Report ITOVEBI® - Inavolisib

Product & Mechanism of action	Authorized indications Licensing status	Essential therapeutic features	NHS impact
Substance: Inavolisib **Brand Name:** Itovebi **Originator/licensee:** Roche Registration GmbH **Classification:** NCE **ATC code:** Not yet assigned **Orphan Status:** **Eu:** No **Us:** No **Mechanism of action:** Inavolisib is a PI3K inhibitor. It inhibits the activity of downstream targets in the PI3K signalling pathway, including Akt, resulting in reduced cellular proliferation and apoptosis in PIK3CA-mutated breast cancer cell lines [1].	**Authorized Indication:** **EMA**: Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with PIK3CA-mutated, ER-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or within 12 months of completing adjuvant endocrine treatment [1]. **FDA:** Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy [2]. **Route of administration:** OS **Licensing status** **EU CHMP P.O. date:** 22/05/2025 **FDA M.A. date:** 10/10/2024 **EU Speed Approval Pathway:** No **FDA Speed Approval Pathway:** Yes --- **ABBREVIATIONS:** **1L:** first-line **AE**: Adverse Event **CHMP**: Committee for Medicinal Products for Human Use **CI**: Confidential Interval **ECOG**: Eastern Cooperative Oncology Group **ER:** Oestrogen receptor **HER**: human epidermal growth factor receptor **HR:** hormone receptor **HR**: Hazard Ratio **IM:** intramuscularly **M.A.:** Marketing Authorization **OS**: Oral administration **PFS**: Progression-Free Survival **PI**: Proteasome inhibitor **PI3K**: Phosphatidylinositol 3-kinase **P.O.**: Positive Opinion **PS**: Performance Status **Pts**: Patients **RECIST**: Response Evaluation Criteria in Solid Tumors **SAE**: Serious adverse events **TRAE**: Treatment related AEs **WHO**: World Health Organization	**Summary of clinical EFFICACY:** **INAVO120 (NCT04191499)** is a double-blind, randomized, placebo-controlled, phase III trial comparing 1L inavolisib plus palbociclib–fulvestrant with placebo plus palbociclib–fulvestrant in pts. with PIK3CA-mutated, HR–positive, HER2-negative locally advanced or metastatic breast cancer, who had had disease recurrence during or within 12 months after the completion of adjuvant endocrine therapy. Eligible pts. were premenopausal, perimenopausal, or postmenopausal women or men with PIK3CA-mutated, HR–positive, HER2-negative locally advanced or metastatic breast cancer. Pts. had to have progression during or within 12 months of completing adjuvant endocrine therapy and have not received prior systemic therapy for locally advanced or metastatic disease. Pts. with de novo metastatic breast cancer were excluded. Pts. (n=325) were randomly assigned in a 1:1 ratio to receive inavolisib (n=161) or placebo (n=164). Inavolisib was administered orally at a dose of 9 mg once daily on days 1 to 28 of each 28-day cycle. Each treatment was given in combination with palbociclib (125 mg OS on days 1 to 21) and fulvestrat (500 mg IM, on days 1, 15, and 29, then every 28 days thereafter). Randomization was stratified according to visceral disease, resistance to endocrine therapy and region. The primary end point was PFS as assessed by the investigator according to RECIST v. 1.1 in the full analysis population, which included all the pts., who had undergone randomization. After a median follow-up of 21.3 months in the inavolisib group and 21.5 months in the placebo group, the median PFS was 15.0 (11.3–20.5) months and 7.3 months (5.6–9.3), respectively (stratified HR for disease progression or death, 0.43; 95% CI, 0.32 to 0.59; P<0.001). The probability of PFS was 82.9% at six months, 55.9% at 12 months, and 46.2% at 18 months in the inavolisib group and 55.9%, 32.6%, and 21.1%, respectively, in the placebo group. **Summary of clinical SAFETY:** Safety analyses were conducted in all the pts., who had received at least one dose of any trial agent. At least one AE occurred in 98.8% of the pts. in the inavolisib group and in 100% of those in the placebo group. Grade ≥3 AEs were reported in 88.3% of the pts., who received inavolisib and in 82.1% of those, who received placebo. Neutropenia of grade 3-4 in severity occurred in 80.2% and 78.4% of pts., respectively; stomatitis or mucosal inflammation, in 5.6% and 0%; hyperglycemia, in 5.6% and 0%; and diarrhoea, in 3.7% and 0%. No grade 3-4 rash was reported. Death occurred in 3.7% of the pts., who received inavolisib and in 1.2% of those who received placebo. **Ongoing studies:** ● ***For the same indication:*** Yes ● ***For other indications:*** No **Discontinued studies (for the same indication):** No --- **References:** [1] https://www.ema.europa.eu/en/medicines/human/EPAR/itovebi [2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219249s000lbl.pdf [3] https://www.nejm.org/doi/full/10.1056/NEJMoa2404625 [4] https://pmc.ncbi.nlm.nih.gov/articles/PMC8428369/ [5] https://www.aiom.it/wp-content/uploads/2025/01/2024_NDC_web-def.pdf [6] https://pmc.ncbi.nlm.nih.gov/articles/PMC8188964/ [7] https://gecoopendata.registrotumoriveneto.it/incidenza.php?sede=mammella&codSede=C50-C50.9	**Cost of therapy:** The price is not available yet. **Epidemiology:** Breast cancer is the most frequently diagnosed cancer in women worldwide [4]. In Italy, approximately 53,686 new diagnoses were estimated in 2024. In the 6-7% of the cases, breast cancer is already metastatic when diagnosed [5]. HR-positive and HER2-negative breast cancers account for at least 60% to 70% of all breast cancer cases [6]. In the Veneto Region, breast cancer accounts for 16.3% of cancer diagnoses [7]. ------- **POSSIBLE PLACE IN THERAPY**: For pts. with ER-positive, HER2-negative metastatic breast cancer, the 1L is represented by CDK4/6 inhibitors combined with endocrine therapy. CDK4/6 inhibitors are effective in de novo or recurrent MBC, in cases of primary or secondary endocrine resistance, in postmenopausal or premenopausal women. In pts., who relapse determination of somatic PIK3CA and oestrogen receptor 1 mutations are recommended. Available options for second line therapy include fulvestrant-alpelisib for PIK3CA mutated tumours. Inavolisib could represent another option for these pts. **OTHER INDICATIONS IN DEVELOPMENT: -** **SAME INDICATION IN EARLIER LINE(S) OF TREATMENT**: - **OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:** Ribociclib and Letrozole for pts. with PIK3CA mutation (NCT03439046). *Service reorganization: No *Possible off label use: Yes