Media & Investor Release

CHMP recommends EU approval of Roche's Itovebi for *PIK3CA*-mutated, ER-positive, HER2-negative, advanced breast cancer

- **Positive recommendation based on phase III INAVO120 data showing Itovebi™ (inavolisib) in combination with palbociclib and fulvestrant more than doubled progression-free survival in the first-line setting[1]**
- **The Itovebi-based regimen also demonstrated a statistically significant and clinically meaningful benefit in overall survival (OS) in the final OS analysis**
- **Final OS data will be presented in an oral session at the 2025 American Society of Clinical Oncology Annual Meeting**

Basel, 23 May 2025 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for Itovebi™ (inavolisib), in combination with palbociclib (Ibrance®) and fulvestrant, for the treatment of adult patients with *PIK3CA*-mutated, oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment. If approved, the Itovebi-based regimen has the potential to transform the standard of care in this first-line setting, where treatments are currently limited.[1] A final decision regarding the approval is expected from the European Commission in the near future.

"The positive CHMP recommendation for the Itovebi-based regimen represents a significant step towards providing people in the EU with *PIK3CA*-mutated, ER-positive advanced breast cancer with a targeted therapy in the first-line setting," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "This recommendation is further enforced by the recent final overall survival results from the INAVO120 study, showing the regimen can meaningfully extend survival."

The presence of a *PIK3CA* mutation, found in approximately 40% of hormone receptor (HR)-positive breast cancers, can make the disease more aggressive and worsen survival outcomes.[2,3] This underscores the importance of testing for *PIK3CA* mutations prior to first-line treatment so that people with a poor prognosis can benefit from an effective, PI3K-targeted therapy as soon as possible.

The CHMP's positive opinion is based on the phase III INAVO120 results, published in the *New England Journal of Medicine* in October 2024, which showed a 57% reduction in the risk of disease worsening or death (progression-free survival [PFS]) with the Itovebi-based regimen compared with palbociclib and fulvestrant alone (15.0 months vs. 7.3 months; hazard ratio [HR]=0.43, 95% CI: 0.32-0.59, p<0.001) in the first-line setting.[1] The PFS benefit was consistent

across all pre-specified subgroups, including people whose disease had spread to three or more locations, characterised as difficult-to-treat disease.[1] The Itovebi-based regimen was well tolerated, with no new safety signals observed.[1]

Positive topline results from the final overall survival (OS) analysis, announced in January 2025, showed a statistically significant and clinically meaningful OS benefit with the Itovebi-based regimen. OS data were immature at the time of primary analysis, but a clear positive trend was observed (stratified HR=0.64, 95% CI: 0.43-0.97, p=0.0338 (boundary of 0.0098)).[1] The full results from the OS analysis will be presented in an oral session at the 2025 American Society of Clinical Oncology Annual Meeting.

The Itovebi-based regimen is approved for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer in the United States, Switzerland, Canada, Australia, United Arab Emirates and China, with data from INAVO120 under review with other global health authorities.

Beyond INAVO120, Itovebi is currently being investigated in three company-sponsored phase III studies (INAVO121, INAVO122, INAVO123), all in *PIK3CA*-mutated, locally advanced or metastatic breast cancer in various combinations.[4-7] We are exploring additional studies in breast cancer and other tumour types with the hope of providing the benefit of this targeted therapy to more people with *PIK3CA* mutations.

About Itovebi ™ (inavolisib)

Itovebi is an oral, targeted treatment that has been shown to provide well-tolerated and durable disease control in people with advanced *PIK3CA*-mutated, hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer, who often have a poor prognosis and are in urgent need of new treatment options.[1-3] Itovebi 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.[8,9]

About the INAVO120 study

The INAVO120 study [NCT04191499] is a phase III, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of Itovebi™ (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.[4]

The study included 325 patients, who were randomly assigned to either the investigational or control treatment arm.[4] 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.[4] Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.[4]

Beyond INAVO120, Itovebi is currently being investigated in three additional company-sponsored phase III clinical studies in *PIK3CA*-mutated, locally advanced or metastatic breast cancer in various combinations:[5-7]

- in combination with fulvestrant versus alpelisib plus fulvestrant in HR-positive/HER2-negative breast cancer post cyclin-dependent kinase 4/6 (CDK4/6) inhibitor and endocrine combination therapy (INAVO121; NCT05646862).
- 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).
- in combination with a CDK4/6 inhibitor and letrozole versus placebo plus a CDK4/6 inhibitor and letrozole in the first-line setting in *PIK3CA*-mutated HR-positive/HER2-negative, endocrine-sensitive breast cancer (INAVO123; NCT06790693).

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.[10,11] 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.[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 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 human epidermal growth factor 2-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.[10,11]

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.

For over 125 years, sustainability has been an integral part of Roche's business. As a science-driven company, our greatest contribution to society is developing innovative medicines and diagnostics that help people live healthier lives. Roche is committed to the Science Based Targets initiative and the Sustainable Markets Initiative to achieve net zero by 2045.

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

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