Media & Investor Release

FDA grants Breakthrough Therapy Designation to Roche's inavolisib for advanced hormone receptor-positive, HER2-negative breast cancer with a *PIK3CA* mutation

- **The designation is based on Phase III INAVO120 results, showing the inavolisib-based regimen more than doubled progression-free survival compared with palbociclib and fulvestrant alone in the first-line setting[1]**
- **Approximately 40% of people with HR-positive breast cancer have a *PIK3CA* mutation and often face poorer prognosis and resistance to endocrine treatment[2,3]**
- **This is the 29th Breakthrough Therapy Designation for Roche's oncology portfolio, a testament to our enduring ambition to deliver transformative medicines for patients[4]**

Basel, 21 May 2024 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for inavolisib, an investigational oral therapy, in combination with palbociclib (Ibrance®) and fulvestrant, for the treatment of adult patients with *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment.

"We are pleased that the FDA granted Breakthrough Therapy Designation for inavolisib in recognition of the substantial clinical benefit observed with this regimen," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "This promising inavolisib-based regimen could transform the PI3K inhibitor class, potentially becoming the standard of care for this patient population in the first-line setting."

Breakthrough Therapy Designation is designed to accelerate the development and regulatory review of medicines intended to treat serious or life-threatening conditions where preliminary clinical evidence has indicated they may demonstrate substantial improvement over existing therapies.[5]

The FDA's decision is based on positive Phase III INAVO120 results, which showed the inavolisib-based regimen reduced the risk of disease worsening or death (progression-free survival) by 57% compared to palbociclib and fulvestrant alone (15.0 months vs. 7.3 months; hazard ratio [HR]=0.43, 95% CI: 0.32-0.59, p<0.0001).[1] Overall survival (OS) data were immature at this time, but a clear positive trend has been observed (stratified HR=0.64, 95% CI: 0.43-0.97, p=0.0338 (boundary of 0.0098).[1] Follow-up for OS will continue to the next

analysis. These data reinforce the potential for this inavolisib-based regimen to benefit patients with *PIK3CA*-mutated locally advanced or metastatic breast cancer.[1]

PIK3CA is one of the most commonly mutated genes in advanced or metastatic breast cancer.[6] Despite the prevalence of *PIK3CA* mutations, many patients are not tested until later in their treatment journey.[7] Early testing for *PIK3CA* prior to initiating first-line treatment helps clinicians make a personalised treatment decision.[7,8]

Data from INAVO120 are also being submitted to other global health authorities, including the European Medicines Agency.

Inavolisib is currently being investigated in three company-sponsored Phase III clinical studies (INAVO120, INAVO121, INAVO122) in *PIK3CA*-mutated locally advanced or metastatic breast cancer in various combinations.[9-11] We continue to evaluate potential clinical development programme expansion opportunities to address patient unmet needs in various tumour types across oncology.

About inavolisib

Inavolisib is an investigational, oral targeted treatment with best-in-class potential that could provide well-tolerated, durable disease control and potentially improved outcomes for people with *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer, who often have a poor prognosis and are in urgent need of new treatment options.[1-3] Inavolisib has been designed to help minimise the overall burden and toxicity of treatment and is differentiated from other PI3K inhibitors due to its high potency and specificity for the PI3K alpha isoform versus other isoforms, and unique mechanism of action that facilitates the degradation of mutated PI3K alpha.[12,13]

About the INAVO120 study

The INAVO120 study [NCT04191499] is a Phase III, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of inavolisib in combination with palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in people with *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for metastatic disease.[9]

The study included 325 patients, who were randomly assigned to either the investigational or control treatment arm.[9] The primary endpoint is progression-free survival, as assessed by investigators, defined as the time from randomisation in the clinical trial to the time when the disease progresses, or a patient dies from any cause.[9] Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.[9]

Beyond INAVO120, inavolisib is currently being investigated in two additional company-sponsored Phase III clinical studies in *PIK3CA*-mutated locally advanced or metastatic breast cancer in various combinations:

- in combination with fulvestrant versus alpelisib plus fulvestrant in HR-positive/HER2-negative breast cancer post cyclin-dependent kinase 4/6 inhibitor and endocrine combination therapy (INAVO121; NCT05646862), and
- in combination with pertuzumab plus trastuzumab for subcutaneous injection (SC) versus pertuzumab plus trastuzumab for SC and optional physician's choice of endocrine therapy as a maintenance treatment in HER2-positive disease (INAVO122; NCT05894239).[10,11]

About hormone receptor (HR)-positive breast cancer

HR-positive breast cancer is the most prevalent type of all breast cancers, accounting for approximately 70% of cases.[14,15] A defining feature of HR-positive breast cancer is that its tumour cells have receptors that attach to one or both hormones – oestrogen or progesterone – which can contribute to tumour growth. People diagnosed with HR-positive metastatic breast cancer often face the risk of disease progression and treatment side effects, creating a need for additional treatment options.[15-17] The PI3K signalling pathway is commonly dysregulated in HR-positive breast cancer, often due to activating *PIK3CA* mutations, which have been identified as a potential mechanism of intrinsic resistance to standard of care endocrine therapy in combination with cyclin-dependent kinase 4/6 inhibitors.[3]

About Roche in breast cancer

Roche has been advancing breast cancer research for more than 30 years with the goal of helping as many people with the disease as possible. Our medicines, along with companion diagnostic tests, have contributed to bringing breakthrough outcomes in HER2-positive and triple-negative breast cancers. As our understanding of breast cancer biology rapidly improves, we are working to identify new biomarkers and approaches to treatment for other subtypes of the disease, including oestrogen receptor-positive breast cancer, which is a form of hormone receptor-positive breast cancer, the most prevalent type of all breast cancers.[14]

About Roche

Founded in 1896 in Basel, Switzerland, as one of the first industrial manufacturers of branded medicines, Roche has grown into the world's largest biotechnology company and the global leader in in-vitro diagnostics. The company pursues scientific excellence to discover and develop medicines and diagnostics for improving and saving the lives of people around the world. We are a pioneer in personalised healthcare and want to further transform how healthcare is delivered to have an even greater impact. To provide the best care for each

person we partner with many stakeholders and combine our strengths in Diagnostics and Pharma with data insights from the clinical practice.

In recognising our endeavour to pursue a long-term perspective in all we do, Roche has been named one of the most sustainable companies in the pharmaceuticals industry by the Dow Jones Sustainability Indices for the fifteenth consecutive year. This distinction also reflects our efforts to improve access to healthcare together with local partners in every country we work.

Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan.

For more information, please visit www.roche.com.

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