Media & Investor Release

Roche's inavolisib combination reduces the risk of disease progression by 57% in people with advanced hormone receptor-positive, HER2-negative breast cancer with a *PIK3CA* mutation

- **Inavolisib in combination with palbociclib and fulvestrant more than doubled progression-free survival compared to palbociclib and fulvestrant alone1**
- **The inavolisib combination has the potential to address resistance to treatment and poor prognosis associated with PIK3CA mutations[2-5]**
- **These new data are being presented today in an oral presentation at the 2023 San Antonio Breast Cancer Symposium and shared with health authorities**

Basel, 8 December 2023 - Roche (SIX: RO, ROG; OTCQX: RHHBY) presented today positive results from the Phase III INAVO120 study evaluating inavolisib in combination with palbociclib (Ibrance®) and fulvestrant as a first-line treatment for people with *PIK3CA*-mutated, hormone receptor (HR)-positive, HER2-negative, endocrine-resistant, locally advanced or metastatic breast cancer.[1]

The inavolisib combination reduced the risk of disease worsening or death (progression-free survival; PFS) 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). The benefit was consistent across subgroups. 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)). Follow-up for OS will continue to the next analysis. Data available for other secondary endpoints at this analysis showed clinically meaningful increases in objective response rate, duration of response and clinical benefit rate.[1]

"The importance of the PI3K pathway has long been recognised across many cancers, and inavolisib could transform the way breast cancer is treated in patients whose tumours harbour *PIK3CA* mutations," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "The clinically meaningful benefit observed with the inavolisib combination speaks to its potential to become a new standard of care in this patient population and builds on our commitment to improve outcomes across all types of breast cancer. We look forward to bringing inavolisib to patients as soon as possible."

The inavolisib combination was well tolerated and adverse events were consistent with the known safety profiles of the individual study treatments, with no new safety signals observed.[1] The most common Grade 3-4 adverse effects (≥ 5 percent) with the inavolisib combination compared to palbociclib and fulvestrant alone were neutropenia (80.2% vs 78.4%), thrombocytopenia (14.2% vs 4.3%), anaemia (6.2% vs 1.9%), stomatitis (5.6% vs 0) and

hyperglycaemia (5.6% vs 0).[1] The discontinuation rate in the inavolisib treatment group was 6.8% compared to 0.6% for palbociclib and fulvestrant alone.[1]

Inavolisib, an investigational oral therapy, is currently being investigated in three Phase III clinical studies in people with *PIK3CA*-mutated locally advanced or metastatic breast cancer (INAVO120, INAVO121, INAVO122).[6-8] *PIK3CA* mutations are found in approximately 40% of HR-positive breast cancers and can lead to mutated PI3Kα protein, which contributes to uncontrolled tumour growth, disease progression and resistance to endocrine-based treatment. [2,3]

Data from the INAVO120 study will be submitted to health authorities with the view of bringing this potential treatment option to patients as soon as possible.

About the INAVO120 study[6]

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, 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.

The study included 325 patients, who were randomly assigned to either the investigational or control treatment arm. 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. Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.

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 hormone receptor (HR)-positive, *PIK3CA*-mutated breast cancer, a common yet often overlooked mutation found in approximately 40% of this population.[2] Inavolisib has been designed to help minimise the overall toxicity of treatment and is differentiated from other PI3K inhibitors due to its high in vitro potency and specificity for the PI3K alpha (PI3Kα) isoform inhibition, together with its unique mechanism of action, that leads to specific degradation of mutant PI3K alpha.[4,5]

Inavolisib is currently being investigated in three Roche-sponsored Phase III clinical studies in *PIK3CA*-mutated locally advanced or metastatic breast cancer:

- in combination with palbociclib and fulvestrant versus palbociclib and fulvestrant in first-line HR-positive, HER2-negative breast cancer (INAVO120; NCT04191499),[6]
- in combination with fulvestrant versus alpelisib plus fulvestrant in HR-positive/HER2-negative breast cancer post-CDK4/6 inhibitor and endocrine combination therapy (INAVO121; NCT05646862), and[7]
- in combination with pertuzumab plus trastuzumab for subcutaneous injection (SC) versus pertuzumab plus trastuzumab for SC as maintenance therapy in first-line HER2-positive breast cancer (INAVO122; NCT05894239).[8]

About hormone receptor-positive breast cancer

Hormone receptor (HR)-positive breast cancer is the most prevalent type of all breast cancers, accounting for approximately 70% of all cases.[9] 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.[10] 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.[11-13] 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 for resistance to endocrine therapy and CDK4/6 inhibitors.[14]

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.

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 thirteenth 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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