disruptive knowledge in biology that we can exploit for the development of transformative medicines in cancer. Because there has not previously been a systematic approach to drug discovery in this field, we have had to demonstrate significant major advances, including:

- identification of unique and specific metabolic enzymes that are altered from normal cells within cancer cells and are directly involved in the pathogenesis of cancer;
- creation of selective small molecules with drug-like properties that preferentially target disease-associated enzymes;
- achievement of pharmacologic efficacy in *in vitro* and *in vivo* models; and
- discovery of novel biomarkers that identify the appropriate patients for clinical trials.

Our two most advanced cancer programs are targeting mutations in the enzymes isocitrate dehydrogenase 1 and 2, referred to as IDH1 and IDH2. Both program targets are genetically validated, which means the importance of such targets have been demonstrated based on genetics, and represent two of the most promising metabolic targets in cancer biology, as concluded by the leading scientific journal *Nature* in 2011. Extensive publications led by Agios scientists validate our belief that these mutations are initiating and driving events in many cancers. These two otherwise normal metabolic enzymes are mutated in a wide range of cancers, including both solid tumors and hematological malignancies. Our drug candidates are selective for the mutated form of IDH1 and IDH2 found in cancer cells. In September 2013, we initiated a phase 1 study for AG-221, the lead candidate for patients with

advanced hematologic malignancies with an IDH2-mutation. In the IDH1 program, we initiated a phase 1 study for our lead development candidate, AG-120, in patients with advanced hematologic malignancies with an IDH1 mutation in March 2014. We expect to initiate a second phase 1 clinical trial in patients with IDH1-mutation positive cancers for AG-120 in early 2014. We elected to exercise the option to U.S. development and commercial rights for AG-120, in accordance with the terms of our agreement with Celgene, with Celgene retaining its option to ex-U.S. rights.

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We are also focused on developing medicines to address IEMs, with a novel approach to orphan diseases for which no effective or disease-modifying therapy is currently available. A hallmark of IEMs is abnormal cellular metabolic activity due to a genetic defect, which results in the accumulation or deficit of certain metabolites or proteins, disrupting normal metabolic functions. We utilize stringent criteria when identifying which IEMs Agios will pursue. We focus on IEMs with a common set of attributes:

- single gene, single disease (i.e., monogenic disorders);
- high unmet medical need with evidence that there is progressive disease post-birth that can be addressed with therapy; and
- an adequate number of patients for prospective clinical trials.

We apply our core capabilities in exploring cellular metabolism to identify key cellular targets in affected cells and design novel small molecules with the potential to correct the metabolic defect in patients afflicted with these diseases. We have successfully used this approach in our most advanced IEM program pyruvate kinase deficiency, or PK deficiency, a rare form of hereditary hemolytic anemia. The disease is characterized by mild to severe forms of anemia. There are no currently available treatments other than supportive care, which includes splenectomy, transfusion support and chelation, which refers to the removal of excess iron from the human body with a therapeutic agent. Our lead development candidate, AG-348, is a potent, orally available small molecule activator of the PKR enzyme, an isoform of PK that, when mutated, leads to PK deficiency. We expect to start single and multiple ascending dose-escalation phase 1 clinical trials for AG-348 in healthy volunteers in mid-2014.

Our Guiding Principles

We aim to build a long-term company with a disciplined focus on developing medicines that transform the lives of patients with cancer and IEMs. We maintain a culture of high integrity that embraces the following guiding principles, which we believe will provide long-term benefits for all our stakeholders:

- ***Follow the science and do what is right for patients.***
- ***Maintain a culture of incisive decision-making driven by deep scientific interrogation and respectful irreverence.***
- ***Foster collaborative spirit that includes all employees regardless of function or level.***
- ***Leverage deep strategic relationships with our academic and commercial partners to improve the quality of our discovery and development efforts.***

Our Focus Cellular Metabolism

Cellular metabolism refers to the set of life-sustaining chemical transformations within the cells of living organisms. The conversion of nutrients into energy via enzyme-catalyzed reactions allows organisms to grow and reproduce, maintain their structures, and respond to their environments. The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes catalyze quick and efficient reactions, serve as key regulators of metabolic pathways, and respond to changes in the cell s environment or signals from other cells. We believe our deep understanding of metabolic pathways within normal cells enables us to identify altered metabolic pathways within abnormal cells such as in rapidly proliferating cancers and IEMs.

Fundamental differences in the metabolism of normal cells and rapidly proliferating cancer cells were first discovered by Otto Warburg more than 80 years ago an observation that earned him the Nobel Prize. Warburg demonstrated that in contrast to normal cells, which convert nutrients, such as sugar, into energy via a process known as the Krebs cycle, cancer cells ferment their sugar into lactic acid a process known as aerobic glycolysis. It is now known that this allows the cancer cells to generate the building blocks they need to grow rapidly. The ability of the cancer cell to rewire its metabolic pathways to fuel its growth and survival has

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spawned an entirely new field of cancer biology known as cancer metabolism or tumor metabolism. It is only in the last decade that scientists have developed sophisticated tools to interrogate and evaluate metabolism within cancer or rapidly dividing cells. Agios founders and scientific advisors have largely driven this intense focus on studying the metabolism of cancer cells.

Cancer metabolism is a new and exciting field of biology that provides a fundamentally different approach to treating cancer. Cancers become addicted to certain fuel sources and inherently alter their cellular machinery to change how they consume and utilize nutrients. Cancer cells increase the transport of nutrients into the cell by 200-400 fold compared to normal cells while also mutating metabolic enzymes to generate metabolites that fuel growth and altering gene expression of enzymes to divert energy production. Collectively, these changes afford cancer cells the ability to generate the building blocks that drive tumor growth. Inhibiting key enzymes in cancer cell specific metabolic pathways has the potential to disrupt tumor cell proliferation and survival without affecting normal cells, thus providing a powerful new intervention point for discovery and development of novel targeted, cancer therapeutics. We believe that this is an entirely novel approach to treating cancer, and our research is directed at identifying such metabolic targets and discovering medicines against them.

Validation of the concept of cancer cell metabolic rewiring and excessive nutrient uptake comes from the widespread use of positron emission tomography, or PET, to detect cancers. This medical imaging technology relies on the uptake of nutrients, namely sugar, into cells. Patients are injected with a radioactively labeled form of sugar, which is more rapidly consumed by cancer cells given their profound requirement for nutrients relative to normal tissues. PET imaging precisely locates cancerous areas throughout the body and provides for both a diagnostic and prognostic tool throughout cancer therapy.

The metabolic rewiring of cancer cells can also be linked to specific genetic alterations in oncogenes (which are genes that transform normal cells into tumor cells) and tumor suppressor genes (which are genes that are anti-oncogenic) responsible for cell signaling. These mutations in signaling pathways can drive excessive uptake of nutrients and altered metabolic pathways, thereby causing cancer formation. This cross-talk between cell signaling and metabolism offers multiple opportunities to treat cancer by combining Agios therapies directed against metabolic enzymes with existing or emerging standards of care.

In cancer, our target universe for creating novel transformative medicines is derived from the human cellular metabolic machinery, referred to as the metabolome, containing 2,000-3,000 cellular metabolic enzymes, from which we anticipate that there will likely be between 50-100 novel targets for oncology. This represents one of the largest unexploited new classes of important targets in oncology. The Agios team has already studied more than 50 metabolic enzymes as possible important cancer targets. With our focus on targets that are distinct in cancer versus normal cells, we believe that they are likely to fall within three broad categories:

a mutation leading to a unique metabolic enzyme only found in cancer;

unique isoforms of metabolic enzymes that are found in the cancer and that are different in normal cells; and

dysregulation of an entire metabolic pathway to feed the cancer s need for a specific metabolite or nutrient.

An understanding of metabolic pathways based solely on traditional biochemistry would underestimate the pervasive role of metabolism in essentially every aspect of biology. Recent work has demonstrated that many human diseases

involve altered cellular metabolism often genetically programmed that disrupts normal physiology and leads to severe tissue dysfunction. Another area of unmet medical need is IEMs, severe and often life-threatening inherited childhood and adult diseases caused by a defect in a metabolic enzyme or pathway. Our core capabilities to interrogate the metabolic pathway of the disease have allowed us to create potential medicines that can restore the metabolic balance and potentially lead to disease-modifying therapies for these orphan diseases. Our approach is designed to develop treatment for the right patient identified by the genetic and metabolic alteration marked by their inherited disease.

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Our Core Capabilities and Science

We believe that our capabilities in understanding both static and dynamic aspects of cellular metabolism are unique in the industry as demonstrated by our ability to identify and validate four novel, druggable targets. Among our key core capabilities to identify and validate novel enzyme targets are:

Measurement of metabolites and metabolic pathways in cells and tissues using high throughput mass spectrometry.

Identification of candidate metabolic enzymes using flux biochemistry: In many circumstances, cancers and normal cells utilize multiple routes to produce the same metabolite. To identify the relevant target, we evaluate the kinetics of enzymes to determine the speed at which metabolites are moving along enzymatic pathways. This critically important technology is called flux biochemistry and is distinguished from the more conventional static metabolomics view. Flux biochemistry, by labeling the nutrients, allows us to create a pathway map by measuring the rate of filling and emptying of metabolic pools. This methodology, which precisely measures the rate at which a nutrient source is broken down and reassembled into cellular building blocks and biochemical energy, has been automated in a high throughput fashion at Agios. Experimental data is integrated with mathematical modeling of enzyme pathways to generate an accurate understanding of the metabolic dysregulation. This allows us to determine which enzyme is the Achilles Heel of a particular cancer or IEM.

Mining of genomic data emerging from the public cancer genome sequencing efforts, utilizing our state of the art genomics and bioinformatics capabilities, to identify metabolic enzymes that are mutated or amplified in tumors: This provides insight into novel targets for therapy while facilitating a precision medicine approach to patient selection based on the genetic defect (e.g., mutant IDH1 and IDH2).

Development of a multiplexed, barcoded RNAi depletion screening strategy, enabling us to interrogate the entire metabolome in a single experiment, both in cells and in tumor bearing animals: This technology allows us to identify novel targets in cancers of interest.

Inhibition and activation of metabolic enzymes using structure-based design from crystal structures, computational chemistry, and high throughput chemical and fragment library screening.

Our Approach to Drug Discovery and Development, and the Utilization of Precision Medicine

We intend to apply our deep understanding of metabolism, coupled with our ability to create medicines that can inhibit or activate metabolic enzymes, to fundamentally change the way cancer and IEMs are treated. We have the ability to identify and validate novel and druggable targets in both cancer and IEMs.

We begin the process to find and validate new targets by evaluating a cancer s dependency on certain nutrients or enzymes in comparison to normal cells. We then utilize a number of techniques to determine if the cancer is dependent on the identified enzyme. The candidate enzyme target is inactivated, or turned off using genetic tools, first in tissue culture and then in xenograft models, in which representative tumors have been implanted in animals. Once

inactivated, we can determine if turning off the enzyme stops the growth of the cancer cells *in vitro* and slows or stops the growth of a tumor in the xenograft model. If our findings are positive, we begin the process of searching for biomarkers that will enable our precision medicine approach of identifying the right patients to be eventually treated. In the early stages of biomarker development, we create a responder hypothesis, comparing the molecular genetics and metabolite patterns between cancers that respond to treatment to those that do not respond to enzyme inhibition. The process to design a small molecule drug candidate begins by determining the crystal structure of the enzyme. We create candidate molecules using structure-based design coupled with high throughput chemical screening, searching for small molecules that can inhibit the enzyme. The decision to enter the final and most expensive part of drug discovery, which is the refinement of the small molecule product candidates, is only made when we have completed all of these critical steps. The target is then considered validated . This rigorous process only allows the most promising programs to enter the last stage of drug discovery.

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In our IEM portfolio, we use an equally rigorous set of validation techniques. We begin with an assessment of scientific literature and disease and genomic databases, applying text and data mining techniques, to identify IEMs that are caused by a mutation in a single metabolic enzyme, referred to as monogenic disorders. We perform a full evaluation of the clinical aspects of the disease, which includes an understanding of the severity of the disease, the progression of the disease manifestations post-birth and currently available treatments. We intend to focus only on diseases of a severe nature for which there are no available effective treatments, where intervention is likely to ameliorate disease manifestations, and where there are an adequate number of patients to conduct appropriate clinical trials. We conduct a detailed mutational and structural analysis of the metabolic enzyme and the entire pathway of interest to determine the scientific feasibility of intervention using small molecules to restore metabolic balance within the diseased cell. As in our efforts to develop therapeutics for cancer, we create a crystal structure of the enzyme to begin the process of drug design. We make candidate tool molecules using structure-based design coupled with high throughput chemical screening. To fully evaluate the potential of our lead molecules to lead to disease modifying effects we strive to develop an animal model of the disease by genetically inserting the mutated enzyme into animals (knock-in mouse model). Agios has selected a product candidate for the treatment of PK deficiency to advance into clinical development. Drug discovery for several IEMs are in various stages of research.

We will only progress drug candidates forward into phase 1 trials if we have the ability to select patients who are most likely to respond to a given therapy based on genetic or metabolic biomarkers. While many factors are considered critical to maximize the probability of technical success in the drug development process, perhaps none is more important than identifying highly specific and selective molecules aimed at the best possible targets for therapy coupled with the patients most likely to respond to that therapy. Our goal is to develop increasing confidence in the target and the patient population prior to entering human clinical trials and then initiate those first human trials in a patient population that has been selected based on target dependence using a biomarker. This approach, known as personalized or precision medicine, is used in the industry to lead to the potential for clear proof of concept in early human trials.

We believe our approach to drug discovery and development will lead to transformative medicines for patients. We plan to partner closely with worldwide regulatory authorities and to utilize all available methodologies such as orphan, fast track, accelerated approval and/or breakthrough therapy designations as appropriate. We expect that conducting clinical trials with a targeted agent in the appropriate clinical population has the potential to lead to very rapid development timelines. There are now multiple examples within oncology of drugs against novel targets that have progressed from first in human trial to regulatory approval in less than five years (e.g., Gleevec ®, VELCADE ® and Xalkori ®).

Our Development Programs

We have leveraged our core capabilities in cellular metabolism to build a research and development engine that is focused in the therapeutic areas of cancer and IEMs. This engine has permitted us to discover proprietary first-in-class orally available small molecules as potential lead product candidates for each of several novel programs in development. All of our lead programs focus on diagnostically-identified patient populations with the potential for early clinical proof of concept and accelerated approval paths.

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The following table summarizes key information about our most advanced product candidates, each of which is described and discussed in further detail below:

Product candidate	Biomarker(s)	Initial indications	Stage of development	Commercial rights
Cancer metabolism programs:				
AG-221 (IDH2 mutant inhibitor)	Genotyping of IDH2 mutation; 2HG	All cancer patients with an IDH2 mutation in the following diseases: acute myelogenous leukemia, high risk myelodysplasia and myeloproliferative disorders, angio-immunoblastic non-Hodgkins T cell lymphoma, glioma, chondrosarcoma and other solid tumors	Phase 1 on-going	Agios: milestones and royalties Celgene: worldwide
AG-120 (IDH1 mutant inhibitor)	Genotyping of IDH1 mutation; 2HG	All cancer patients with an IDH1 mutation in the following diseases: glioma, chondrosarcoma, cholangiocarcinoma, acute myelogenous leukemia, high risk myelodysplasia and myeloproliferative disorders, and other hematological and solid tumors	Phase 1 initiated	Agios: Milestones, cross-royalties, and U.S. rights Celgene: ex-U.S. rights
Inborn errors of metabolism programs:				
AG-348 (Pyruvate kinase (R) activator)	Genetic testing for mutation in the pyruvate kinase R gene	Patients with pyruvate kinase deficiency	IND-enabling studies completed	Agios: worldwide
AG-221 or other mutant inhibitor (IDH2 mutant inhibitor)	Genotyping of IDH2 mutation; 2HG	Patients with Type II D-2-hydroxyglutaric aciduria	Research	Agios: milestones and royalties Celgene: worldwide

Cancer

Background

In most cases of advanced cancer, the diagnosis still represents a death sentence to patients and their families. The American Cancer Society estimates that 1.66 million new cancer cases will be diagnosed in the U.S. in 2013. According to the Society, approximately 580,000 Americans and 7.1 million people worldwide will die of cancer in 2013. Cancer is the second leading cause of death in the United States, exceeded only by heart disease. Lung, colon and rectal, breast, and prostate cancer are the most prevalent cancers. Causes of cancer include environmental factors

such as tobacco, chemicals, radiation and diet, genetic factors, such as inherited mutations, and endogenous hormone levels, and associated medical conditions such as certain viral infections and immunodeficiency.

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when the repair of genetic material in normal cells begins to fail and genes that regulate cell growth become disrupted. Carcinogens, or cancer causing agents, such as radiation, chemicals and hormones, can trigger changes to the genetic material of a cell, and typically prompt this disruption. Cells that have been disrupted may become cancerous, leading to changes in the cells DNA, and ultimately uncontrolled growth. Cancer cells can spread to other areas of the body, or metastasize, and form tumors, which can destroy normal tissue or organs. Risk factors for cancer include family history, age,

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diet, and exogenous factors, such as exposure to ultraviolet sunlight and smoking. Cancers can be classified in stages to document disease severity, measured in stages of I to IV, generally based on tumor size, involvement of lymph nodes, and metastases.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy. A cancer patient often receives treatment with a combination of these methods. Surgery and radiation therapy are particularly effective in patients in whom the disease is localized. Physicians generally use systemic drug therapies in situations in which the cancer has spread beyond the primary site or cannot otherwise be treated through surgery. The goal of drug therapy is to kill cancer cells or to damage cellular components required for rapid growth and survival of cancer cells. In many cases, drug therapy entails the administration of several different drugs in combination. Over the past several decades, drug therapy has evolved from non-specific drugs that kill both healthy and cancerous cells to drugs that target specific molecular pathways involved in cancer.

Cytotoxic chemotherapies

The earliest approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, that kill rapidly proliferating cancer cells through non-specific mechanisms, such as disrupting cell metabolism or causing damage to cellular components required for survival and rapid growth. While these drugs, (e.g. CYTOXAN ®, Adriamycin ®) have been effective in the treatment of some cancers they act in an indiscriminate manner, killing healthy as well as cancerous cells. Due to their mechanism of action, many cytotoxic drugs have a narrow dose range above which the toxicity causes unacceptable or even fatal levels of damage and below which the drugs are not effective in eradicating cancer cells.

Targeted therapies

The next approach to pharmacological cancer treatment was to develop drugs, referred to as targeted therapeutics, that target specific biological molecules in the human body that play a role in rapid cell growth and the spread of cancer. Targeted therapeutics are designed to preferentially kill cancer cells and spare normal cells, to improve efficacy and minimize side effects. The drugs are designed to either attack a target that causes uncontrolled growth of cancer cells because of either a specific genetic alteration primarily found in cancer cells but not in normal cells or a target that cancer cells are more dependent on for their growth in comparison to normal cells. Examples of effective targeted therapies include Herceptin ®, Avastin ® and Zelboraf ®.

Emerging areas

Several new approaches to develop novel cancer treatments are underway. They include: treatment with drugs or other methods that stimulate the normal immune system to attack the cancer; antibody drug conjugates (Kadcyla) that carry a powerful chemotherapy payload that is only released into the cancer cell; and drugs that target the changes in gene activity that occurs in cancer cells (epigenetics).

We believe that interrogating altered cellular metabolism the way cancers take up and break down their nutrients will lead to a new wave of important cancer treatments. Further, we believe that we must utilize a precision medicine approach, which will enable us to only enroll patients in clinical trials based on a biomarker likely to predict response and benefit.

Programs in isocitrate dehydrogenase (IDH)

The isocitrate dehydrogenase (IDH) protein is a critical enzyme in the citric acid cycle, also known as the tricarboxylic acid, or Krebs, cycle. The Krebs cycle is centrally important to many biochemical pathways, and is one of the earliest established components of cellular metabolism. The Krebs cycle converts an essential cellular metabolite called isocitrate into another metabolite, alpha-ketoglutarate (a -ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme (IDH1, IDH2, and IDH3) but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the same reaction but in different cellular compartments: IDH1 is found in the cytoplasm of the cell and IDH2 in the mitochondria. Tumor cells are generally observed to carry either an IDH1 or IDH2 mutation, but not both.

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We have identified selective development candidates that target the mutated forms of IDH1 and IDH2 which are each found in a wide range of solid and hematological cancers. We and our collaborators have demonstrated that these mutations initiate and drive cancer growth by blocking differentiation, also referred to as maturation, of primitive cells which leads to tumor formation and maintenance. We believe that inhibition of these mutated proteins may lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations.

Agios research in IDH mutations in cancer

Academic researchers first identified mutations in either IDH1 or IDH2 in over 70% of patients with brain tumors, also known as gliomas. They also demonstrated that the mutated form of the enzyme IDH was no longer able to conduct its normal function of converting the metabolite isocitrate into alpha-ketoglutarate. Our scientists decided to examine the mutated pathway using our metabolic platform and discovered that the mutated IDH enzymes had adopted a novel gain of function activity that allows only the mutated IDH enzyme to produce large amounts of a metabolite called 2 hydroxygluturate, or 2HG. This discovery was the subject of the first Agios publication in the scientific journal *Nature* (Dang et al 2009), and was subsequently deemed by *Nature* to be one of the most important recent discoveries in cancer research.

We believe that the excessive levels of the metabolite 2HG produced by the tumor, fuel cancer growth and survival via multiple cellular changes that lead to a block in cell maturation, or differentiation. Recently, two published preclinical studies confirm that 2HG promotes tumorigenesis and that the effects of 2HG can be reversed with an IDH1 or IDH2 mutant specific inhibitor. 2HG is also an ideal biomarker to identify and follow cancer patients as they receive treatment with an IDH mutant specific inhibitor. In normal cells, 2HG is present at extremely low levels. However, in cancer cells that carry the IDH mutation, 2HG is produced at massively higher levels than in normal cells. It can easily be detected in samples from cancer specimens and in the blood of certain cancer patients. In patients with brain tumors it can also be imaged on an MRI.

In a cell based model it was demonstrated that the IDH1 mutation (R132H) promotes growth factor independence (i.e., transformation into cancerous cells) and blocks differentiation in hematopoietic cells. It was also demonstrated in this model that the cell s transformation into cancer could be driven solely by the metabolite 2HG without any mutant enzyme. Lastly the transformation by IDH1 mutation was reversible with the use of an IDH1 mutant inhibitor. (*Science* Kaelin et al 2013). These results are illustrated in the graph below.

Figure A demonstrates that insertion of R132H IDH1 mutation into TF-1 cells leads to growth factor independence which can be reversed by the addition of an Agios IDH1 mutant inhibitor. ***Figure B*** demonstrates that this transformation to growth factor independence can be replicated solely by the addition of 2HG(R). As expected, the IDH1 mutant inhibitor has no effect on the ability of exogenously administered 2HG to transform cells.

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An *ex vivo* model is shown in the figure below, in which human acute myelogenous leukemia, or AML, bone marrow cells removed directly from a patient with a leukemia positive for an IDH2 mutation were maintained in short term culture. Treatment with the Agios clinical candidate AG-221 at concentrations achievable *in vivo* revealed a significant decrease in leukemia cells (myeloblasts) associated with evidence that normal cell maturation is returning, as noted by the increase in normal maturing cells (promyeocytes, myeocytes, metamyelocytes and granulocytes). These data provide *ex vivo* proof of concept that inhibitors targeting mutant IDH2 could induce differentiation in cells previously destined to form undifferentiated leukemic cells.

Taken together, these data provide compelling evidence that IDH1 or IDH2 mutant inhibitors induce differentiation in both cell based models and primary patient samples. The best example of an approved treatment that can reverse the block in differentiation induced by a mutation is all trans-retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia. This single agent leads to complete responses in this form of leukemia, which is driven by a genetic alteration in the retinoic acid receptor, and is proof of principle that differentiation therapy can lead to major clinical activity in patients with acute leukemia.

In addition we have been able to generate AML mouse models leveraging primary samples from both IDH1 and IDH2 mutant positive patients. In an IDH1 mutant positive AML model, after 28 days of treatment with an Agios IDH1 mutant inhibitor, we were able to demonstrate early signs of single agent activity and synergy in combination with chemotherapy. In an IDH2 mutant positive AML model, we were able to reproduce an aggressive form of leukemia. Using our lead IDH2 mutant inhibitor AG-221, we demonstrated a dose dependent survival advantage in comparison to standard chemotherapy. The group of animals receiving the highest dose of AG-221 all survived until the study was completed. A dose dependent decrease in leukemia and evidence of normal differentiation was seen in all AG-221 treated animals. As we enter clinical development, these models help to inform our early strategies in designing single agent and combination clinical studies.

Incidence of IDH mutations

To date, IDH1 and IDH2 mutations have been found to be prevalent in both solid and hematologic tumors. Mutations in IDH1 were identified through a genome-wide mutation analysis in glioblastoma multiforme, or

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GBM, the most common and aggressive type of brain cancer. High throughput deep sequencing revealed the presence of mutations in either IDH1 or IDH2 in more than 70% of grade II-III gliomas and secondary glioblastomas. Subsequent sequencing efforts revealed alterations in these two genes across additional cancers, including hematologic malignancies. Mutations in IDH1 and IDH2 are generally mutually exclusive and occur at very early stages of tumor development suggesting that they can promote tumorigenesis.

IDH2 mutations appear to be most prevalent in hematologic tumors. Among patients with AML, IDH2 mutations have been observed in 15% of adult patients. Outside of AML, IDH2 mutations are found in a subset of other hematologic and non-hematologic cancers. Sequence analysis has shown that IDH2 mutations occur in approximately 5% of patients with myelodysplastic syndrome, or MDS, or myeloproliferative neoplasms, or MPN. IDH2 mutations have also been found in several solid tumor types such as melanoma, glioma and chondrosarcoma.

IDH1 mutations appear to be most prevalent in solid tumors. Among patients with gliomas (low grade glioma and secondary glioblastoma), IDH1 mutations have been observed in 70% of patients. Outside of gliomas, mutations have been found in a subset of other solid and hematologic cancers. Importantly, mutations in IDH1 have been identified in difficult to treat cancers such as chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. IDH1 mutations have also been found in several other solid tumor types such as colon, melanoma and lung.

The following table summarizes our current initial estimates on the prevalence of IDH2 and IDH1 mutations in hematologic and solid tumors. We believe our estimates may expand as more cancer treatment centers screen for these IDH mutations.

Mutation	Indications	% with IDH mutations	Estimated patient numbers (1)
IDH2	Acute Myeloid Leukemia (AML)	15%	7,200
	MDS/MPN	5%	2,000
	Angio-immunoblastic T cell NHL	25%	400
	Others (melanoma, glioma, chondrosarcoma)	3-5%	1,500
	Total		**11,100**
IDH1	Grade II, III glioma & secondary GBM	70%	11,000
	Chondrosarcoma	>50%	4,600
	AML	7.50%	3,600
	MDS/MPN	5%	2,000
	Intrahepatic Cholangiocarcinoma	20%	1,600
	Others (colon, melanoma, lung)	1-2%	8,000
	Total		**30,800**

(1) Estimated U.S., Europe and Japan incidence

AG-221: lead IDH2 program

AG-221 is an orally available, selective, potent inhibitor of the mutated IDH2 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH2 mutations, including those with AML. Based on our established non-clinically-based target profiling, as well as non-clinical *in vitro* and *in vivo* efficacy data, there is a clear rationale to develop AG-221 in defined target populations that harbor the IDH2 gene mutation.

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We have conducted exploratory pharmacology studies to develop a model of IDH2 mutant-induced tumorigenesis and to characterize the binding, inhibition, and selectivity of AG-221. AG-221 is a potent inhibitor of the IDH2 mutant protein. We have demonstrated in *in vitro* experiments and in *in vivo* models that exposure to AG-221 reduces 2HG levels to those found in normal cells, reverses 2HG-induced histone hypermethylation, and induces differentiation in multiple leukemia cell models. Targeted inhibition of the IDH2 mutant also reversed the differentiation block in both TF-1 leukemia cells and primary AML cells derived from patients.

During 2013, we successfully completed IND-enabling studies on AG-221. The molecule has excellent pharmacological properties with a wide therapeutic index. In September 2013, we initiated our first phase 1 study for AG-221 in patients with advanced hematologic malignancies with an IDH2 mutation. This multi-center, global, multiple ascending dose trial will primarily assess safety and tolerability for AG-221 in adults with AML or related diseases. Secondary endpoints will evaluate the pharmacokinetics and pharmacodynamics properties of AG-221 and determine if any efficacy signals can be measured. The initial proof of mechanism will require the reduction of the metabolite 2HG in response to drug treatment. Multiple disease specific cohorts of 10-20 patients will be enrolled after a safe biologically active dose has been determined to evaluate the single-agent disease modifying activity of AG-221. We expect to report initial clinical data at the 2014 American Association for Cancer Research annual meeting in April 2014. We intend to conduct subsequent trials in patients with other cancers carrying the IDH2 mutation and in combination with other anti-cancer agents. We plan to pursue additional clinical studies, evaluating both single-agent as well as combination therapy in patients with serious and life-threatening hematological and solid tumors that harbor IDH2 mutation, in the most efficient manner as we seek to establish the safety and effectiveness of AG-221. The potential regulatory pathway (i.e., conventional or accelerated approval) will be determined by data emerging from the early development program.

AG-120: lead IDH1 program

AG-120 is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH1 mutations. Importantly, mutations in IDH1 have been identified in difficult to treat cancers such as chondrosarcoma and cholangiocarcinoma where both the treatment options and prognosis for patients are poor. These are indications where the standard of care treatment options are limited, thus providing an opportunity for more rapid development of an IDH1 mutant inhibitor. Based on our nonclinical *in vitro* and *in vivo* efficacy data, there is a clear rationale to develop AG-120 in defined target populations that harbor the IDH1 gene mutation.

We have successfully filed an IND for AG-120 that has been accepted by the FDA. The molecule has excellent pharmacological properties with a wide therapeutic index. In March 2014, we initiated a phase 1 study for AG-120 in patients with advanced hematologic malignancies. In early 2014, we plan to initiate a second phase I clinical trial in advanced solid tumors. Both trials will only enroll patients that carry the IDH1 mutation.

Other programs

In addition to our lead IDH2 and IDH1 programs, we are in earlier stages of validation and drug discovery on multiple novel programs.

Inborn Errors of Metabolism

Background

IEMs are a broad group of more than 600 orphan genetic diseases caused by mutations of single metabolic genes. In these disorders, the defect of a single metabolic enzyme disrupts the normal functioning of a metabolic pathway, leading to either aberrant accumulation of upstream metabolites which may be toxic or interfere with normal function or reduced ability to synthesize essential downstream metabolites or other critical cellular components. IEMs are also referred to as congenital metabolic diseases or rare genetic metabolic diseases.

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The term inborn error of metabolism was coined by a British physician, Archibald Garrod (1857 1936), in the early 20th century. He is known for work that prefigured the one gene-one enzyme hypothesis, and his seminal text, Inborn Errors of Metabolism, was published in 1923. Traditionally, IEMs were categorized as disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, or lysosomal storage diseases. In recent decades, hundreds of new IEMs have been discovered and the categories have proliferated.

Most of these diseases are rare or ultra-rare orphan diseases, often with severe or life-threatening features. A disorder is considered orphan if it affects fewer than 200,000 people in the United States, or fewer than five per 10,000 people in the European Union. In a study in British Columbia, the overall incidence of IEMs was estimated to be 70 per 100,000 live births or one in 1,400 births, overall representing more than approximately 15% of single gene disorders in the population. Incidence of a single IEM can vary widely but is generally rare, usually equal to or less than one per 100,000 births. Many IEMs are likely to be under-diagnosed given the lack of available therapies or diagnostics and the rarity of the condition.

Current treatment options for these disorders are limited. Diet modification or nutrient supplementation can be beneficial in some IEMs. Several of these disorders, from a group known as lysosomal storage diseases, have been treated successfully with enzyme replacement therapy, or ERT, the therapeutic administration of a functional version of the defective enzyme. Examples of ERTs for lysosomal storage disorders include Fabrazyme ® for Fabry disease, Myozome ® for Pompe disease, Cerezyme ® for Gaucher disease, and Elaprase ® for Hunter syndrome.

Unfortunately, most mutations driving IEMs are intracellular and not amenable for treatment with enzyme replacement therapies. As a result, despite the promising progress made for patients with a small group of these diseases, the vast majority of patients with IEMs have few therapeutic options available, and the standard of care is palliative, meaning treatment of symptoms with no effect on underlying disease mechanisms. We are taking a novel small molecule approach to correct the metabolic defects within diseased cells with a goal of developing transformative medicines for patients.

Pyruvate kinase deficiency program

Pyruvate kinase, or PK, is the enzyme involved in the second to last reaction in glycolysis the conversion of glucose into lactic acid. This enzyme is critical for the survival of the cell and has several tissue-specific isoforms (PKR, PKL, PKM1 and PKM2). PKR is the isoform of pyruvate kinase which is present in red blood cells. Mutations in PKR cause defects in red cell glycolysis and leads to a hematological IEM known as pyruvate kinase deficiency, or PK deficiency. Glycolysis is the only pathway available for red blood cells to maintain the production of ATP, or Adenosine-5 -triphosphate, which transports chemical energy within cells for metabolism. Accordingly, total absence of the PKR gene is not compatible with life. PK deficiency leads to a shortened life-span for red blood cells and is the most common form of non-spherocytic hemolytic anemia in humans. The disease is autosomal recessive, meaning children inherit one mutated form of PKR from one parent and the second mutated form from the other parent. Children with the disease produce PKR enzyme that has only a fraction of the normal level of activity (generally <50%). Parents of affected children have only one copy of the mutated PKR enzyme and are clinically normal.

PK deficiency is a rare disorder and disease understanding is still evolving. Several published epidemiology studies estimated prevalence of PK deficiency between three to nine affected patients per million. Agios estimates that between 1,000-3,000 diagnosed patients are alive in the U.S., with similar numbers in Europe, and we believe that the disease is likely under-diagnosed. There is no unique ethnic or geographic representation of the disease. The disease manifests by mild to severe forms of anemia caused by the excessive premature destruction of red blood cells. The precise mechanism for the destruction is not well understood but is thought to result from membrane instability secondary to the metabolic defect caused by the low level of PKR enzyme. The hemolysis is extra-vascular in that the

red blood cells are destroyed in small capillaries or organs and not spontaneously breaking open in the circulation.

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The disease typically presents during early infancy with jaundice and severe anemia, which can require immediate life-saving intervention via replacement of the infant s entire blood system with a donor s blood, referred to as an exchange transfusion. Children are classified as either severe disease (hemoglobin <8gm/dl and life-long need for transfusions) or moderate (hemoglobin levels of 8-10 gm/dl and i