

INFINITY PHARMACEUTICALS, INC.

Form 10-K

March 14, 2019

Table of Contents

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended: December 31, 2018

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number: 000-31141

INFINITY PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware 33-0655706

(State or other jurisdiction of (I.R.S. Employer incorporation or organization) Identification No.)

784 Memorial Drive, Cambridge, Massachusetts 02139

(Address of principal executive offices) (zip code)

Registrant's telephone number, including area code: (617) 453-1000

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

Common Stock, \$0.001 par value Nasdaq Global Select Market

(Title of each class) (Name of each exchange on which listed)

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 ☒

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 ☒

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 ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted 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 such files). Yes ☒ 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, a smaller reporting company, or an emerging growth company. See definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☒ Non-accelerated filer ☐ Smaller reporting company ☒ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

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The aggregate market value of voting Common Stock held by non-affiliates of the registrant as of June 29, 2018 was \$105,426,361 based on the last reported sale price of the registrant's Common Stock on the Nasdaq Global Select Market on that date.

Number of shares outstanding of the registrant's Common Stock as of March 8, 2019: 56,925,528

Documents incorporated by reference:

Portions of our definitive proxy statement to be filed with the Securities and Exchange Commission no later than April 30, 2019 in connection with our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

TABLE OF CONTENTS

	Page No.
Part I	
Item 1: <u>Business</u>	<u>3</u>
Item 1A: <u>Risk Factors</u>	<u>35</u>
Item 1B: <u>Unresolved Staff Comments</u>	<u>68</u>
Item 2: <u>Properties</u>	<u>68</u>
Item 3: <u>Legal Proceedings</u>	<u>68</u>
Item 4: <u>Mine Safety Disclosures</u>	<u>68</u>
Part II	
Item 5: <u>Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</u>	<u>68</u>
Item 6: <u>Selected Financial Data</u>	<u>68</u>
Item 7: <u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	<u>68</u>
Item 7A: <u>Quantitative and Qualitative Disclosures about Market Risk</u>	<u>76</u>
Item 8: <u>Financial Statements and Supplementary Data</u>	<u>76</u>
Item 9: <u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	<u>99</u>
Item 9A: <u>Controls and Procedures</u>	<u>100</u>
Part III	
Item 10: <u>Directors, Executive Officers and Corporate Governance</u>	<u>102</u>
Item 11: <u>Executive Compensation</u>	<u>102</u>
Item 12: <u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</u>	<u>102</u>
Item 13: <u>Certain Relationships and Related Transactions, and Director Independence</u>	<u>102</u>
Item 14: <u>Principal Accounting Fees and Services</u>	<u>102</u>
Part IV	
Item 15: <u>Exhibits, Financial Statement Schedules</u>	<u>102</u>
Item 16: <u>Form 10-K Summary</u>	<u>106</u>
<u>Signatures</u>	<u>103</u>

Table of Contents

Forward-Looking Information

The following discussion of our financial condition and results of operations contained in this Annual Report on Form 10-K should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Some of the information contained in this discussion and analysis and set forth elsewhere in this report, including information with respect to our plans and strategies for our business, the possible achievement of clinical development goals and milestones in 2019 and beyond, our future development efforts, our collaborations, and our future operating results and financial position, includes forward-looking statements that involve risks and uncertainties. We often use words such as “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “practise,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and other words and terms of similar meaning to help identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify these forward-looking statements by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause actual results or events to differ materially from those indicated by forward-looking statements made herein. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug development activities, decisions made by the U.S. Food and Drug Administration, or FDA, and other regulatory authorities with respect to the development and commercialization of our product candidates, our ability to obtain, maintain and enforce intellectual property rights for our product candidates, our dependence on our alliance partners, competition, our ability to obtain any necessary financing to conduct our planned activities and other risk factors described herein. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A, Risk Factors, that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Unless required by law, we do not undertake any obligation to update any forward-looking statements.

PART I

Item 1. Business

Overview

We are an innovative biopharmaceutical company dedicated to developing novel medicines for people with cancer. We combine proven scientific expertise with a passion for developing novel small molecule drugs that target disease pathways for potential applications in oncology. We are focused on advancing IPI-549, an orally administered, clinical-stage, immuno-oncology product candidate that selectively inhibits the enzyme phosphoinositide-3-kinase-gamma, or PI3K-gamma. We believe IPI-549 is the only clinical-stage selective inhibitor of PI3K-gamma currently being investigated.

Selective inhibition of PI3K-gamma by IPI-549 targets tumor-associated myeloid cells, thereby reducing pro-tumor macrophage function and increasing anti-tumor macrophage function. In preclinical studies, detailed further below, IPI-549 demonstrated the ability to reprogram macrophages from a pro-tumor, immunosuppressive function, to an anti-tumor immune activating function and to enhance the activity of, and overcome resistance to, checkpoint inhibitors. These preclinical findings indicate that IPI-549 may have the potential to treat a broad range of solid tumors and represents a potentially additive or synergistic approach to restoring anti-tumor immunity in combination with other immunotherapies such as checkpoint inhibitors. Further, preclinical studies showed that IPI-549 significantly inhibits the regrowth of tumors that can occur following treatment with chemotherapy.

We have worldwide development and commercialization rights to IPI-549, subject to certain success-based milestone payment obligations to our licensor, Takeda Pharmaceutical Company Limited, or Takeda, as described in more detail under the heading Collaborations —Takeda. Additionally, we are obligated to pay our former strategic collaborators Mundipharma International Corporation Limited, or Mundipharma, and Purdue Pharmaceutical Products L.P., or Purdue, a 4% royalty in the aggregate on worldwide net sales of products, including IPI-549, that were previously subject to the strategic alliance with Mundipharma and Purdue that was terminated in 2012. We refer to such royalties as Trailing Mundipharma Royalties. After Mundipharma and Purdue have recovered approximately \$260 million in royalty payments from all products that were previously subject to the strategic alliance, which represents the funding paid to us for research and development services performed by us under this strategic alliance, the Trailing Mundipharma Royalties will be reduced to a 1% royalty on net sales in the United States of products that were

previously subject to the strategic alliance, including IPI-549.

3

Table of Contents

Preclinical Rationale for Development of IPI-549: Targeting the Immunosuppressive Microenvironment in Solid Tumors

Role of PI3K-gamma in Cancer Growth and Survival

The body's immune system is responsible for fighting infections and disease, including cancer, and helping the body to heal. The immune system functions by identifying and destroying foreign cells and substances within the body. When confronted by pathogens or disease, an early response of the body's immune system comes in the form of macrophages, a type of white blood cell that produces pro-inflammatory proteins called cytokines. These cytokines activate T cells, another type of immune cell, to attack the threat to the body's health. The macrophages then transition to producing other types of cytokines that dampen T cell activation and promote tissue growth, which, in turn, stimulates repair of the affected tissue.

Cancer cells arise from normal cells that have changed in a way that allows them to grow in an unregulated manner. Cancer cells are not always recognized by the immune system as foreign cells that should be destroyed. However, even if cancer cells are recognized by the immune system, both normal homeostatic and cancer cell-induced mechanisms exist to dampen this immune response, including upregulation of "checkpoint proteins," such as programmed death receptor 1, or PD-1, on T cells and programmed-death ligand 1, or PD-L1, on tumor cells. Additionally, in solid tumors there exists a tumor microenvironment, or TME, which refers to the non-cancerous cells present in the tumor. Cells within the TME, including macrophages, can suppress the immune response and provide signals to cancer cells that facilitate tumor growth. The presence of the supportive TME is thought to be one reason why some cancer therapies, including checkpoint inhibitors, have shown limited durability and efficacy to date. Research has demonstrated that PI3K-gamma plays an important role in maintaining the immunosuppressive nature of tumor-associated macrophages and myeloid-derived suppressor cells, or MDSCs. Targeting these cells that suppress the immune system represents an emerging approach within the field of cancer immunotherapy, and inhibition of PI3K-gamma by IPI-549 represents a novel approach to targeting this immunosuppressive microenvironment.

Anti-Tumor Activity of IPI-549 in Preclinical Models

Our preclinical research has shown that macrophage PI3K-gamma signaling results in a type of macrophage that suppresses anti-tumor T cells. Preclinical data demonstrated that blockade of PI3K-gamma by treatment with IPI-549 leads to a shift in the type of macrophages present in the TME from macrophages associated with suppression of the immune response, known as the M2 phenotype, to macrophages that are supportive of a pro-inflammatory, anti-tumor immune response, known as the M1 phenotype. In preclinical studies, treatment with IPI-549 in tumor models was shown to increase the M1/M2 macrophage ratio, the number of T cells that attack the tumor, and the production of pro-inflammatory, anti-tumor cytokines.

Preclinical studies to investigate the anti-tumor activity of IPI-549 have demonstrated dose-dependent, single-agent, anti-tumor activity in multiple solid tumor models, including models of lung cancer, colon cancer and breast cancer. Additionally, in preclinical models, treatment with IPI-549 in combination with a checkpoint inhibitor showed greater tumor growth inhibition and survival, including a greater number of complete tumor regressions, compared to treatment with either IPI-549 or the checkpoint inhibitor alone. The combination treatment resulted in long-lasting anti-tumor immune memory as evidenced by the lack of tumor growth when animals were re-challenged with the same tumor cells in the absence of any treatment.

Further, as illustrated below, a preclinical study in a murine glioblastoma model indicated that administration of IPI-549 following tumor regression with temozolomide, or TMZ, led to greater inhibition of tumor growth compared to no treatment.

Table of Contents

IPI-549 Inhibits Tumor Regrowth Post Temozolomide (TMZ) in GL261 Glioblastoma Model

Two GL261 tumor bearing C57/BL6 Albino mice groups were treated with temozolomide 1mg/kg intraperitoneally, once daily for 7 days to regress tumors and then subsequently treated with either vehicle (left) or IPI-549 15 mg/kg orally, once daily (right).

Fig. source: McGovern et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics Meeting, November 6, 2015, Boston, MA, USA

These findings support the hypothesis that inhibition of PI3K-gamma by IPI-549 reprograms macrophages from a pro-tumor immunosuppressive function to an anti-tumor immune-activating function and can augment the activity of checkpoint inhibitor therapies in models that are sensitive to checkpoint inhibitors. Additionally, IPI-549 can significantly inhibit tumor regrowth in a tumor model previously treated with chemotherapy.

Overcoming Resistance to Checkpoint Inhibition

In recent years, checkpoint inhibitors have shown promising results as a treatment for multiple types of cancer, but most patients do not respond, and most who do respond eventually become resistant to and require treatment with an additional therapy. Our preclinical studies in a number of tumor models demonstrated that resistance to checkpoint inhibition is associated with increased numbers of tumor-associated macrophages and is directly mediated by the immunosuppressive activity of these macrophages on T cells. Furthermore, the data demonstrated that inhibition of PI3K-gamma by IPI-549 switched the function of the macrophages from a pro-tumor, immunosuppressive state to an anti-tumor, immune-activating state, leading to enhanced anti-tumor cytotoxic T cell activity, particularly when combined with checkpoint inhibitors. These data demonstrated that IPI-549 treatment was able to reverse the lack of response to checkpoint inhibitors in models that were initially insensitive to checkpoint inhibition as a single therapy.

IPI-549 Clinical Development Program

2019 Clinical Development Goals

Our ongoing Phase 1/1b study MARIO-1: MACrophage Reprogramming in Immuno-Oncology, or MARIO-1, is designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity for IPI-549 both as a monotherapy and in combination with nivolumab, also known as Opdivo®, in approximately 220 patients with advanced solid tumors. Nivolumab is an immune checkpoint inhibitor therapy commercialized by Bristol-Myers Squibb Company, or BMS, that targets PD-1. We announced interim data from MARIO-1 in 2018 that showed that IPI-549 was well tolerated and associated with a favorable safety profile, both as a monotherapy and in combination with nivolumab, and demonstrated clinical activity both as a monotherapy and in combination with nivolumab. We further expanded our clinical trial pipeline in November 2018 with the announcement that we and BMS had entered into a clinical supply agreement, which we refer to as the BMS Agreement, under which we would operationalize MARIO-275, a global, randomized Phase 2 study designed to evaluate the effect of adding IPI-549 to nivolumab in checkpoint-naïve advanced urothelial cancer patients who have progressed or recurred following treatment with platinum-based chemotherapy.

Our clinical development goals for IPI-549 include the initiation in the first half of 2019 of MARIO-275, a global Phase 2 study in immuno-oncology naïve patients with urothelial cancer. In the second half of 2019 we intend to complete enrollment in the MARIO-1 combination expansion cohorts, initiate a study with Arcus Biosciences, Inc., or Arcus, investigating IPI-549 in a triple therapy combination in previously treated patients with advanced triple-negative breast cancer, or TNBC, and to initiate MARIO-3, a Phase 2 combination study of IPI-549 in front-line patients with advanced TNBC and renal cell carcinoma, or RCC. The following table summarizes our ongoing and planned clinical trials and the associated milestones we expect to achieve in 2019:

Table of Contents

~~Study~~/Cohort

MARIO-1 (Phase 1/1b)

IPI-549 Monotherapy

Dose-Escalation

and

Expansion

Completed

(all

Solid

Tumors)

IPI-549 Combo with Nivolumab

Dose-Escalation

(all

Completed

Solid

Tumors)

~~Expansion~~ Completion Expected Second Half 2019

Non-Small-Cell

Lung

Enrollment Ongoing

Carcinoma

(NSCLC)

Expansion

Enrollment Ongoing

Melanoma

Squamous

Cell

Carcinoma

of

~~Head~~ Enrolled

Head

and

Neck

(SCCHN)

Triple-Negative

Breast

Enrollment Ongoing

Cancer

(TNBC)

~~Myeloid-Derived~~

Myeloid-Derived

Suppressor

Cells

(MDSC)-High

MARIO-275 (Phase 2)

IPI-549 Combo with Nivolumab

Immuno-Oncology

~~Initiation~~ Expected

First Half 2019

Cancer

Arcus Biosciences Collaboration (Phase 1b)

IPI-549 Combo with AB928 and Chemo

~~TNBC~~ Expected

Second Half 2019

MARIO-3 in Collaboration with Roche/Genentech

(Phase 2)

IPI-549 Combo with Atezolizumab/Chemo (TNBC)

and Atezolizumab/Bevacizumab (RCC)

Front-Line Expected

Second Half 2019

Front-Line

Renal

Initiation Expected

Second Half 2019

Cell

Carcinoma

(RCC)

MARIO-1: Phase 1/1b Dose-Escalation and Combination Expansion Study in Solid Tumors

MARIO-1 is our Phase 1/1b clinical study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity for IPI-549 — both as a monotherapy and in combination with nivolumab — in approximately 220 patients with advanced solid tumors. The dose-escalation portions of MARIO-1 are complete, and enrollment is ongoing in the combination therapy expansion cohorts designed to evaluate patients dosed at 40 mg once daily, or QD, of IPI-549 in combination with the standard regimen of nivolumab. Three cohorts are designed to evaluate IPI-549 in combination in patients with non-small cell lung cancer, melanoma, or head and neck cancer whose tumors show initial resistance or initially respond to but subsequently develop resistance to immune checkpoint blockade therapy. Another combination cohort is evaluating patients with TNBC who have not been previously treated with immune checkpoint blockade therapy. The remaining combination cohorts are designed to evaluate combination treatment in patients with mesothelioma; and patients with high baseline blood levels of MDSCs. We have closed the cohort designed to evaluate combination treatment in patients with adrenocortical carcinomas. The cohorts investigating mesothelioma, MDSC-high, and head and neck cancers are all fully enrolled.

Table of Contents

We reported data from the combination expansion cohorts of the MARIO-1 study in a late-breaking poster presentation at the 33rd Annual Meeting of the Society for Immunotherapy of Cancer on November 10, 2018. Among the 44 patients evaluable for activity as of the October 14, 2018 data-cutoff date, 15 patients showed a best response of stable disease or better, including one partial response in an advanced melanoma patient who progressed on immediate prior nivolumab therapy. In addition, a patient with chemotherapy-resistant TNBC showed a 26% reduction in tumor target lesions at the first assessment. Reductions in elevated baseline levels of MDSCs were seen in these patients, as well as corresponding increases in the proliferative fraction of previously exhausted memory cytotoxic T cells. Twenty-five patients remained on study and were not evaluable for activity as of the data-cutoff date. The data included long-term follow up on additional partial responses in two patients from the combination dose escalation component of the study. One patient with microsatellite stable gallbladder cancer and another with adrenocortical carcinoma each achieved a partial response and had been on study over 12 months and 17 months, respectively. These patients also demonstrated sustained inhibition of MDSCs during the period in which the partial response was maintained.

Among the 82 patients evaluable for safety as of October 14, 2018, the majority of side effects reported were Grade 1 or Grade 2, with three (4%) patients discontinuing the study due to treatment-related toxicities. The most common Grade 3+ adverse events were rash (n=6, 7%) and increased liver enzymes AST (n=7, 9%) and ALT (n=5, 6%). There were no treatment-related deaths. The majority of the study population is in fourth-line therapy and resistant to anti-PD1/PDL1 therapy. This safety profile is consistent with the safety data from the dose-escalation portion of MARIO-1 that we presented on June 4, 2018, during a poster session and poster discussion session at the American Society of Clinical Oncology Annual Meeting, or ASCO. The data demonstrated that IPI-549 combined with nivolumab was well tolerated at all doses tested, up to the recommended combination therapy expansion dose of IPI-549 at 40 mg QD plus nivolumab at 240 mg once every two weeks. No maximum tolerated dose was determined, and there were no treatment-related deaths. Of the 31 patients evaluable for safety as of the April 25, 2018 data-cutoff date for ASCO, the majority of adverse events were Grade 1 or 2, and the only treatment-related Grade 3 adverse events were uncomplicated rash (19%), increased liver enzymes AST or ALT (10%), and abdominal pain (3%). The pharmacokinetic/pharmacodynamic profile of IPI-549 (up to the recommended combination expansion dose of 40 mg QD) was unaffected by nivolumab co-administration, and IPI-549 in combination with nivolumab reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood.

At ASCO, we also presented updated clinical and translational data from the fully enrolled monotherapy expansion portion of MARIO-1 that demonstrated that IPI-549 as a monotherapy continued to be well tolerated at all doses studied up to the recommended dose for monotherapy expansion of 60 mg QD. IPI-549 demonstrated evidence of monotherapy clinical activity, with one durable partial response in peritoneal mesothelioma, where a patient remained on study after 20 months as of the ASCO 2018 data-cutoff date of April 25, 2018. Further, IPI-549 monotherapy reduced immune suppression and increased immune activation, as indicated by analyses of peripheral blood and paired tumor biopsies.

MARIO-275: Investigating IPI-549 in Urothelial Cancer in Patients Naïve to Immuno-Oncology Treatment

On November 2, 2018, we and BMS entered into a clinical supply agreement under which we will operationalize MARIO-275, a global, randomized study designed to evaluate the effect of adding IPI-549 to nivolumab in checkpoint-naïve advanced urothelial cancer patients who have progressed or recurred following treatment with platinum-based chemotherapy. BMS has agreed to supply nivolumab for the study. Approximately 160 patients will be randomized between combination therapy and nivolumab monotherapy plus placebo. The primary endpoint of the trial will be the overall response rate, which will be assessed in the overall population as well as in subsets of patients with different baseline levels of MDSCs. The design of MARIO-275 is supported by data from MARIO-1 presented at ASCO 2018, which showed that MDSCs were reduced in the majority of patients treated with IPI-549 monotherapy, as well as an exploratory analyses of data from a BMS clinical study evaluating nivolumab monotherapy in patients with urothelial cancer, referred to as CheckMate-275, that showed that high levels of MDSCs were associated with shorter overall survival in patients treated with nivolumab.

Instances of urothelial cancer in the United States, Japan, France, Germany, Italy, Spain and the United Kingdom are expected to increase from 402,726 to 482,037 from 2016 to 2025. Bladder cancer, of which urothelial cancer makes

up approximately 96% of all instances, is the fourth most prevalent cancer in men. In 2019 alone, the American Cancer Society estimates that there will be approximately 80,470 new cases and 17,670 deaths from bladder cancer.

Phase 1b Study of Novel Triple Combination Therapy in Advanced TNBC with Arcus

We will also be seeking to advance novel triple combination therapies with Arcus, initially evaluating IPI-549 in combination with AB928, Arcus's dual adenosine receptor antagonist, and chemotherapy in patients with previously treated, advanced TNBC. As both macrophages and high adenosine levels are believed to play critical roles in creating a highly immunosuppressive tumor microenvironment in cancer after chemotherapy, the novel immuno-oncology combination being evaluated in this setting represents a potentially promising approach to treating TNBC.

Table of Contents

MARIO-3: IPI-549 Combinations as Front-Line Treatment

On March 7, 2019, we entered into a master clinical supply agreement and F. Hoffmann-La Roche Ltd., or Roche, which we refer to as the Roche Agreement. Under the Roche Agreement, Roche will supply atezolizumab to us for our use in MARIO-3, a Phase 2 multi-arm study evaluating IPI-549 in combination with atezolizumab and nab-paclitaxel in front-line TNBC and in combination with atezolizumab and bevacizumab in front-line RCC. We intend to initiate MARIO-3 in the second half of 2019.

Collaborations

Since our inception, corporate alliances and license agreements have been integral to our strategy. Many of these alliances have provided access to breakthrough science, significant research and development support and funding, and innovative drug development programs, all intended to help us realize the full potential of our product pipeline.

Verastem

On October 29, 2016, we and Verastem Inc., or Verastem, entered into a license agreement, which we and Verastem amended and restated on November 1, 2016, effective as of October 29, 2016. We refer to the amended and restated license agreement as the Verastem Agreement. Under the Verastem Agreement, we granted to Verastem an exclusive worldwide license for the research, development, commercialization, and manufacture of duvelisib, a selective PI3K-delta,gamma inhibitor, and products containing duvelisib, which we refer to as the Licensed Products, in each case in oncology indications. Upon entry into the Verastem Agreement, Verastem assumed financial responsibility for activities that were part of our ongoing duvelisib program, including a randomized, Phase 3 monotherapy clinical study in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma, which we refer to as the DUO Study. Verastem is obligated to use diligent efforts, as defined in the Verastem Agreement, to develop and commercialize one Licensed Product. During the term of the Verastem Agreement, we have agreed not to research, develop, manufacture or commercialize duvelisib in any indication in humans or animals. Following a short transition period, which terminated December 31, 2016, Verastem assumed all financial and operational responsibility for the duvelisib program except for the clinical shutdown costs and certain clinical close-out activities that we agreed to retain.

On September 6, 2017, Verastem notified us that the DUO Study met certain pre-specified criteria at completion triggering a \$6.0 million payment under the Verastem Agreement, which we received in cash on October 13, 2017. On November 2, 2018, we received a \$22.0 million cash payment earned upon the approval by the U.S. Food and Drug Administration, or FDA, on September 24, 2018 of duvelisib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies, as well as adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.

Verastem is also obligated to pay us royalties on worldwide net sales of Licensed Products ranging from the mid-single digits to the high-single digits. The royalty obligation will continue on a product-by-product and country-by-country basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the applicable country, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the applicable country and (iv) ten years following the first commercial sale of a Licensed Product in the applicable country, provided that upon the expiration of the last-to-expire patent right covering the Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. The royalties are also subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period. On March 5, 2019, we entered into a purchase and sale agreement, or the HCR Agreement, with HealthCare Royalty Partners III, L.P., or HCR, providing for the acquisition by HCR of our interest in the royalty payments from Verastem described above. See Part II, Notes to Consolidated Financial Statements, Note 14 for details of the transaction with HCR.

Table of Contents

In addition to the foregoing, Verastem is obligated to pay us a royalty of 4% on worldwide net sales of Licensed Products to cover the Trailing Mundipharma Royalties owed by us to Mundipharma and Purdue. Once we have fully reimbursed Mundipharma and Purdue, the Trailing Mundipharma Royalties will be reduced to 1% of net sales in the United States. The Trailing Mundipharma Royalties are payable on a product-by-product basis until the latest to occur of (i) the last-to-expire patent right covering the applicable Licensed Product in the United States, (ii) the last-to-expire patent right covering the manufacture of the applicable Licensed Product in the country of manufacture of such Licensed Product, (iii) the expiration of non-patent regulatory exclusivity for such Licensed Product in the United States and (iv) ten years following the first commercial sale of such Licensed Product in the United States, provided that, upon the expiration of the last-to-expire patent right covering a Licensed Product in the United States, the applicable royalty on net sales for such Licensed Product in the United States will be reduced by 50%. In addition, the Trailing Mundipharma Royalties are subject to reduction by 50% of certain third-party royalty payments or patent litigation damages or settlements which might be required to be paid by Verastem if litigation were to arise, with any such reductions capped at 50% of the amounts otherwise payable during the applicable royalty payment period. The Verastem Agreement expires when each party no longer has any obligations to the other party under the Verastem Agreement. Verastem has the right to terminate the Verastem Agreement upon at least 180 days' prior written notice to us at any time. Either party may terminate the Verastem Agreement if the other party materially breaches or defaults in the performance of its obligations. If we terminate the Verastem Agreement for Verastem's material breach, patent challenge, or insolvency, or if Verastem terminates for convenience, then, at our request and subject to our execution of a waiver of certain types of damages, Verastem will transition the duvelisib program back to us at Verastem's cost. If Verastem terminates for our breach or insolvency, Verastem will effect a more limited transition of the duvelisib program to us at our request and cost, subject to our execution of a waiver of certain types of damages, and we will thereafter pay to Verastem a low single-digit royalty on net sales of Licensed Products.

We and Verastem have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

Takeda

In July 2010, we entered into a development and license agreement with Intellikine, Inc., or Intellikine, under which we obtained rights to discover, develop and commercialize pharmaceutical products targeting the gamma and/or delta isoforms of PI3K, including IPI-549 and duvelisib. In January 2012, Intellikine was acquired by Takeda. In December 2012, we amended and restated our development and license agreement with Takeda and further amended the agreement in July 2014, September 2016, July 2017, and March 2019. We refer to the amended and restated development and license agreement, as amended, as the Takeda Agreement.

Under the terms of the Takeda Agreement, we are obligated to pay Takeda up to \$5.0 million in remaining success-based milestone payments for the development of a product candidate other than duvelisib, which could include IPI-549. We are also obligated to pay Takeda up to \$165.0 million in remaining success-based milestone payments related to the approval and commercialization of one product candidate other than duvelisib, which could be IPI-549.

Due to amendments to the Takeda Agreement, described below, we are no longer obligated to pay Takeda royalties on net sales of IPI-549, other products containing a selective inhibitor of PI3K-gamma, or duvelisib in oncology indications. However, we remain obligated to pay Takeda tiered royalties ranging from 7% to 11% on worldwide net sales of products containing a selective inhibitor of PI3K-delta or a selective dual inhibitor of PI3K delta and gamma, as described in the Takeda Agreement, including duvelisib if commercialized outside oncology indications. Such royalties are payable until the later to occur of (i) the expiration of specified patent rights and (ii) the expiration of non-patent regulatory exclusivities in a country, subject to reduction of the royalties and, in certain circumstances, limits on the number of products subject to a royalty obligation.

Under the September 2016 amendment to the Takeda Agreement, and in connection with our entry into the Verastem Agreement, we are no longer obligated to pay Takeda any remaining milestone payments for the development, approval or commercialization of duvelisib. In return, we became obligated to pay Takeda 50% of all revenue arising from certain qualifying transactions for duvelisib, including the Verastem Agreement, subject to certain exceptions including revenue we receive as reimbursement for duvelisib research and development expenses. We amended this

obligation by entry into a fourth amendment to the Takeda Agreement on March 4, 2019, or Takeda Amendment. See Part II, Notes to Consolidated Financial Statements, Note 14, for details of the Takeda Amendment.

Table of Contents

The July 2017 amendment to the Takeda Agreement terminated our obligation to pay royalties to Takeda with respect to worldwide net sales of products containing or comprised of a selective inhibitor of PI3K gamma, including but not limited to IPI-549. In consideration for such termination, we concurrently executed a convertible promissory note, which we refer to as the Takeda Note, which obligated us to pay Takeda, or its designated affiliate, the principal amount of \$6.0 million together with interest accruing at a rate of 8% per annum on or before July 26, 2018 in cash or in shares of our common stock, at the election of Takeda. On March 12, 2018, we exercised our right to prepay in full the Takeda Note in the principal amount of \$6.0 million together with interest of approximately \$0.3 million. Takeda elected to receive \$4.0 million of such payment in cash and approximately \$2.3 million of such payment in shares of our common stock. Pursuant to the terms of the Takeda Note, we issued 1,134,689 shares of common stock, calculated using an average price of \$2.028 per share, to Takeda's designated subsidiary, Millennium Pharmaceuticals, Inc. The Takeda Agreement expires on the later of the expiration of certain patents and the expiration of the royalty payment terms for the products, unless earlier terminated in accordance with its terms. Either party may terminate the Takeda Agreement on 75 days' prior written notice if the other party materially breaches the agreement and fails to cure such breach within the applicable notice period, provided that the notice period is reduced to 30 days where the alleged breach is non-payment. Takeda may also terminate the Takeda Agreement if we are not diligent in developing or commercializing the licensed products and do not, within three months after notice from Takeda, demonstrate to Takeda's reasonable satisfaction that we have not failed to be diligent. The foregoing periods are subject to extension in certain circumstances. Additionally, Takeda may terminate the Takeda Agreement upon 30 days' prior written notice if we or a related party bring an action challenging the validity of any of the licensed patents, provided that we have not withdrawn such action before the end of the 30-day notice period. We may terminate the agreement at any time upon 180 days' prior written notice. The Takeda Agreement also provides for customary reciprocal indemnification obligations of the parties.

PellePharm

In June 2013, we entered into a license agreement with PellePharm, Inc., or PellePharm, under which we granted PellePharm exclusive global development and commercialization rights to our hedgehog inhibitor program, including IPI-926, a clinical-stage product candidate. We refer to our license agreement with PellePharm as the PellePharm Agreement and products covered by the PellePharm Agreement as Hedgehog Products.

Under the PellePharm Agreement, PellePharm is obligated to pay us up to \$11.0 million in success-based milestone payments through the first commercial sale of a Hedgehog Product. We anticipate receiving a \$2.0 million milestone payment for the initiation of a Phase 3 study of a Hedgehog Product in 2019. PellePharm is also obligated to pay us up to \$37.5 million in success-based milestone payments upon the achievement of certain annual net sales thresholds as well as a share of certain revenue received by PellePharm in the event that PellePharm sublicenses its rights under the PellePharm Agreement.

PellePharm is also obligated to pay us tiered royalties on annual net sales of Hedgehog Products, which are subject to reduction after a certain aggregate funding threshold has been achieved.

PellePharm's royalty obligations to us expire on a country-by-country and Hedgehog Product-by-Hedgehog Product basis, and the PellePharm Agreement expires upon the expiration of the last royalty obligation owed by PellePharm to us, at which time the license to Hedgehog Products and licenses to our know-how as described in the PellePharm Agreement become fully-paid-up and non-royalty-bearing licenses. PellePharm has the right to terminate the PellePharm Agreement upon at least 180 days' prior written notice to us at any time, and we may terminate the PellePharm Agreement if PellePharm puts forth or actively assists a patent challenge related to our Hedgehog Product patent rights. Either party may terminate the PellePharm Agreement if the other party materially breaches or defaults in the performance of its obligations. Upon termination by either party, all rights and licenses granted by us to PellePharm under the PellePharm Agreement terminate and PellePharm shall, to the extent applicable, transfer and assign to us all rights, title, and interest in and to the trademark(s) used for Hedgehog Products in the territory covered under the PellePharm Agreement.

We and PellePharm have made customary representations and warranties and have agreed to certain customary covenants, including confidentiality and indemnification.

Table of Contents

Intellectual Property

Our intellectual property consists of patents, trademarks, trade secrets and know-how. Our ability to compete effectively depends in large part on our ability to obtain patents and trademarks for our technologies and products, maintain trade secrets, operate without infringing the rights of others and prevent others from infringing our proprietary rights. We will be able to protect our proprietary technologies from unauthorized use by third parties only to the extent that they are covered by valid and enforceable patents, or are effectively maintained as trade secrets. As a result, patents or other proprietary rights are an essential element of our business.

We have ten issued or allowed U.S. patents related to our PI3K-gamma program, which expire on various dates between 2033 and 2036, excluding any potential patent term extension. In addition, we have approximately 70 patents and patent applications pending worldwide related to our PI3K-gamma program. Any patents that may issue from our pending patent applications would expire between 2033 and 2036, excluding any potential patent term extension. These patents and patent applications disclose compositions of matter, pharmaceutical compositions, methods of use and synthetic methods.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be extended by patent term adjustment, which compensates a patentee for administrative delays by the United States Patent and Trademark Office, or USPTO, in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims, if granted. However, our pending patent applications, and any patent applications that we may in the future file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

Our policy is to obtain and enforce the patents and proprietary technology rights that are commercially important to our business, and we intend to continue to file patent applications to protect such technology and compounds in countries where we believe it is commercially reasonable and advantageous to do so. We also rely on trade secrets to protect our technology where patent protection is deemed inappropriate or unobtainable. We seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. The confidentiality agreements we enter into are designed to protect our proprietary information, and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that these agreements will afford us adequate protection of our intellectual property and

proprietary information rights.

11

Table of Contents

Competition

The pharmaceutical and biotechnology industries are intensely competitive. Many companies, including biotechnology and pharmaceutical companies, are actively engaged in the research and development of drugs for the treatment of the same diseases and conditions as our current and potential future product candidates. Many of these companies have substantially greater financial and other resources, larger research and development staffs and more extensive marketing and manufacturing organizations than we do. In addition, some of them have considerably more experience than us in preclinical testing, clinical trials and other regulatory approval procedures. There are also academic institutions, governmental agencies and other research organizations that are conducting research in areas in which we are working. They may also develop products that may be competitive with our product candidates, either on their own or through collaborative efforts.

We expect to encounter significant competition for any drugs we develop. Companies that complete clinical trials, obtain required regulatory approvals and commence commercial sales of their products before their competitors may achieve a significant competitive advantage. We are aware that many other companies or institutions are pursuing the development of drugs in the areas in which we are currently seeking to develop our own product candidates, and there may be other companies working on competitive projects of which we are not aware.

Our competitors may commence and complete clinical testing of their product candidates, obtain regulatory approvals and begin commercialization of their products sooner than we may for our own product candidates. These competitive products may have superior safety or efficacy, or be manufactured less expensively, than our product candidates. If we are unable to compete effectively against these companies on the basis of safety, efficacy or cost, then we may not be able to commercialize our product candidates or achieve a competitive position in the market. This would adversely affect our business.

We believe that IPI-549 is the only PI3K-gamma selective inhibitor in clinical development. However, there are many competitors developing or commercializing therapies targeting macrophage biology, including the following competitors which we believe to be conducting clinical studies of product candidates targeting one or more aspects of macrophage biology: Array Biopharma, Inc., Deciphera Pharmaceuticals, Inc., Incyte Corporation (through its collaboration with Calithera Inc.), Bristol-Myers Squibb Company (through its collaboration with Five Prime Therapeutics, Inc.), Plexxikon Inc., GlaxoSmithKline plc, Eli Lilly and Company, Amgen Inc., F. Hoffmann-La Roche Ltd, Janssen Research & Development, LLC, a subsidiary of Johnson & Johnson, Forty Seven Inc., Surface Oncology, Inc., Celgene Corporation, Trillium Therapeutics Inc., Pfizer Inc., XBiotech, Inc., AbbVie Inc., Takeda Pharmaceuticals International, Inc., Novartis AG, Efranat Ltd., Seattle Genetics, Inc., AstraZeneca PLC, Apexigen Inc., X4 Pharmaceuticals, Inc., Syndax Pharmaceuticals, Inc., Syntrix Biosystems, Inc., Eisai Co., Ltd., Vaccinex, Inc., and Alligator Bioscience AB.

Further, the broader field of immuno-oncology is crowded with innovative therapies that may compete with IPI-549, including checkpoint inhibitor therapies such as PD-1 inhibitors nivolumab and pembrolizumab; PDL-1 inhibitors atezolizumab, avelumab, and durvalumab; and CTLA-4 inhibitors ipilimumab and tremelimumab. Many of these checkpoint inhibitor therapies are being evaluated in combination with other non-checkpoint inhibitor immuno-oncology product candidates. For example, nivolumab, which we are currently testing in combination with IPI-549, is being evaluated in multiple clinical trials by others in combination with non-checkpoint inhibitor candidates such as BMS-986016, an anti-LAG3 antibody; elotuzumab, a CD319 antibody; urelumab, a CD137 antibody; cabiralizumab, an anti-CSF1R antibody; and NKTR-214, an IL-2R agonist. The success of competing immuno-oncology therapies may limit the number of patients available for enrollment in our clinical trials.

Research and Development

As of March 1, 2019, our research and development group consisted of 10 employees, of whom six hold Ph.D. or M.D. degrees and three hold a masters degree. Our research and development group is focused on preclinical research, translational medicine, clinical trials and manufacturing technologies. Our research and development expense for the years ended December 31, 2018 and 2017 was approximately \$19.8 million and \$20.8 million, respectively.

Manufacturing and Supply

We rely primarily on third parties, and, in some instances, we rely on only one third party, to manufacture critical raw materials, drug substance and final drug product for our research, preclinical development and clinical trial activities.

Commercial quantities of any drugs we seek to develop will have to be manufactured in facilities and by processes that comply with the FDA and other regulations, and we plan to rely on third parties to manufacture commercial quantities of any products we successfully develop.

Table of Contents

Sales and Marketing

We currently have no marketing, commercial sales, or distribution capabilities. We do, however, currently have worldwide commercialization rights for our PI3K-gamma inhibitor program, including IPI-549. In order to commercialize IPI-549, if and when it is approved for sale, we will need to, and we intend to, develop the necessary marketing, sales and distribution capabilities.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the European Union, or EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, sales, pricing, reimbursement, post-approval monitoring and reporting,