Comparative Outcomes in Breast Cancer Patients Treated with Alpelisib With and Without Type 2 Diabetes Mellitus: A Real-World Analysis from the TriNetX Network

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Background

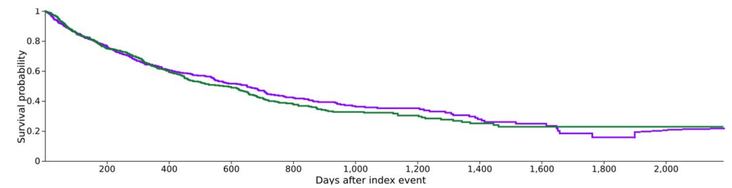
- Alpelisib, a PI3Kα-specific inhibitor, is approved for use in hormone receptor-positive (HR+), HER2-negative advanced breast cancer withPIK3CA mutations.
- However, its known metabolic side effects, particularly hyperglycemia, raise concerns for patients with pre-existing Type 2 Diabetes Mellitus (T2DM).
- This study aimed to evaluate real-world treatment patterns and clinical outcomes in breast cancer patients treated with Alpelisib, stratifiedby

Objectives

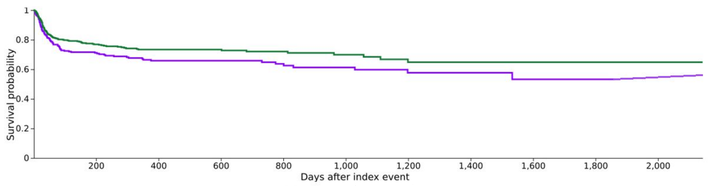
- To evaluate real-world treatment patterns and clinical outcomes in breast cancer patients treated with Alpelisib, stratified by the presence or absence of Type 2 Diabetes Mellitus

Methods

- We conducted a retrospective analysis using the TriNetX US Collaborative Network. Two cohorts were identified:
- (1) patients with breast cancerand T2DM treated with Alpelisib (n=655), and
- (2) patients without diabetes treated with Alpelisib (n=1,102).
- Treatment pathways were analyzed separately for each cohort.
- A comparative outcomes analysis was performed using 1:1 propensity score matching (503 patients per cohort) to balance baseline characteristics.
- Kaplan-Meier survival analysis was used to evaluate time-to-event outcomes. Patients with prior outcomes were excluded from each respective analysis.



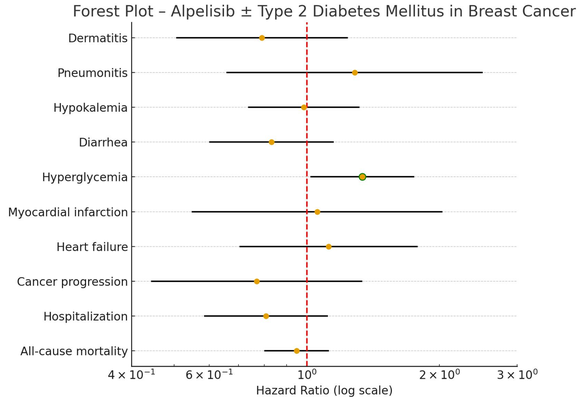
All-cause Mortality

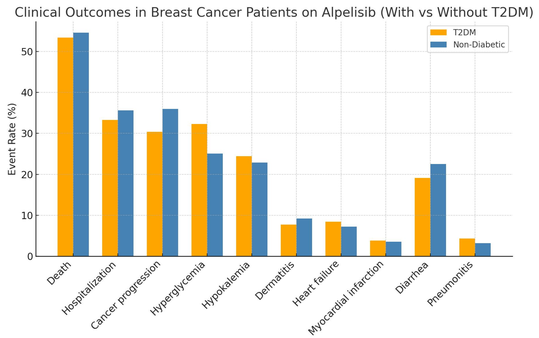


Hyperglycemia

Results

- After matching, each cohort included 503 patients. Mean follow-up was 562.2 days (SD 484.1) for the T2DM group and 525.1 days (SD 459.7) for the non-diabetic group.
- 268 of 502 (53.4%) T2DM patients and 274 of 502 (54.6%) non-diabetic patients died during follow-up (median survival: 651 vs. 575 days; HR 0.948, 95% CI: 0.801-1.122, p=0.747).
- For hospitalization, 67 of 201 (33.3%) T2DM patients and 83 of233 (35.6%) non-diabetics were hospitalized (median time: 1,178 vs. 1,009 days; HR 0.808, 95% CI: 0.584-1.116, p=0.631).
- Cancer progression occurred in 24 of 79 (30.4%) T2DM patients and 27 of 75 (36.0%) non-diabetics (median time: 799 vs. 765 days; HR 0.769, 95% CI: 0.443-1.337, p=0.381).





Results (continued)

- T2DM patients had a higher risk of hyperglycemia (95 of 294 [32.3%] vs. 116 of 463 [25.1%]; HR 1.336, 95% CI: 1.018-1.752,p=0.036). For hypokalemia, rates were similar (HR 0.985, 95% CI: 0.735-1.318, p=0.444)
- Dermatitis was seen in 35 of 453 (7.7%) T2DM patients vs. 42 of 455 (9.2%) non-diabetics (HR 0.791, 95% CI: 0.505-1.239, p=0.249).
- Heart failure rates were similar (HR 1.120, 95% CI: 0.703-1.785, p=0.282). Myocardial infarction rates were 19 of 494 (3.8%) T2DM and 17 of 484 (3.5%) non-diabetics (HR 1.055, 95% CI: 0.548-2.031, p=0.593).
- Diarrhea occurred in 62 of 324 (19.1%) T2DM and 87 of 386 (22.5%) non-diabetics (HR 0.831, 95% CI: 0.600-1.152, p=0.283).
- Pneumonitis developed in 20 of 468 (4.3%) T2DM vs. 15 of 467 (3.2%) non-diabetics (HR 1.284, 95% CI:0.657-2.509, p=0.806).
- Treatment pathway analysis revealed that breast cancer patients with T2DM were seven times more likely to discontinue therapy after Alpelisib compared to non-diabetics, despite similar follow-up durations.

Conclusions

- In this large real-world cohort, breast cancer patients with T2DM treated with Alpelisib experienced comparable survival and cancer progression outcomes to those without diabetes.
- However, they were at significantly higher risk for hyperglycemia and had less complete treatment documentation, potentially reflecting clinical complexity or data capture limitations.
- These findings underscore the importance of proactive metabolic monitoring and individualized care strategies for patients with comorbid diabetes receiving Alpelisib.
- Further research is warranted to optimize treatmentsequencing and mitigate toxicity in this high-risk population.

Limitations

- Retrospective real-world design may introduce bias and unmeasured confounders.
- Some treatment and follow-up data may be incomplete in electronic health records.
- Diabetes status was identified through ICD codes, which may cause misclassification.
- Low event numbers for some outcomes limited statistical power.
- Residual confounding may persist despite matching.
- Biological correlates of hyperglycemia were not assessed.

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