NEWS RELEASE

Bayer Unveils Latest Data from Oncology Portfolio at ESMO Congress 2023

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- Bayer's focus remains on prostate cancer care with NUBEQA® (darolutamide), supported by additional ARASENS and ARAMIS trial analyses, evaluating prostate-specific antigen (PSA) outcomes in metastatic hormone-sensitive prostate cancer (mHSPC), and health-related quality of life (HRQoL) deterioration-free survival (DetFS) in patients with non-metastatic castration-resistant prostate cancer (nmCRPC)
- New data from the REASSURE observational study of Xofigo® (radium Ra 223 dichloride) will explore clinical outcomes in patients with metastatic castration-resistant prostate cancer (mCRPC)
- Real-world data will explore Stivarga® (regorafenib) in refractory metastatic colorectal cancer (mCRC), in addition to the safety and effectiveness in unresectable hepatocellular carcinoma (uHCC)
- Bayer will present data from a post-hoc pooled analysis of three clinical trials evaluating Vitrakvi® (larotrectinib) in the treatment of patients with treatment-naïve non-primary central nervous system (CNS) TRK fusion cancer, alongside updated efficacy and safety data from three pooled clinical trials evaluating Vitrakvi for the treatment of patients with TRK fusion cancer
- Bayer will highlight the first disclosure of investigational clinical data from a first-in-human, Phase I trial of BAY 2927088, an oral tyrosine kinase inhibitor (TKI) in patients with EGFR or HER2 mutant non-small cell lung cancer (NSCLC)

Presentations: 1784P, 1781P, 1816P, 616P, 994P, 667P, 668P, 1320MO

WHIPPANY, N.J.--(BUSINESS WIRE)-- Bayer will present new data from across its oncology portfolio at the upcoming **European Society for Medical Oncology (ESMO) Congress** taking place in Madrid, Spain from October 20-24, 2023. The breadth of new data showcases Bayer's ongoing commitment to supporting patients living with cancer.

NUBEQA® (darolutamide) data includes further analyses from the Phase III ARASENS trial which evaluates prostate-specific antigen (PSA) outcomes of NUBEQA plus androgen deprivation therapy (ADT) and docetaxel, compared to ADT and docetaxel by disease volume in metastatic hormone-sensitive prostate cancer (mHSPC). In addition, Bayer will present new data on health-related quality of life (HRQoL) deterioration-free survival (DetFS) by PSA decline in the Phase III ARAMIS trial in patients with non-metastatic castration-resistant prostate cancer (nmCRPC). NUBEQA is currently indicated in the U.S. in combination with docetaxel for the treatment of adult patients with mHSPC and for the treatment of adult patients with nmCRPC.1

Bayer will also present new data from the REASSURE observational study, evaluating the clinical outcomes of patients with metastatic castration-resistant prostate cancer (mCRPC) who received combined treatment with Xofigo® (radium Ra 223 dichloride) and enzalutamide. Xofigo is indicated for the treatment of patients with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease.2

Bayer remains committed to gastrointestinal (GI) cancer care. New real-world data featuring Stivarga® (regorafenib) explores the clinical outcomes of Stivarga-treated patients when administered prior to trifluridine/tipiracil ± bevacizumab in patients with refractory metastatic colorectal cancer (mCRC). Additionally, Bayer will highlight data from the REFINE study, evaluating the safety and effectiveness of Stivarga in patients with unresectable hepatocellular carcinoma (uHCC) and prior liver transplantation (PLT). Stivarga is indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. Stivarga is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.3

Bayer will highlight the latest efficacy and safety data of Vitrakvi® (larotrectinib), including data from a post-hoc pooled analysis of three clinical trials evaluating Vitrakvi in the treatment of patients with treatment-naïve non-primary central nervous system (CNS) TRK fusion cancer, and updated data from a pooled analysis from three clinical trials of patients with longer follow-up. Vitrakvi is approved for the treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. Patients should be selected for therapy based on a FDA-approved test. This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.4

Bayer will highlight the latest data from its precision oncology pipeline, including the first disclosure of investigational clinical data from a first-in-human, Phase I trial of BAY 2927088, an oral tyrosine kinase inhibitor (TKI) in patients with non-small cell lung cancer (NSCLC).

Details on presentations from Bayer for the 2023 ESMO Congress are listed below:

Darolutamide

- Prostate-specific antigen (PSA) outcomes with darolutamide (DARO), androgen-deprivation therapy (ADT) and docetaxel (DOC) in patients (pts) with high- and low-volume metastatic hormone-sensitive prostate cancer (mHSPC) in ARASENS
    - E-Poster: 1784P; October 22
- Health-related quality of life (HRQoL) deterioration-free survival (DetFS) by prostate-specific antigen (PSA) decline in darolutamide (DARO)-treated patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) from ARAMIS
    - E-Poster: 1781P; October 22

Radium-223 dichloride (Ra-223)

- Combination treatment with radium-223 (223Ra) and enzalutamide (enza) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) in the REASSURE study
    - E-Poster: 1816P; October 22

Regorafenib

- Sequential treatment with regorafenib (REG) and trifluridine/tipiracil (TAS) +/- bevacizumab (Bev) in refractory metastatic colorectal cancer (mCRC) in community clinical practice in the USA
    - E-Poster: 616P; October 22
- Regorafenib (REG) in patients (pts) with unresectable hepatocellular carcinoma (uHCC) in real-world (RW) practice: Final analysis of the prospective, observational REFINE study by prior liver transplantation (PLT)
    - E-Poster: 994P; October 23

Larotrectinib

- Efficacy and safety of larotrectinib (laro) as first-line treatment for patients (pts) with tropomyosin receptor kinase (TRK) fusion cancer
    - E-Poster: 667P; October 23
- Efficacy and Safety of Larotrectinib in a Pooled Analysis of Patients (Pts) with Tropomyosin Receptor Kinase (TRK) Fusion Cancer
    - E-Poster: 668P; October 23

Precision Oncology Pipeline

- Early evidence of efficacy in patients (pts) with non-small cell lung cancer (NSCLC) with HER2 exon20 insertion (ex20ins) mutations treated in a Phase I study with BAY 2927088
    - Oral Presentation: 1320MO; October 23

About NUBEQA® (darolutamide)1

NUBEQA is an androgen receptor inhibitor (ARi) with a distinct chemical structure that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription.

On July 30, 2019, the FDA approved NUBEQA® (darolutamide) based on the ARAMIS trial, a randomized, double-blind, placebo-controlled, multi-center Phase III study, which evaluated the safety and efficacy of oral NUBEQA in patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

Based on results from the ARASENS trial, a randomized, Phase III, multi-center, double-blind, placebo-controlled trial, NUBEQA plus androgen deprivation therapy (ADT) and docetaxel was approved on August 5, 2022 for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC).

NUBEQA is also being investigated in additional studies across various stages of prostate cancer, including in the ARANOTE Phase III trial evaluating NUBEQA plus ADT versus ADT alone for mHSPC, as well as in the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) led international Phase III co-operative group DASL-HiCaP (ANZUP1801) trial evaluating NUBEQA as an adjuvant treatment for localized prostate cancer with very high risk of recurrence. Information about these trials can be found at **www.clinicaltrials.gov.**

Developed jointly by Bayer and Orion Corporation, a globally operating Finnish pharmaceutical company, NUBEQA is indicated for the treatment of adults with nmCRPC or with mHSPC in combination with docetaxel.1 Filings in other regions are underway or planned.

INDICATIONS

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of adult patients with:

- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Ischemic Heart Disease – In a study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA versus 2.5% receiving placebo, including Grade 3-4 events in 1.7% vs. 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA vs. 0.2% receiving placebo. In a study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 2.9% of patients receiving NUBEQA with docetaxel vs. 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% vs. 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel vs. 0% receiving placebo with docetaxel. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

Seizure – In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA vs. 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA. In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, vs. 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA. It is unknown whether anti-epileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

Embryo-Fetal Toxicity – Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

In ARAMIS, serious adverse reactions occurred in 25% of patients receiving NUBEQA vs. 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA vs. 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%). The most common adverse reactions (>2% with a ≥2% increase over placebo), including laboratory test abnormalities, were increased AST, decreased neutrophil count, fatigue, increased bilirubin, pain in extremity, and rash. Clinically relevant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease and heart failure.

In ARASENS, serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel vs. 42% of patients receiving placebo with docetaxel. Serious adverse reactions in ≥2% of patients who received NUBEQA with

docetaxel included febrile neutropenia (6%), decreased neutrophil count (2.8%), musculoskeletal pain (2.6%), and pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel vs. 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%). The most common adverse reactions (≥10% with a ≥2% increase over placebo with docetaxel) were constipation, decreased appetite, rash, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities (≥30%) were anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT, and hypocalcemia. Clinically relevant adverse reactions in <10% of patients who received NUBEQA with docetaxel included fractures, ischemic heart disease, seizures, and drug-induced liver injury.

Drug Interactions

Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the Prescribing Information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

For important risk and use information about NUBEQA, please see the accompanying full **Prescribing Information** .

About Xofigo® (radium Ra 223 dichloride) Injection2

Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Important Safety Information for Xofigo® (radium Ra 223 dichloride) Injection

Warnings and Precautions:

- Bone Marrow Suppression: In the phase 3 ALSYMPCA trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression–notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia–has been reported in patients treated with Xofigo.

  Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure

- Hematological Evaluation: Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 109/L, the platelet count ≥100 × 109/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 109/L and the platelet count ≥50 × 109/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care

- Concomitant Use With Chemotherapy: Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued

- Increased Fractures and Mortality in Combination With Abiraterone Plus Prednisone/Prednisolone: Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. At the primary analysis of the Phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly

symptomatic mCRPC patients, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established

- Embryo-Fetal Toxicity: The safety and efficacy of Xofigo have not been established in females. Xofigo can cause fetal harm when administered to a pregnant female. Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise male patients to use condoms and their female partners of reproductive potential to use effective contraception during and for 6 months after completing treatment with Xofigo

Administration and Radiation Protection: Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations

Fluid Status: Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting, which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia

Injection Site Reactions: Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo

Secondary Malignant Neoplasms: Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow-up for patients on the trial

Subsequent Treatment With Cytotoxic Chemotherapy: In the randomized clinical trial, 16% of patients in the Xofigo group and 18% of patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy

Adverse Reactions: The most common adverse reactions (≥10%) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)

Please see the full **Prescribing Information** for Xofigo (radium Ra 223 dichloride).

About Stivarga® (regorafenib)3

In April 2017, Stivarga was approved for use in patients with hepatocellular carcinoma who have been previously treated with sorafenib. In the United States, Stivarga is also indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. It is also indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

Regorafenib is a compound developed by Bayer. In 2011, Bayer entered into an agreement with Onyx, now an Amgen subsidiary, under which Onyx receives a royalty on all global net sales of regorafenib in oncology.

Indication

Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild- type, an anti-EGFR therapy.

Stivarga is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

Stivarga is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Important Safety Information for STIVARGA® (regorafenib)

WARNING: HEPATOTOXICITY

- Severe and sometimes fatal hepatotoxicity has occurred in clinical trials.
- Monitor hepatic function prior to and during treatment.
- Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients across all clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury. In metastatic colorectal cancer (mCRC), fatal hepatic failure occurred in 1.6% of patients in the STIVARGA arm and in 0.4% of patients in the placebo arm. In gastrointestinal stromal tumor (GIST), fatal hepatic failure occurred in 0.8% of patients in the STIVARGA arm. In hepatocellular carcinoma (HCC), there was no increase in the incidence of fatal hepatic failure as compared to placebo.

Liver Function Monitoring: Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit of normal (ULN) or baseline values. Temporarily hold and then reduce or permanently discontinue STIVARGA, depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis.

Infections: STIVARGA caused an increased risk of infections. The overall incidence of infection (Grades 1-5) was higher (32% vs 17%) in 1142 STIVARGA-treated patients as compared to the control arm in randomized placebo-controlled trials. The incidence of grade 3 or greater infections in STIVARGA treated patients was 9%. The most common infections were urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Fatal outcomes caused by infection occurred more often in patients treated with STIVARGA (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% vs 0.2%). Withhold STIVARGA for Grade 3 or 4 infections, or worsening infection of any grade. Resume STIVARGA at the same dose following resolution of infection.

Hemorrhage: STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with STIVARGA vs 9.5% with placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with STIVARGA was 3.0%. The incidence of fatal hemorrhagic events was 0.7%, involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts. Permanently discontinue STIVARGA in patients with severe or life-threatening hemorrhage and monitor INR levels more frequently in patients receiving warfarin.

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation occurred in 0.6% of 4518 patients

treated with STIVARGA across all clinical trials of STIVARGA administered as a single agent; this included eight fatal events. Gastrointestinal fistula occurred in 0.8% of patients treated with STIVARGA and in 0.2% of patients in the placebo arm across randomized, placebo-controlled trials. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

Dermatological Toxicity: In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients with STIVARGA arm and 25.5% of patients in the placebo arm including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES) and severe rash, requiring dose modification. In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 STIVARGA-treated patients (53% vs 8%) than in the placebo-treated patients. Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment. The incidences of Grade 3 HFSR (16% vs <1%), Grade 3 rash (3% vs <1%), serious adverse reactions of erythema multiforme (<0.1% vs 0%), and Stevens-Johnson syndrome (<0.1% vs 0%) were higher in STIVARGA-treated patients. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 72%; Grade 3:18%). Toxic epidermal necrolysis occurred in 0.02% of 4518 STIVARGA-treated patients across all clinical trials of STIVARGA administered as a single agent. Withhold STIVARGA, reduce the dose, or permanently discontinue depending on the severity and persistence of dermatologic toxicity.

Hypertension: Hypertensive crisis occurred in 0.2% in STIVARGA-treated patients and in none of the patients in placebo arm across all randomized, placebo-controlled trials. STIVARGA caused an increased incidence of hypertension (30% vs 8% in mCRC, 59% vs 27% in GIST, and 31% vs 6% in HCC). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo-controlled trials). Do not initiate STIVARGA until blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold STIVARGA for severe or uncontrolled hypertension.

Cardiac Ischemia and Infarction: STIVARGA increased the incidence of myocardial ischemia and infarction (0.9% with STIVARGA vs 0.2% with placebo) in randomized placebo-controlled trials. Withhold STIVARGA in patients who develop new or acute cardiac ischemia or infarction and resume only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristics finding on MRI occurred in one of 4800 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion, or altered mental function. Discontinue STIVARGA in patients who develop RPLS.

Wound Healing Complications: Impaired wound healing complications can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, STIVARGA has the potential to adversely affect wound healing. Withhold STIVARGA for at least 2 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of STIVARGA after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity: STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose.

Nursing Mothers: Because of the potential for serious adverse reactions in breastfed infants from STIVARGA, do not breastfeed during treatment with STIVARGA and for 2 weeks after the final dose.

Most Frequently Observed Adverse Drug Reactions in mCRC (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in mCRC, respectively, were: asthenia/fatigue (64% vs 46%), pain (59% vs 48%), decreased appetite and food intake (47% vs 28%), HFSR/PPE (45% vs 7%), diarrhea (43% vs 17%), mucositis (33% vs 5%), weight loss (32% vs 10%), infection (31% vs 17%), hypertension (30% vs 8%), and dysphonia (30% vs 6%).

Most Frequently Observed Adverse Drug Reactions in GIST (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo treated patients in GIST, respectively, were: HFSR/PPE (67% vs 12%), pain (60% vs 55%), hypertension (59% vs 27%), asthenia/fatigue (52% vs 39%), diarrhea (47% vs 9%), mucositis (40% vs 8%), dysphonia (39% vs 9%), infection (32% vs 5%), decreased appetite and food intake (31% vs 21%), and rash (30% vs 3%).

Most Frequently Observed Adverse Drug Reactions in HCC (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in HCC, respectively, were: pain (55% vs 44%), HFSR/PPE (51% vs 7%), asthenia/fatigue (42% vs 33%), diarrhea (41% vs 15%), hypertension (31% vs 6%), infection (31% vs 18%), decreased appetite and food intake (31% vs 15%).

Please see full **Prescribing Information** , including **Boxed Warning** for Stivarga (regorafenib).

About Vitrakvi® (larotrectinib)4

Vitrakvi® (larotrectinib) is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are

metastatic or where surgical resection will likely result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Important Safety Information for Vitrakvi® (larotrectinib)

Warnings and Precautions

- Central Nervous System Effects: Central nervous system (CNS) adverse reactions occurred in patients receiving VITRAKVI, including dizziness, cognitive impairment, mood disorders, and sleep disturbances.

  In patients who received VITRAKVI, all grades CNS effects including cognitive impairment, mood disorders, dizziness and sleep disorders were observed in 42% with Grades 3-4 in 3.9% of patients.

  Cognitive impairment occurred in 11% of patients. The median time to onset of cognitive impairment was 5.6 months (range: 2 days to 41 months). Cognitive impairment occurring in ≥ 1% of patients included memory impairment (3.6%), confusional state (2.9%), disturbance in attention (2.9%), delirium (2.2%), cognitive disorders (1.4%), and Grade 3 cognitive adverse reactions occurred in 2.5% of patients. Among the 30 patients with cognitive impairment, 7% required a dose modification and 20% required dose interruption.

  Mood disorders occurred in 14% of patients. The median time to onset of mood disorders was 3.9 months (range: 1 day to 40.5 months). Mood disorders occurring in ≥1% of patients included anxiety (5%), depression (3.9%), agitation (2.9%), and irritability (2.9%). Grade 3 mood disorders occurred in 0.4% of patients.

  Dizziness occurred in 27% of patients, and Grade 3 dizziness occurred in 1.1% of patients. Among the 74 patients who experienced dizziness, 5% of patients required a dose modification and 5% required dose interruption.

  Sleep disturbances occurred in 10% of patients. Sleep disturbances included insomnia (7%), somnolence (2.5%), and sleep disorder (0.4%). There were no Grade 3-4 sleep disturbances. Among the 28 patients who experienced sleep disturbances, 1 patient each (3.6%) required a dose modification or dose interruption.

Advise patients and caretakers of these risks with VITRAKVI. Advise patients not to drive or operate hazardous machinery if they are experiencing neurologic adverse reactions. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

- Skeletal Fractures: Among 187 adult patients who received VITRAKVI across clinical trials, fractures were reported in 7% and among 92 pediatric patients, fractures were reported in 9% (N=279; 8%). Median time to fracture was 11.6 months (range 0.9 to 45.8 months) in patients followed per fracture. Fractures of the femur, hip or acetabulum were reported in 4 patients (3 adult, 1 pediatric). Most fractures were associated with minimal or moderate trauma. Some fractures were associated with radiologic abnormalities suggestive of local tumor involvement. VITRAKVI treatment was interrupted due to fracture in 1.4% patients.

  Promptly evaluate patients with signs or symptoms of potential fracture (e.g., pain, changes in mobility, deformity). There are no data on the effects of VITRAKVI on healing of known fractures or risk of future fractures.

- Hepatotoxicity: In patients who received VITRAKVI, increased AST of any grade occurred in 52% of patients and increased ALT of any grade occurred in 45%. Grade 3-4 increased AST or ALT occurred in 3.1% and 2.5% of patients, respectively. The median time to onset of increased AST was 2.1 months (range: 1 day to 4.3 years). The median time to onset of increased ALT was 2.3 months (range: 1 day to 4.2 years). Increased AST and ALT leading to dose modifications occurred in 1.4% and 2.2% of patients, respectively. Increased AST or ALT led to permanent discontinuation in 3 (1.1%) patients.

  Monitor liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue VITRAKVI based on the severity. If withheld, modify the VITRAKVI dosage when resumed.

- Embryo-Fetal Toxicity: VITRAKVI can cause fetal harm when administered to a pregnant woman. VITRAKVI resulted in malformations in rats and rabbits at maternal exposures that were approximately 11- and 0.7-times, respectively, those observed at the clinical dose of 100 mg twice daily. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment and for 1 week after the final dose of VITRAKVI.

Adverse Reactions

- The most common adverse reactions (≥20%), including laboratory abnormalities, were: increased AST (52%), increased ALT (45%), anemia (42%), musculoskeletal pain (42%), fatigue (36%), hypoalbuminemia (36%),

neutropenia (36%), increased alkaline phosphatase (34%), cough (32%), leukopenia (28%), constipation (27%), diarrhea (27%), dizziness (27%), hypocalcemia (25%), nausea (25%), vomiting (25%), pyrexia (24%), lymphopenia (22%) and abdominal pain (21%).

Drug Interactions

- Avoid coadministration of VITRAKVI with strong CYP3A4 inhibitors (including grapefruit or grapefruit juice), strong CYP3A4 inducers (including St. John's wort), or sensitive CYP3A4 substrates. If coadministration of strong CYP3A4 inhibitors or inducers cannot be avoided, modify the VITRAKVI dose as recommended. If coadministration of sensitive CYP3A4 substrates cannot be avoided, monitor patients for increased adverse reactions of these drugs. For coadministration with moderate CYP3A4 inhibitors, monitor for adverse reactions more frequently and reduce the dosage based on severity. For coadministration with moderate CYP3A4 inducers, modify dose as recommended.

Use in Specific Populations

- Lactation:Advise women not to breastfeed during treatment with VITRAKVI and for 1 week after the final dose.

Please see the full **Prescribing Information** for VITRAKVI® (larotrectinib).

About Oncology at Bayer

Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The oncology franchise at Bayer includes six marketed products and several other assets in various stages of clinical development. Together, these products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. Its products and services are designed to help people and the planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to driving sustainable development and generating a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2022, the Group employed around 101,000 people and had sales of 50.7 billion euros. R&D expenses before special items amounted to 6.2 billion euros. For more information, go to **www.bayer.com**.

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Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at **www.bayer.com**. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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Media:

Carolyn Nagle, Tel + 201.419.0337

Email: **Carolyn.Nagle@bayer.com**

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