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Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. Receive Priority Review From FDA for LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Applications for Advanced Renal Cell Carcinoma and for Advanced Endometrial Carcinoma

Applications Based on Progression-Free Survival, Overall Survival, and Objective Response Rate Data From Respective Pivotal Phase 3 Trials

TOKYO and KENILWORTH, N.J., May 6, 2021 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada) today announced that the U.S. Food and Drug Administration (FDA) has accepted and granted priority review for applications seeking two new approvals for the combination of LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A. The first set of applications (a supplemental New Drug Application [sNDA] for LENVIMA and a supplemental Biologics License Application [sBLA] for KEYTRUDA) are for the first-line treatment of patients with advanced renal cell carcinoma (RCC), based on progressionfree survival (PFS), overall survival (OS) and objective response rate (ORR) data from the pivotal Phase 3 CLEAR study (Study 307/KEYNOTE-581). The second set of applications are for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation, based on PFS, OS, and ORR data from the pivotal Phase 3 Study 309/KEYNOTE-775 trial. These are the first applications to be submitted in the U.S. for this combination therapy based on Phase 3 clinical data. The FDA has set Prescription Drug User Fee Act (PDUFA) dates, or target action dates, of August 25 and 26, 2021, for the advanced RCC sNDA and sBLA applications, respectively, and September 3, 2021, for the advanced endometrial carcinoma applications.

"Advanced renal cell carcinoma and advanced endometrial carcinoma are aggressive cancers, and patients urgently need new treatment options that may help improve outcomes," said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. "We appreciate that the FDA has recognized this significant unmet need and the potential for the combination of KEYTRUDA plus LENVIMA in these patients by granting priority review for these applications."

"We are pleased that the FDA has granted priority review for LENVIMA plus KEYTRUDA—both in advanced renal cell carcinoma and advanced endometrial carcinoma—underscoring the potential significance of the outcomes observed in the CLEAR study (Study 307/KEYNOTE-581) and Study 309/KEYNOTE-775 trials," said Dr. Takashi Owa, Chief Medicine Creation Officer and Chief Discovery Officer, Oncology Business Group at Eisai. "Many patients are still in need of new and effective therapies, which fuels our commitment to advancing the development of this combination even more. These milestones reinforce our unwavering dedication to helping the patients we aim to serve."

The applications in advanced RCC are based on results from the CLEAR study (Study 307/KEYNOTE-581), in which LENVIMA plus KEYTRUDA demonstrated statistically significant improvements in PFS, OS and ORR versus sunitinib. These data were presented in February at the virtual 2021 Genitourinary Cancers Symposium (ASCO GU) and simultaneously published in the *New England Journal of Medicine*. <sup>1</sup>

The applications in advanced endometrial carcinoma are based on results from Study 309/KEYNOTE-775, in which LENVIMA plus KEYTRUDA demonstrated statistically significant improvements in PFS, OS and ORR versus chemotherapy (investigator's choice of doxorubicin or paclitaxel), regardless of mismatch repair (MMR) status. These data were presented in March at the virtual Society of Gynecologic Oncology (SGO) 2021 Annual Meeting on Women's Cancer. Study 309/KEYNOTE-775 is the confirmatory trial for Study 111/KEYNOTE-146, which supported the 2019 accelerated approval of the combination for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication was an accelerated approval based on tumor response and durability of response and reviewed under the FDA's Real-Time Oncology Review pilot program and the FDA's Project Orbis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. are studying the LENVIMA plus KEYTRUDA combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program in

14 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer, pancreatic cancer and triple-negative breast cancer) across more than 20 clinical trials.

#### About LENVIMA® (lenvatinib) Capsules

LENVIMA, discovered and developed by Eisai, is an orally available kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. In syngeneic mouse tumor models, LENVIMA decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

Currently, LENVIMA has been approved for monotherapy as a treatment for thyroid cancer in over 70 countries including Japan, in Europe, China and in Asia, and in the United States for radioiodine-refractory differentiated thyroid cancer. In addition, LENVIMA has been approved for monotherapy as a treatment for unresectable hepatocellular carcinoma in over 70 countries including Japan, the United States, in Europe, China and in Asia. It is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including the United States, in Europe and Asia. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. In addition, it is approved in combination with KEYTRUDA (generic name: pembrolizumab) as a treatment for advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation in over 10 countries including the United States, Canada and Australia. Continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials. LENVIMA has also been approved for monotherapy as a treatment for unresectable thymic carcinoma in Japan.

# About KEYTRUDA® (pembrolizumab) Injection, 100mg

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck & Co., Inc., Kenilworth, N.J., U.S.A. has the industry's largest immuno-oncology clinical research program. There are currently more than 1,400 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient's likelihood of benefitting from treatment with KEYTRUDA, including exploring several different biomarkers.

### **About CLEAR Study (Study 307/KEYNOTE-581)**

The CLEAR study (Study 307/KEYNOTE-581) is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, NCT02811861) evaluating LENVIMA in combination with KEYTRUDA or in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced RCC. The primary endpoint is PFS, as assessed by independent review per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key secondary endpoints include OS, ORR and safety. A total of 1,069 patients were randomized (1:1:1) to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously [IV] every three weeks for up to 24 months); or LENVIMA (18 mg orally once daily) in combination with everolimus (5 mg orally once daily); or sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment).

In the trial's primary endpoint of PFS, as assessed by independent review per RECIST v1.1, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI: 0.32-0.49]; p<0.001), with a median PFS of 23.9 months (95% CI: 20.8-27.7) versus 9.2 months (95% CI: 6.0-11.0) for patients who received sunitinib. In the trial's key secondary endpoints, LENVIMA plus KEYTRUDA reduced the risk of death by 34% (HR=0.66 [95% CI: 0.49-0.88]; p=0.005) versus patients who received sunitinib. Median OS was not reached in either treatment arm after a median follow-up of 27 months. Treatment with LENVIMA plus KEYTRUDA resulted in an ORR of 71.0% (95% CI: 66.3-75.7), with a complete response (CR) rate of 16.1% and a partial response (PR) rate of 54.9%, versus an ORR of 36.1% (95% CI: 31.2-41.1), with a CR rate of 4.2% and a PR rate of 31.9%, for patients who received sunitinib (relative

risk=1.97 [95% CI: 1.69-2.29]). Median duration of response (DOR) for patients who received LENVIMA plus KEYTRUDA was 25.8 months (95% CI: 22.1-27.9) versus 14.6 months (95% CI: 9.4-16.7) for patients who received sunitinib.

In the LENVIMA plus KEYTRUDA arm, treatment-related adverse events (TRAEs) led to discontinuation of LENVIMA in 18.5% of patients, of KEYTRUDA in 25.0% of patients, and of both in 9.7% of patients. In the sunitinib arm, TRAEs led to discontinuation of sunitinib in 10.0% of patients. Grade 5 TRAEs occurred in 1.1% of patients in the LENVIMA plus KEYTRUDA arm versus 0.3% of patients in the sunitinib arm. Grade ≥3 TRAEs occurred in 71.6% of patients in the LENVIMA plus KEYTRUDA arm versus 58.8% of patients in the sunitinib arm. The most common TRAEs of any grade occurring in at least 20% of patients in the LENVIMA plus KEYTRUDA arm were diarrhea (54.5%), hypertension (52.3%), hypothyroidism (42.6%), decreased appetite (34.9%), fatigue (32.1%) and stomatitis (32.1%). In the sunitinib arm, the most common TRAEs of any grade occurring in at least 20% of patients were diarrhea (44.4%), hypertension (39.1%), stomatitis (37.4%), hand-foot syndrome (35.9%), fatigue (32.1%) and nausea (27.6%).

### **About Study 309/KEYNOTE-775**

Study 309/KEYNOTE-775 is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, NCT03517449) evaluating LENVIMA in combination with KEYTRUDA in patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. The dual primary endpoints are PFS, as assessed by blinded independent central review (BICR) per RECIST v1.1, and OS. Select secondary endpoints include ORR and duration of response (DOR), as assessed by BICR. A total of 827 patients were randomized (1:1) to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg IV every three weeks); or Investigator's choice of either doxorubicin (60 mg/m² IV every three weeks) or paclitaxel (80 mg/m² IV on a 28-day cycle, three weeks of receiving weekly paclitaxel and one week of not receiving paclitaxel).

The study met the dual primary endpoints of PFS, as assessed by BICR per RECIST v1.1, OS, as well as the secondary efficacy endpoint of ORR, as assessed by BICR per RECIST v1.1, in the all-comer population (pMMR and dMMR) and in the pMMR subgroup. Median follow-up was 11.4 months for both the all-comer population and pMMR subgroup. A statistically significant improvement in PFS was seen in the all-comer population, in which LENVIMA plus KEYTRUDA (n=411) reduced the risk of disease progression or death by 44% (HR=0.56 [95% CI: 0.47-0.66];

p<0.0001), with a median PFS of 7.2 months (95% CI: 5.7-7.6; number of events=281) versus 3.8 months (95% CI: 3.6-4.2; number of events=286) for patients who received TPC (n=416). Additionally, a statistically significant improvement in OS was seen in the all-comer population, in which LENVIMA plus KEYTRUDA reduced the risk of death by 38% (HR=0.62 [95% CI: 0.51-0.75]; p<0.0001), with a median OS of 18.3 months (95% CI: 15.2-20.5; number of events=188) versus 11.4 months (95% CI: 10.5-12.9; number of events=245) for patients who received TPC. The safety profile of LENVIMA plus KEYTRUDA was generally consistent with the established safety profiles of the individual monotherapies.

In the all-comer population, the secondary efficacy endpoint of ORR was 31.9% (95% CI: 27.4-36.6), with a CR rate of 6.6% and a PR rate of 25.3%, for patients who received LENVIMA plus KEYTRUDA versus 14.7% (95% CI: 11.4-18.4), with a CR rate of 2.6% and a PR rate of 12.0% for patients who received TPC (ORR difference versus TPC: 17.2 percentage points; p<0.0001). For patients who responded, the median duration of response (DOR) was 14.4 months (range: 1.6-23.7) for patients who received LENVIMA plus KEYTRUDA versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

Results were similar across the all-comer population and the pMMR subgroup. In the pMMR subgroup, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI: 0.50-0.72]; p<0.0001), with a median PFS of 6.6 months (95% CI: 5.6-7.4; number of events=247) versus 3.8 months (95% CI: 3.6-5.0; number of events=238) for patients who received TPC. LENVIMA plus KEYTRUDA reduced the risk of death by 32% (HR=0.68 [95% CI: 0.56-0.84]; p=0.0001), with a median OS of 17.4 months (95% CI: 14.2-19.9; number of events=165) versus 12.0 months (95% CI: 10.8-13.3; number of events=203) for patients who received TPC. The secondary endpoint of ORR was 30.3% (95% CI: 25.5-35.5), with a CR rate of 5.2% and a PR rate of 25.1%, for patients who received LENVIMA plus KEYTRUDA versus 15.1% (95% CI: 11.5-19.3), with a CR rate of 2.6% and a PR rate of 12.5%, for patients who received TPC (ORR difference versus TPC: 15.2 percentage points: p<0.0001). For patients who responded, the median DOR was 9.2 months (range: 1.6-23.7) for patients who received LENVIMA plus KEYTRUDA versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

In the all-comer population, in the LENVIMA plus KEYTRUDA arm (n=406), any grade treatment-emergent adverse events (TEAEs) led to discontinuation of LENVIMA in 30.8% of patients, of KEYTRUDA in 18.7% of patients, and of both in 14.0% of patients. In the TPC arm (n=388), any grade TEAEs led to discontinuation of chemotherapy in 8.0% of patients. Grade 5 TEAEs of any cause occurred in 5.7% of patients in the LENVIMA plus KEYTRUDA arm and in

4.9% of patients in the TPC arm. Grade ≥3 TEAEs occurred in 88.9% of patients in the LENVIMA plus KEYTRUDA arm and in 72.7% of patients in the TPC arm. In the LENVIMA plus KEYTRUDA arm, the most common TEAEs of any grade occurring in at least 25% of patients were hypertension (64.0%), hypothyroidism (57.4%), diarrhea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decrease (34.0%), fatigue (33.0%), arthralgia (30.5%), proteinuria (28.8%), anemia (26.1%), constipation (25.9%), and urinary tract infection (25.6%). In the TPC arm, the most common TEAEs of any grade occurring in at least 25% of patients were anemia (48.7%), nausea (46.1%), neutropenia (33.8%), alopecia (30.9%), and fatigue (27.6%). Median treatment duration was 231 days (range: 1-817) with LENVIMA plus KEYTRUDA and 104.5 days (range: 1-785) with TPC.

### **About Renal Cell Carcinoma (RCC)**<sup>2,3,4,5,6,7</sup>

Worldwide, it is estimated there were more than 431,000 new cases of kidney cancer diagnosed and more than 179,000 deaths from the disease in 2020. In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020. In the U.S. alone, it is estimated there will be more than 76,000 new cases of kidney cancer diagnosed and almost 14,000 deaths from the disease in 2021. Renal cell carcinoma is by far the most common type of kidney cancer; about nine out of 10 kidney cancers are RCCs. Renal cell carcinoma is about twice as common in men as in women. Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. Approximately 30% of patients with RCC will have metastatic disease at diagnosis, and as many as 40% will develop metastases after primary surgical treatment for localized RCC. Survival is highly dependent on the stage at diagnosis, and the five-year survival rate is 13% for patients with metastatic disease.

# **About Endometrial Carcinoma**<sup>8,9,10,11,12</sup>

Endometrial carcinoma begins in the inner lining of the uterus, which is known as the endometrium, and is the most common type of cancer in the uterus. In 2020, it was estimated there were more than 417,000 new cases and more than 97,000 deaths from uterine body cancers worldwide (these estimates include both endometrial cancers and uterine sarcomas; more than 90% of uterine body cancers occur in the endometrium, so the actual numbers for endometrial cancer cases and deaths are slightly lower than these estimates). In Japan, there were more than 17,000 new cases of uterine body cancer and more than 3,000 deaths from the disease in 2020. In the U.S., it is estimated there will be more than 66,000 new cases of uterine

body cancer and nearly 13,000 deaths from the disease in 2021. The five-year survival rate for metastatic endometrial cancer (stage IV) is estimated to be approximately 17%.

### About the Merck & Co., Inc., Kenilworth, N.J., U.S.A. and Eisai Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A., known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A.

In addition to ongoing clinical studies evaluating the LENVIMA plus KEYTRUDA combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in 14 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer, pancreatic cancer and triple-negative breast cancer) across more than 20 clinical trials.

#### Eisai's Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (*Ricchi*) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these *Ricchi*, with the aim of contributing to the cure of cancers.

#### **About Eisai**

Eisai is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our *human health care* (*hhc*) philosophy. We strive to realize our *hhc* philosophy by delivering innovative products in therapeutic areas with high unmet medical needs, including Oncology and Neurology. In the spirit of *hhc*, we take that

commitment even further by applying our scientific expertise, clinical capabilities and patient insights to discover and develop innovative solutions that help address society's toughest unmet needs, including neglected tropical diseases and the Sustainable Development Goals.

For more information about Eisai, please visit <a href="www.eisai.com">www.eisai.com</a> (for global), <a href="www.eisai.com">us.eisai.com</a> (for U.S.) or <a href="www.eisai.eu">www.eisai.eu</a> (for Europe, Middle East, Africa), and connect with us on Twitter (<a href="www.eisai.eu">U.S.</a> and <a href="mailto:global">global</a>) and <a href="mailto:LinkedIn">LinkedIn</a> (for U.S.).

#### Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck & Co., Inc., Kenilworth, N.J., U.S.A., the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck & Co., Inc., Kenilworth, N.J., U.S.A. is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit <a href="https://www.merck.com/clinicaltrials">www.merck.com/clinicaltrials</a>.

#### About Merck & Co., Inc., Kenilworth, N.J., U.S.A.

For 130 years, Merck & Co., Inc., Kenilworth, N.J., U.S.A., known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck & Co., Inc., Kenilworth, N.J., U.S.A. continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases - as we aspire to be the premier research-intensive world. For biopharmaceutical company in the information. more visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

# Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs

and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2020 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

<sup>&</sup>lt;sup>1</sup> Motzer R. et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *The New England Journal of Medicine* 

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<sup>&</sup>lt;sup>4</sup> American Cancer Society. Key Statistics About Kidney Cancer, https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html.

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<sup>&</sup>lt;sup>6</sup> Shinder B. et al. Surgical Management of Advanced and Metastatic Renal Cell Carcinoma: A Multidisciplinary Approach. *Frontiers in Oncology*. 2017; 7: 107. <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5449498/#">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5449498/#</a> ffn sectitle.

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