Media Release

New England Journal of Medicine publishes landmark phase III results for Roche's Itovebi, showing more than doubling of progression-free survival in certain type of HR-positive advanced breast cancer

- **Itovebi™ (inavolisib)-based regimen demonstrated a statistically significant and clinically meaningful benefit, reducing the risk of disease worsening or death by 57% compared with palbociclib and fulvestrant alone in the INAVO120 study[1]**
- **The U.S. FDA recently approved the Itovebi-based regimen as a first-line treatment for people with HR-positive, HER2-negative breast cancer with a *PIK3CA* mutation, one of the most commonly mutated genes in HR-positive disease[2]**

Basel, 31 October 2024 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today that a detailed analysis of the positive phase III INAVO120 results, evaluating Itovebi™ (inavolisib) in combination with palbociclib (Ibrance®) and fulvestrant were published in the *New England Journal of Medicine*.[1] The United States Food and Drug Administration (FDA) recently approved Itovebi in combination with palbociclib and fulvestrant, for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. Data from INAVO120 are also being used for filing submissions to other global health authorities, including the European Medicines Agency.

"With a doubling of progression-free survival and consistent benefits in people whose disease had spread to multiple challenging-to-treat locations, including the liver and lungs, these INAVO120 data are significant for patients," said Komal Jhaveri, M.D., section head for the endocrine therapy research portfolio and clinical director of the early drug development service at Memorial Sloan Kettering Cancer Center and one of the principal investigators of the INAVO120 study. "I'm confident this Itovebi-based regimen could become a new first-line standard of care for this patient population with one of the most commonly mutated genes in metastatic breast cancer, associated with a poor prognosis."

Results showed the Itovebi-based regimen 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<0.001).[1] PFS benefit was consistent across all pre-specified subgroups, including people whose disease had spread to three or more locations, which is characterised as difficult-to-treat disease.[1] Overall survival (OS) data were immature at the time of analysis, but a clear positive trend has been observed (stratified HR=0.64, 95% CI: 0.43-0.97, p=0.03 [boundary of 0.0098]).[1] Follow-up for OS will continue to the next analysis.[1]

F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Group Communications Roche Group Media Relations
Phone +41 61 688 88 88 www.roche.com

"Publication of these phase III results in the *New England Journal of Medicine* further highlights the transformative potential of the Itovebi-based regimen," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "This new treatment exemplifies our ambition to target specific disease pathways more effectively and improve outcomes in people with breast cancer, while also emphasising the importance of comprehensive testing for mutations like *PIK3CA* at the time of diagnosis."

The *PIK3CA* mutation is found in approximately 40% of HR-positive metastatic breast cancers and is associated with a poor prognosis.[2,3] Historically, the use of PI3K targeted therapy in the first-line advanced setting has been limited and therefore testing for *PIK3CA* mutations is not common at the time of diagnosis.[4] Early biomarker testing with an FDA-approved test, such as Foundation Medicine's FoundationOne®Liquid CDx, before first-line treatment is crucial to help identify people who may benefit from targeted therapy, such as Itovebi.[4,5]

Itovebi 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.[6-8] We are exploring additional studies in breast cancer and other tumour types with the hope of bringing the benefit of this targeted therapy to more people with *PIK3CA* mutations and addressing patient unmet needs.

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.[6]

The study included 325 patients, who were randomly assigned to either the investigational or control treatment arm.[6] 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.[6] Secondary endpoints include overall survival, objective response rate, and clinical benefit rate.[6]

Beyond INAVO120, Itovebi 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:[7,8]

- 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).

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.[9,10] 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.[10-12] 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.[9,10]

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.

References

[1] Turner NC, et al. Inavolisib-Based Therapy in PIK3CA-Mutated Advanced Breast Cancer. NEJM. 2024;391(17).
[2] Fillbrunn M, et al. *PIK3CA* mutation status, progression and survival in advanced HR+/HER2- breast cancer: a meta-analysis of published clinical trials. BMC Cancer. 2022;22:1002.
[3] Anderson E, et al. A Systematic Review of the Prevalence and Diagnostic Workup of PIK3CA Mutations in HR+/HER2– Metastatic Breast Cancer. Int J Breast Cancer. 2020;2020:3759179.
[4] Princic N, et al. Abstract P1-18-18: PIK3CA mutation testing prevalence among post-menopausal (PM) women with hormone receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (mBC) using real world data. Cancer Res. 2020;80(4):P1-18-18.
[5] Wales Cancer Network. PIK3CA-mutated breast cancer clinical guidance document [Internet; cited 2024 October]. Available from: https://executive.nhs.wales/functions/networks-and-planning/cancer/wcn-documents/mutated-breast-cancer-clinical-guidance-document//.
[6] ClinicalTrials.gov. A Study Evaluating the Efficacy and Safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With *PIK3CA*-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer (INAVO120) [Internet; cited 2024 October]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04191499.
[7] ClinicalTrials.gov. A Study Evaluating the Efficacy and Safety of Inavolisib Plus Fulvestrant Compared With Alpelisib Plus Fulvestrant in Participants With HR-Positive, HER2-Negative, *PIK3CA* Mutated, Locally Advanced or Metastatic Breast Cancer Post CDK4/6i and Endocrine Combination Therapy (INAVO121) [Internet; cited 2024 October]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05646862.
[8] ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Inavolisib in Combination With Phesgo Versus Placebo in Combination With Phesgo in Participants With *PIK3CA*-Mutated HER2-Positive Locally Advanced or Metastatic Breast Cancer [Internet; cited 2024 October]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05894239.
[9] National Cancer Institute: Surveillance, Epidemiology and Ends Result Program. Cancer Stat Facts: Female Breast Cancer Subtypes [Internet; cited 2024 October]. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.
[10] Lim E, et al. The natural history of hormone receptor-positive breast cancer. Oncology (Williston Park). 2012;26(8):688-94,696.
[11] Tomas R and Barrios CH. Optimal management of hormone receptor positive metastatic breast cancer in 2016. Ther Adv Med Oncol. 2015;7(6):304-20.
[12] Galipeau N, et al. Understanding key symptoms, side effects, and impacts of HR+/HER- advanced breast cancer: qualitative study findings. J Patient-Rep Outcomes. 2019;3(1):10.

Dr. Jhaveri has financial interests related to Roche and Genentech.

F. Hoffmann-La Roche Ltd 4070 Basel Switzerland
Group Communications Roche Group Media Relations
Phone +41 61 688 88 88 www.roche.com

Roche Global Media Relations
Phone: +41 61 688 8888 / e-mail: media.relations@roche.com

Hans Trees, PhD
Phone: +41 79 407 72 58

Nathalie Altermatt
Phone: +41 79 771 05 25

Simon Goldsborough
Phone: +44 797 32 72 915

Nina Mählitz
Phone: +41 79 327 54 74

Yvette Petillon
Phone: +41 79 961 92 50

Sileia Urech
Phone: +41 79 935 81 48

Lorena Corfas
Phone: +41 79 568 24 95

Karsten Kleine
Phone: +41 79 461 86 83

Kirti Pandey
Phone: +49 172 6367262

Dr Rebekka Schnell
Phone: +41 79 205 27 03