EXELIXIS, INC.
Form 10-K
February 22, 2019
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K
ý ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 28, 2018
or
¨ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
Commission File Number: 000-30235
EXELIXIS, INC.
(Exact name of registrant as specified in its charter)

Delaware	04-3257395
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification Number)

1851 Harbor Bay Parkway
Alameda, CA 94502
(650) 837-7000
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)
Securities Registered Pursuant to Section 12(b) of the Act:

Title of Each Class	Name of Each Exchange on Which Registered
Common Stock $.001 Par Value per Share	The Nasdaq Stock Market LLC

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 ý No ¨
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ¨ No ý
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 ý 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 during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ý 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 emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	ý	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 7(a)(2)(B) of the Securities Act. ¨
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No ý

State the aggregate market value of the voting and non-voting common equity held by non-affiliates computed by reference to the price at which the common equity was last sold, or the average bid and asked price of such common equity, as of the last business day of the registrant's most recently completed second fiscal quarter: $5,531.1 million (based on the closing sales price of the registrant's common stock on June 29, 2018. Excludes an aggregate of approximately 40.9 million shares of the registrant's common stock held by persons who were directors and/or executive officers of the registrant at June 29, 2018 on the basis that such persons may be deemed to have been affiliates of the registrant at such date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.)

As of February 12, 2019, there were 300,129,630 shares of the registrant's common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A, not later than April 27, 2019, in connection with the registrant's 2018 Annual Meeting of Stockholders are incorporated herein by reference into Part III of this Annual Report on Form 10-K.

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PART I

Some of the statements under the captions “Risk Factors,” “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and “Business” and elsewhere in this Annual Report on Form 10-K are forward-looking statements. These statements are based on our current expectations, assumptions, estimates and projections about our business and our industry and involve known and unknown risks, uncertainties and other factors that may cause our company’s or our industry’s results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied in, or contemplated by, the forward-looking statements. Our actual results and the timing of events may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include those discussed in “Item 1A. Risk Factors” as well as those discussed elsewhere in this Annual Report on Form 10-K. These and many other factors could affect our future financial and operating results. We undertake no obligation to update any forward-looking statement to reflect events after the date of this report.

We have adopted a 52- or 53-week fiscal year policy that generally ends on the Friday closest to December 31st. Fiscal year 2016 ended on December 30, 2016; fiscal year 2017 ended on December 29, 2017; fiscal year 2018 ended on December 28, 2018; and fiscal year 2019 will end on January 3, 2020. For convenience, references in this report as of and for the fiscal years ended (or ending, as applicable) December 30, 2016, December 29, 2017, December 28, 2018 and January 3, 2020 are indicated as being as of and for the years ended (or ending, as applicable) December 31, 2016, 2017, 2018 and 2019, respectively. The annual period and quarterly period ending January 3, 2020 are a 53-week fiscal year and a 14-week fiscal quarter, respectively; all other annual periods presented are 52-week fiscal years and all interim periods presented are 13-week fiscal quarters.

Item 1. Business

Overview

Exelixis, Inc. (Exelixis, we, our or us) is an oncology-focused biotechnology company that aims to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Our drug discovery and development capabilities and commercialization platform are the foundations upon which we intend to bring to market novel, effective and tolerable therapies to provide cancer patients with additional treatment options.

Since we were founded in 1994, four products resulting from our discovery efforts have progressed through clinical development and received regulatory approval; three have a growing commercial presence worldwide, and we expect that the fourth will soon enter the marketplace in Japan. Two are derived from cabozantinib, our flagship molecule, an inhibitor of multiple tyrosine kinases including MET, AXL, VEGF receptors and RET. These are: CABOMETYX® (cabozantinib) tablets approved for advanced renal cell carcinoma (RCC) and previously treated hepatocellular carcinoma (HCC); and COMETRIQ® (cabozantinib) capsules approved for progressive, metastatic medullary thyroid cancer (MTC). For these types of cancer, cabozantinib has become or is becoming a standard of care. Beyond its approved indications, cabozantinib is currently the focus of a broad clinical development program, and is being investigated both alone and in combination with other therapies in a wide variety of cancers. The growth that we have experienced in recent years is largely attributable to cabozantinib’s clinical and commercial success; consistent with our values and legal obligations, we are committed to ensuring that all patients who are prescribed cabozantinib are able to access this essential medicine.

The other two products resulting from our discovery efforts are: COTELLIC® (cobimetinib), an inhibitor of MEK approved as part of a combination regimen to treat advanced melanoma and marketed under a collaboration with Genentech, Inc. (a member of the Roche Group) (Genentech); and MINNEBRO™ (esaxerenone), an oral, non-steroidal, selective blocker of the mineralocorticoid receptor (MR) approved for the treatment of hypertension in Japan and licensed to Daiichi Sankyo Company, Limited (Daiichi Sankyo).

Over the course of 2018, revenues from the sales of CABOMETYX and COMETRIQ and from the royalties and milestone payments received pursuant to collaboration agreements with our partners, coupled with disciplined expense management, have fueled the growth of our organization. We believe we can continue to grow in a sustainable manner, supported by a healthy cash position and profitability over the past two fiscal years. We are utilizing our cash and investments to enable future success by expanding the development program for cabozantinib and by building a pipeline of new drug candidates through reinitiated internal drug discovery efforts and the execution

of strategic transactions that align with our oncology drug development and commercialization expertise. The following report details the progress we made executing our growth strategy in 2018.

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Exelixis Marketed Products: CABOMETYX and COMETRIQ

CABOMETYX was first approved by the U.S. Food and Drug Administration (FDA) on April 25, 2016, for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy and by the European Commission (EC) on September 9, 2016, similarly for the treatment of advanced RCC in adults in the European Union (EU) following prior VEGF-targeted therapy. On December 19, 2017, the FDA approved the expanded indication for CABOMETYX to include previously untreated patients with advanced RCC, and the EC approved CABOMETYX on May 17, 2018 as a first-line treatment for adults with intermediate- or poor-risk advanced RCC. Most recently, CABOMETYX was approved by the FDA on January 14, 2019, for the treatment of patients with HCC who have been previously treated with sorafenib, which followed the EC's earlier approval of CABOMETYX on November 15, 2018, for the treatment of HCC in adults previously treated with sorafenib. COMETRIQ, our first marketed product, was approved by the FDA on November 29, 2012, for the treatment of patients with progressive, metastatic MTC, and in March 2014, the EC granted COMETRIQ a conditional marketing authorization for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. In 2018 and 2017, we generated $619.3 million and $349.0 million, respectively, in net product revenues from sales of CABOMETYX and COMETRIQ in the U.S.

Outside the U.S. and Japan, CABOMETYX and COMETRIQ are marketed by our collaboration partner Ipsen Pharma SAS (Ipsen). Should CABOMETYX and COMETRIQ be approved in Japan, they will be marketed by our collaboration partner Takeda Pharmaceutical Company Limited (Takeda). In 2018 and 2017, we earned $32.3 million and $3.8 million, respectively, of gross royalties for net sales of products incorporating cabozantinib outside of the U.S. For additional information on the terms of our collaboration agreements with Ipsen and Takeda, see "—Collaborations—Cabozantinib Commercial Collaborations."

Renal Cell Carcinoma - CABOMETYX is Now the Leading Tyrosine Kinase Inhibitor (TKI) Treatment Option for Patients with Advanced RCC

Kidney cancer is among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S., with approximately 30,000 patients requiring systemic treatment. Globally, approximately 68,000 patients require systemic treatment for kidney cancer. A growing number of these patients with RCC have been or will be treated with CABOMETYX, which has become a new standard of care for the treatment of patients suffering from this difficult-to-treat disease; in fact, as of December 2018, CABOMETYX was the TKI of choice among physicians treating these patients in terms of new prescriptions.

Since CABOMETYX was first approved, our promotional and medical affairs teams have been focused on educating physicians about CABOMETYX's unique clinical profile. We believe that the success of CABOMETYX is attributable to this clinical profile, derived from the results of our clinical trials, METEOR and CABOSUN. CABOMETYX is the first and only single-agent therapy approved for previously treated advanced RCC to demonstrate statistically significant and clinically meaningful improvements in three key efficacy parameters in a global pivotal trial: overall survival (OS); progression-free survival (PFS); and objective response rate (ORR). In addition, in previously untreated patients with advanced RCC, CABOMETYX is the only approved single-agent therapy to improve PFS and ORR compared with sunitinib, a first-generation TKI that was the previous standard of care. It is also noteworthy that on September 7, 2018, the National Comprehensive Cancer Network (NCCN), the nation's foremost non-profit alliance of leading cancer centers, updated its Clinical Practice Guidelines to recommend CABOMETYX as the only TKI with preferred status for advanced RCC patients who have progressed on prior therapy and for the treatment of advanced RCC regardless of patient risk status (favorable-, intermediate-, and poor risk). These updated recommendations strengthened the differentiation of CABOMETYX from other TKIs approved for this indication, leading many physicians to consider CABOMETYX a preferred therapeutic option, despite numerous competing products approved to treat advanced RCC. For additional information about CABOMETYX's profile as expressed in the METEOR and CABOSUN clinical trial data, see "—Cabozantinib Development Program—Clinical Trials Supporting Regulatory Approvals."

In markets outside the U.S. in 2018, we continued to work closely with our partner Ipsen in support of its regulatory strategy and commercialization efforts for CABOMETYX as a treatment for advanced RCC. As a result of the approvals of CABOMETYX for RCC indications in more than ten territories outside of the U.S., including the EU,

Canada, Brazil, Taiwan, South Korea and Australia, CABOMETYX has continued to grow both in sales revenue and the number of RCC patients benefiting from its clinical effect. Additionally, with respect to the Japanese market, our partner Takeda is advancing its clinical development activities in Japan support of potential future regulatory filings for CABOMETYX in both RCC and HCC.

Hepatocellular Carcinoma - the CABOMETYX Label Expanded to Include Previously Treated HCC

According to published studies, liver cancer is a leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year. In the U.S., the incidence of liver cancer has more than tripled since 1980. Although HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new

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cases of liver cancer in the U.S. during 2018, this patient population was long underserved. Prior to 2017, there was only one approved systemic therapy for the treatment of HCC. Then, in 2017 and 2018, four new therapies were approved in the U.S. for HCC, one for previously untreated patients and three for patients previously treated with sorafenib. Given the introduction of new and more effective therapies, we believe the second- and later-line HCC market has the potential to grow significantly in coming years, as the new treatment options are expected to result in an increasing number of patients receiving multiple lines of therapy. With the recent approval of CABOMETYX in January 2019 for HCC patients previously treated with sorafenib, we aim to play a key role in the advancement of therapeutic options for these patients.

The FDA's approval of CABOMETYX for this HCC indication was based on our phase 3 pivotal study, CELESTIAL. The CELESTIAL study met its primary endpoint, demonstrating that cabozantinib significantly improved OS, as compared to placebo. For additional information on CELESTIAL, see "—Cabozantinib Development Program—Clinical Trials Supporting Regulatory Approvals—HCC - CELESTIAL." Upon FDA approval, we were immediately prepared to offer CABOMETYX to all eligible HCC patients in the U.S. who may benefit from this treatment option. We were able to take action so quickly due to the strength of our existing commercial and medical affairs organizations, in addition to our well-established distribution network and our ability to leverage our RCC commercialization experience. The NCCN's inclusion of CABOMETYX in its Clinical Practice Guidelines for Hepatobiliary Cancers as a Category 1 option for the treatment of patients with HCC (Child-Pugh Class A only) who have been previously treated with sorafenib further supports CABOMETYX as an important new treatment option for eligible HCC patients.

Outside the U.S., the EC's approval of CABOMETYX provided physicians in the EU with a second approved therapy for the second-line treatment of this aggressive and difficult-to-treat cancer.

Medullary Thyroid Cancer - COMETRIQ, the First Commercial Approval of Cabozantinib

We estimate that there are between 500 and 700 first-line and second-line patients in the U.S. who will be eligible for COMETRIQ. The FDA's approval of COMETRIQ for this MTC indication was based on our phase 3 trial, EXAM. The EXAM trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful prolongation in PFS for cabozantinib, as compared to placebo. For additional information on EXAM, see "—Cabozantinib Development Program—Clinical Trials Supporting Regulatory Approvals—MTC - EXAM." In 2018 and 2017, we generated $19.3 million and $25.0 million, respectively, in net product revenues from sales of COMETRIQ in the U.S.

Cabozantinib Development Program

Cabozantinib inhibits the activity of tyrosine kinases, including MET, AXL, VEGF receptors, and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, drug resistance and maintenance of the tumor microenvironment. Objective tumor responses have been observed in patients treated with cabozantinib in more than 20 individual tumor types investigated in phase 1 and 2 clinical trials to date, reflecting the medicine's broad clinical potential. We are currently evaluating cabozantinib, both as a single agent and in combination with immune checkpoint inhibitors (ICIs), in a broad development program comprising over 75 ongoing or planned clinical trials across multiple indications. We, along with our clinical and commercial collaboration partners, sponsor some of those trials, and independent investigators conduct the remaining trials through our Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP) or our investigator sponsored trial (IST) program. In addition to co-sponsoring trials with us, our commercial collaboration partners Ipsen and Takeda also conduct trials in their territories through similar independently-sponsored programs.

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The following two tables summarize select cabozantinib clinical development activities, one describing studies that evaluate the potential of cabozantinib as a single-agent, and the other describing studies that evaluate the potential of cabozantinib in combination with one or more ICIs:

CLINICAL DEVELOPMENT PROGRAM FOR CABOZANTINIB, SINGLE-AGENT

Indication	Status Update
Thyroid Cancer	
Progressive, metastatic medullary thyroid cancer	Approved in U.S. and EU (EXAM)
Progressive, metastatic medullary thyroid cancer	Post-marketing study (EXAMINER)
Differentiated thyroid cancer (DTC)	Phase 3 (COSMIC-311)
Renal Cell Carcinoma (RCC)	
Advanced RCC	Approved in U.S. and EU (METEOR and CABOSUN)
First- or second-line papillary RCC	Randomized phase 2† (PAPMET)
Hepatocellular Carcinoma (HCC)	
Second- and later-line HCC	Approved in U.S. on January 14, 2019; approved in EU in November 2018 (CELESTIAL)
Non-Small Cell Lung Cancer (NSCLC)	
EGFR wild-type	Phase 2†
Molecular alterations in RET, ROS1, MET, AXL, or NTRK1	Phase 2*
Additional Trials	
Metastatic urothelial carcinoma (UC)	Phase 2* (ATLANTIS)
Colorectal cancer (CRC)	Phase 2*
High-grade uterine sarcomas	Phase 2§
Metastatic gastrointestinal stromal tumor	Phase 2§ (CABOGIST)
Pancreatic neuroendocrine tumors and carcinoid tumors	Phase 2* and Phase 3† (CABINET)
Plexiform neurofibromas (pediatric and adult cohorts)	Phase 2*
Relapsed osteosarcoma or Ewing sarcoma	Phase 2†
Soft-tissue sarcomas	Phase 2†

* Trial conducted through our IST program.

† Trial conducted through collaboration with NCI-CTEP.

§ Trial sponsored by the European Organization for Research and Treatment of Cancer.

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CLINICAL DEVELOPMENT PROGRAM FOR CABOZANTINIB, IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

Indication	Combination Regimen	Status Update
Genitourinary Cancers		
First-line advanced RCC	+ nivolumab	Phase 3 pivotal trial (CheckMate 9ER)
Cisplatin-Ineligible advanced UC	+ pembrolizumab	Phase 2* (PemCab)
Advanced or metastatic non-clear cell RCC	+ nivolumab	Phase 2*
Gastrointestinal Cancers		
First-line advanced HCC	+ atezolizumab	Phase 3 pivotal trial (COSMIC-312), including a single-agent cabozantinib exploratory arm
Second- and later-line advanced HCC	+ nivolumab ± ipilimumab	Phase 1/2 (Checkmate 040)
Neoadjuvant locally advanced HCC	± nivolumab	Phase 1b*
KRAS wild-type metastatic CRC and cMET amplified metastatic CRC	± panitumumab	Phase 1* (CaboMAb)
Lung Cancers		
NSCLC	+ nivolumab ± ipilimumab	Phase 2†
Gynecologic Cancers		
Advanced or metastatic endometrial cancer	+ nivolumab	Phase 2†
Metastatic, triple negative breast cancer	+ nivolumab	Phase 2*
Breast cancer with brain metastases	± trastuzumab	Phase 2*
Head and Neck Cancers		
Recurrent, metastatic squamous cell carcinoma	+ cetuximab	Phase 1*
Recurrent, metastatic squamous cell carcinoma	+ pembrolizumab	Phase 2*
Additional Trials in Multiple Tumor Types		
Advanced solid tumors	+ atezolizumab	Phase 1b with 18 cabozantinib and atezolizumab expansion cohorts, including RCC, UC, castration-resistant prostate cancer (CRPC), HCC, colorectal adenocarcinoma, DTC, NSCLC, endometrial cancer, ovarian cancer, breast cancer, gastric or gastroesophageal junction adenocarcinoma and head and neck cancer (COSMIC-021), and 2 single-agent cabozantinib exploratory cohorts (UC and NSCLC)
Genitourinary tumors	+ nivolumab ± ipilimumab	Phase 1b†
Advanced CRC, HCC, gastric, gastroesophageal or esophageal adenocarcinoma	+ durvalumab	Phase 1* (CAMILLA)

* Trial conducted through our IST program.
† Trial conducted through collaboration with NCI-CTEP.
§ Trial sponsored by the European Organization for Research and Treatment of Cancer.

Clinical Trials Supporting Regulatory Approvals

RCC - METEOR

In July 2015, we announced positive results of METEOR, a phase 3 pivotal trial comparing CABOMETYX to everolimus in patients with advanced RCC who have experienced disease progression following treatment with at least one prior VEGF receptor inhibitor. METEOR met its primary endpoint, demonstrating a statistically significant and clinically

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meaningful increase in PFS for CABOMETYX. The median PFS was 7.4 months for the CABOMETYX arm versus 3.8 months for the everolimus arm. CABOMETYX also significantly improved ORR, a secondary endpoint, compared with everolimus. In September 2015, The New England Journal of Medicine (NEJM) published the complete, detailed positive results from the primary analysis of METEOR, and these results were also presented at the European Society for Medical Oncology (ESMO) 2015 Congress. After additional follow up, METEOR also met its other secondary endpoint of OS, as presented in June 2016 at the American Society of Clinical Oncology (ASCO) 2016 Annual Meeting and published in Lancet Oncology. The median OS was 21.4 months for patients receiving CABOMETYX versus 16.5 months for those receiving everolimus. The safety profile in the study and in later analyses was consistent with the established profile of cabozantinib and other TKIs.

On the basis of the data from the METEOR trial, the FDA approved CABOMETYX for the treatment of patients with advanced RCC following prior antiangiogenic therapy, and the European Medicines Agency (EMA) approved CABOMETYX for the treatment of advanced RCC in adults following prior VEGF-targeted therapy.

RCC - CABOSUN

In October 2016, we announced positive results from CABOSUN, a randomized, open-label, active-controlled phase 2 trial comparing cabozantinib with sunitinib in patients with previously untreated advanced RCC with intermediate- or poor-risk disease conducted by The Alliance for Clinical Trials in Oncology under our CRADA with NCI-CTEP. These results were presented at the ESMO 2016 Congress in October 2016 and subsequently published in the Journal of Clinical Oncology in November 2016. CABOSUN met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared with sunitinib. The median PFS for cabozantinib was 8.2 months versus 5.6 months for sunitinib. Investigator-assessed ORR, a secondary endpoint, was also significantly improved, at 33% for cabozantinib versus 12% for sunitinib, and median OS, another secondary endpoint, showed a trend favoring cabozantinib with 30.3 months versus 21.8 months for sunitinib.

Updated results from CABOSUN were presented at the ESMO 2017 Congress in September 2017 and subsequently published in the European Journal of Cancer in May 2018. The updated results included the analysis from a blinded independent radiology review committee (IRRC), which confirmed the primary efficacy endpoint results of investigator-assessed PFS, as well as an updated investigator-assessed analysis. Per the IRRC analysis, the median PFS for cabozantinib was 8.6 months versus 5.3 months for sunitinib, and both the updated investigator assessment and IRRC analysis demonstrated consistent and statistically significant improvement of PFS with cabozantinib as compared to sunitinib. The updated OS analysis had a data cut-off of July 1, 2017, and showed a favorable trend for patients randomized to cabozantinib compared to sunitinib that was not statistically significant. Median OS was 26.6 months for patients receiving cabozantinib versus 21.2 months for those receiving sunitinib. The safety profile in the study and in later analyses was consistent with the established profile of cabozantinib and other TKIs.

On the basis of the data from the CABOSUN trial, the FDA approved CABOMETYX for the treatment of patients with previously untreated, advanced or metastatic RCC on December 19, 2017, and we commenced our commercial launch of CABOMETYX for this new indication immediately upon such approval. Additionally, on May 17, 2018, the EC approved cabozantinib as a first-line treatment for adults with intermediate- or poor-risk advanced RCC.

RCC - Retrospective Analyses of CABOSUN and METEOR

As the advanced RCC treatment landscape continues to evolve and include multiple ICI treatment options, biomarker analyses are of increasing importance to help select for advanced RCC patients who would potentially derive the most clinical benefit from CABOMETYX. Two relevant retrospective analyses were presented at the ESMO 2018 Congress in October 2018 that described the potential utility of CABOMETYX in patients with advanced RCC regardless of their PD-L1 status, as well as in those patients with advanced RCC who progressed on previous ICI monotherapy or combination treatment.

The first analysis of data from the CABOSUN and METEOR trials evaluated the effect of PD-L1 expression on clinical outcomes with cabozantinib in advanced RCC and demonstrated that cabozantinib improved clinical outcomes regardless of PD-L1 status, relative to sunitinib or everolimus, the respective comparator arms for each trial. The findings showed that PD-L1 expression was associated with shorter median PFS and OS in both METEOR and CABOSUN. Treatment with cabozantinib, however, improved PFS and OS compared with everolimus (METEOR) and sunitinib (CABOSUN) in both PD-L1 positive and PD-L1 negative patients. An additional retrospective analysis

found that cabozantinib was active in patients previously treated with ICIs, either alone or in combination with anti-VEGF or other therapies. At a median follow-up of 12 months, ORR was 33%, disease control rate (DCR) was 79% and the one-year OS rate was 53%. Together, these analyses evaluating data from the CABOSUN and METEOR clinical trials contribute to cabozantinib's unique product profile, as well as its value as a treatment option for patients with advanced RCC within an evolving and competitive treatment landscape that includes multiple ICI treatment options.

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HCC - CELESTIAL

In October 2017, we announced positive results of CELESTIAL, our phase 3 pivotal trial comparing cabozantinib to placebo in patients with HCC who had received previous treatment with sorafenib. The CELESTIAL trial, which we initiated in September 2013, was designed to enroll 760 patients who had received prior systemic therapy with sorafenib, could have received up to two prior systemic therapies for HCC, and must have progressed following at least one prior therapy. The CELESTIAL trial was conducted at more than 100 sites globally in 19 countries and enrollment was completed in September 2017. Patients were randomized 2:1 to receive 60 mg of cabozantinib daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia or other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms.

In October 16, 2017, we announced that CELESTIAL had met its primary endpoint, with cabozantinib providing a statistically significant and clinically meaningful improvement versus placebo in OS, and that the independent data monitoring committee (IDMC), recommended CELESTIAL be stopped for efficacy. In January 2018, statistically significant and clinically meaningful positive results from the second interim analysis of CELESTIAL were presented during an oral session at the 2018 ASCO's Gastrointestinal Cancers Symposium. In July 2018, the NEJM also published the complete, detailed positive results from CELESTIAL. In the total population of second- and third-line patients, median OS was 10.2 months with cabozantinib versus 8.0 months with placebo (hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.63-0.92; p=0.0049). Median PFS was more than doubled, at 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44; 95% CI 0.36-0.52; p<0.0001). ORR was 4% with cabozantinib and 0.4% with placebo (p=0.0086). Disease control (partial response (PR) or stable disease (SD)) was achieved by 64% of patients in the cabozantinib group compared with 33% in the placebo group. In a subgroup analysis of patients whose only prior therapy for HCC was sorafenib (70% of patients in the study), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70; 95% CI 0.55-0.88). PFS in the subgroup was 5.5 months with cabozantinib versus 1.9 months with placebo (HR 0.40; 95% CI 0.32-0.50).