Overall survival in patients with hormone receptor-positive, HER2-negative advanced breast cancer treated in a phase 1b trial evaluating gedatolisib in combination with palbociclib and endocrine therapy

The results of the dose-expansion portion of our multicentre, open-label, phase 1b study evaluating the combination of gedatolisib, a pan-PI3K–mTORC1/2 inhibitor, with palbociclib and endocrine therapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer, were previously reported.[1] In brief, 103 female participants aged 18 years and older were enrolled across four dose expansion groups (group A, n=31; group B, n=13; group C, n=32; and group D, n=27). An additional 35 female participants were enrolled in initial dose-escalation groups A and B. In the dose-expansion groups, gedatolisib, palbociclib, and endocrine therapy led to an objective response in 23 (85·2%; 90% CI 69·2–94·8) of 27 evaluable first-line participants (group A). In the second-line and higher setting (groups B–D), an objective response was observed in eight (61·5%; 35·5–83·4) of 13 evaluable participants in group B, seven (25·0%; 12·4–41·9) of 28 evaluable participants in group C, and 15 (55·6%; 38·2–72·0) of 27 evaluable participants in group D.[1] Each group included individuals with both wild-type and mutated *PIK3CA* tumours. The most common grade 3–4 treatment-related adverse events were neutropenia (65 [63%] of 103 participants), stomatitis (28 [27%]), and rash (21 [20%]), with grade 3–4 hyperglycaemia occurring in six (6%) participants.[1] Subsequent studies (VIKTORIA-1, NCT05501886; and VIKTORIA-2, NCT06757634) are including steroidal mouth wash and non-sedating antihistamine prophylaxis to prevent or ameliorate stomatitis and rash, respectively. Treatment-related serious adverse events occurred in 23 (22%) participants, with no treatment-related deaths.[1]

Post-hoc overall survival analyses were done in the patient populations who match the eligibility criteria for the VIKTORIA-1 trial (ie, patients in the dose-escalation group D) or VIKTORIA-2 trial (ie, patients in group A, whether in the dose-escalation or dose-expansion portions). Since our previous publication,[1] the overall survival data have matured in these patients who received the combination of gedatolisib, palbociclib, and endocrine therapy in both the first-line setting (group A; n=11 from the dose-escalation cohort and n=30 from the dose-expansion cohort) and second-line or higher setting following previous therapy with a CDK4/6 inhibitor (group D).[2] Patients in group A who received gedatolisib once weekly plus palbociclib and letrozole as first-line treatment (n=41) had a median overall survival of 77·3 months (95% CI 50·3–89·0). Patients in group D who received gedatolisib once weekly (3 weeks on, 1 week off) plus palbociclib and fulvestrant as second-line or higher treatment following previous therapy with a CDK4/6 inhibitor (n=27) had a median overall survival of 33·9 months (95% CI 17·8–52·4).

These encouraging survival outcomes support further evaluation of this combination therapy in patients with hormone receptor-positive, HER2-negative advanced breast cancer. VIKTORIA-1 is an ongoing randomised phase 3 study evaluating gedatolisib plus fulvestrant with or without palbociclib in patients who previously received a CDK4/6 inhibitor. VIKTORIA-2, which is a randomised phase 3 study evaluating gedatolisib plus fulvestrant and a CDK4/6 inhibitor in treatment-naive patients, will begin enrolment in 2025.

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1 Layman RM, Han HS, Rugo HS, et al. Gedatolisib in combination with palbociclib and endocrine therapy in women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the dose expansion groups of an open-label, phase 1b study. *Lancet Oncol* 2024; **25:** 474–87.

2 Layman RM, Rugo HS, Wesolowski R, et al. Overall survival in patients with HR+/HER2– advanced breast cancer treated in a phase 1b trial evaluating gedatolisib in combination with palbociclib and endocrine therapy. San Antonio Breast Cancer Symposium; Dec 10–13, 2024 (abstr SESS-1510).