Media & Investor Release

European Commission approves Roche's Itovebi for people with ER-positive, HER2-negative, advanced breast cancer with a PIK3CA mutation

- **Approval based on INAVO120 data showing the Itovebi™ (inavolisib)-based regimen more than doubled progression-free survival compared with palbociclib and fulvestrant alone[1]**
- **Up to 40% of ER-positive breast cancers have a PIK3CA mutation and are associated with poor prognosis; this approval helps address an urgent unmet need[2-4]**
- **Itovebi is the first PI3K-targeted therapy to significantly extend survival, reinforcing the need for biomarker testing at diagnosis[5]**

Basel, 23 July 2025 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that the European Commission has approved 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.

"Itovebi is the first treatment of its kind to improve survival outcomes for those living with *PIK3CA*-mutated, ER-positive advanced breast cancer," said Levi Garraway, MD, PhD, Roche's Chief Medical Officer and Head of Global Product Development. "Therefore, the Itovebi-based regimen may help address an important unmet need for people with this subtype of breast cancer."

The approval is based on results from the phase III INAVO120 trial, 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 and the Itovebi-based regimen was well tolerated, with no new safety signals observed.[1]

These results were reinforced by the INAVO120 final overall survival analysis that showed the Itovebi-based regimen reduced the risk of death by 33% (stratified HR=0.67; 95% CI: 0.48–0.94, p-value=0.0190 [boundary=0.0469]).[5] Additionally, the treatment regimen substantially delayed the time to chemotherapy by approximately two years compared with palbociclib and fulvestrant alone (stratified HR=0.43; 95% CI: 0.30-0.60).[5] These data were presented at the

2025 American Society of Clinical Oncology Annual Meeting and published in the *New England Journal of Medicine* in May 2025.

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.[6-8] 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 *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer, who often have a poor prognosis and are in urgent need of new treatment options.[1,4,9] 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.[10,11]

In addition to the European Commission's approval, the Itovebi-based regimen is also 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, China and Taiwan, with data from INAVO120 under review with several other global health authorities.

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.[12]

The study included 325 patients, who were randomly assigned to either the investigational or control treatment arm.[12] 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.[12] Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.[12]

Beyond INAVO120, Itovebi is currently being investigated in three 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 (CDK4/6) inhibitor and endocrine combination therapy (INAVO121; NCT05646862).[6]
- 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).[7]
- in combination with 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).[8]

About oestrogen receptor (ER)-positive breast cancer

ER-positive is a subtype of hormone receptor (HR)-positive breast cancer, the most prevalent type of all breast cancers, accounting for approximately 70% of cases.[13,14] A defining feature of ER-positive breast cancer is that its tumour cells have receptors that attach to oestrogen, which can contribute to tumour growth.[15]

People diagnosed with ER-positive and HR-positive metastatic breast cancer often face the risk of disease progression and treatment side effects, creating a need for additional treatment options.[14,16,17] 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.[9]

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.[13,14]

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.

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.

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

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