Media & Investor Release

Roche announces positive Phase III results for inavolisib combination in people with advanced hormone receptor-positive, HER2-negative breast cancer with a *PIK3CA* mutation

- **Phase III (INAVO120) results show that inavolisib in combination with palbociclib and fulvestrant significantly improved progression-free survival in the first-line setting**
- ***PIK3CA* mutations, found in approximately 40% of HR-positive breast cancers, are linked to tumour growth, disease progression, and treatment resistance[1,2]**
- **Data will be shared with health authorities and presented at an upcoming medical meeting**

Basel, 5 December 2023 - Roche (SIX: RO, ROG; OTCQX: RHHBY) announced today positive results from the Phase III INAVO120 study of the investigational therapy, inavolisib, in combination with palbociclib (Ibrance®) and fulvestrant as a potential first-line treatment option for people with *PIK3CA*-mutated, hormone receptor (HR)-positive, HER2-negative, endocrine-resistant, locally advanced or metastatic breast cancer. The study met its primary endpoint of progression-free survival (PFS), demonstrating a statistically significant and clinically meaningful improvement compared to palbociclib and fulvestrant alone. Overall survival data were immature at this time, but a clear positive trend has been observed. Follow-up will continue to the next analysis.

"These pivotal study results for this inavolisib combination could represent a transformative medical advance for people with *PIK3CA*-mutated HR-positive breast cancer," said Levi Garraway, M.D., Ph.D., Roche's Chief Medical Officer and Head of Global Product Development. "We look forward to expanding our portfolio of breast cancer medicines into the HR-positive space and bringing this potentially best-in-class new treatment option to patients as quickly 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.

Inavolisib is an oral therapy with high in vitro potency and selectivity for PI3Kα inhibition and the ability to specifically trigger the breakdown of mutant PI3Kα protein. With this unique dual mechanism of action, inavolisib may provide well-tolerated, durable disease control and potentially improved outcomes for people with HR-positive/HER2-negative, *PIK3CA*-mutated advanced breast cancer. *PIK3CA* mutations can lead to mutated PI3Kα protein which contributes to uncontrolled tumour growth, disease progression and resistance to endocrine-based treatment.[3,4]

Inavolisib is currently being investigated in three Phase III clinical studies in people with *PIK3CA*-mutated metastatic breast cancer (INAVO120, INAVO121, INAVO122) in various combinations.

About the INAVO120 study[5]

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.[1] 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.[3,4]

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 vs. palbociclib and fulvestrant in first-line HR-positive HER2-negative breast cancer (INAVO120),[5]
- in combination with fulvestrant vs. alpelisib plus fulvestrant in HR-positive HER2-negative breast cancer post-CDK4/6 inhibitor and endocrine combination therapy (INAVO121),[6] and
- in combination with pertuzumab plus trastuzumab for subcutaneous injection (Phesgo®) vs. Phesgo as maintenance therapy in 1L HER2-positive breast cancer (INAVO122)[7]

About hormone receptor-positive breast cancer

Hormone receptor (HR)-positive breast cancer is the most prevalent type of all breast cancers.[8] A defining feature of HR-positive breast cancer is that its tumour cells have receptors that attach to one or both hormones – estrogen or progesterone – which can contribute to tumour growth.[9] 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 for resistance to endocrine therapy and CDK4/6 inhibitors.[13]

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 estrogen 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.

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

References

[1] André F, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-40

[2] He Y, et al. Targeting PI3K/Akt signal transduction for cancer therapy. Signals Transduction and Targeted Therapy. 2021; 6: 425

[3] Juric et al. A phase I/Ib study of inavolisib (GDC-0077) in combination with fulvestrant in patients (pts) with PIK3CA-mutated hormone receptor-positive/HER2-negative (HR+/HER2–) metastatic breast cancer. Presented at San Antonio Breast Cancer Symposium, 2020 December 7-10; San Antonio, USA. Abstract #P5-17-05

[4] Hong R., et al. GDC-0077 is a selective PI3K alpha inhibitor that demonstrates robust efficacy in PIK3CA mutant breast cancer models as a single agent and in combination with standard of care therapies. Cancer Res. 2018;78(4):4-14. https://doi.org/10.1158/1538-7445.SABCS17-PD4-14

[5] 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 2023 December] Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04191499

[6] 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 2023 December] Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05646862

[7] 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 2023 December] Available from: https://clinicaltrials.gov/study/NCT05894239?term=WO44263&rank=1

[8] National Cancer Institute: Surveillance, Epidemiology and Ends Result Program. Cancer Stat Facts: Female Breast Cancer Subtypes. [Internet; cited 2023 December] Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html

[9] Lim E., et al. The natural history of hormone receptor-positive breast cancer. Oncology (Williston Park). 2012;26(8):688-94,696.

[10] 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. doi: 10.1186/s41687-019-0098-1

[11] Buonomoa B. and Peccatori FA. Fertility preservation in endocrine responsive breast cancer: data and prejudices. *ecancer*. 2020;14:1157. doi: 10.3332/ecancer.2020.1157

[12] 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. doi: 10.1177/1758834015608993

[13] Schwartzberg LS. and Vidal GA. Targeting PIK3CA Alterations in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2 Negative Advanced Breast Cancer: New Therapeutic Approaches and Practical Considerations. *Clin Breast Cancer*. 2020;20(4):e439-e449. doi: 10.1016/j.clbc.2020.02.002

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

Karsten Kleine
Phone: +41 79 461 86 83

Nina Mählitz
Phone: +41 79 327 54 74

Kirti Pandey
Phone: +49 172 6367262

Dr. Rebekka Schnell
Phone: +41 79 205 27 03

Sileia Urech
Phone: +41 79 935 81 48

Roche Investor Relations

Dr. Bruno Eschli
Phone: +41 61 68-75284
e-mail: bruno.eschli@roche.com

Dr. Sabine Borngräber
Phone: +41 61 68-88027
e-mail: sabine.borngraeber@roche.com

Dr. Birgit Masjost
Phone: +41 61 68-84814
e-mail: birgit.masjost@roche.com

Dr. Gerard Tobin
Phone: +41 61 68-72942
e-mail: gerard.tobin@roche.com

Investor Relations North America

Loren Kalm
Phone: +1 650 225 3217
e-mail: kalm.loren@gene.com