**Bridging Oncology and Endocrinology – Managing Metabolic Toxicity in Targeted Cancer Therapy: A Case Series**

**Background**

*PIK3CA* mutations, found in ~40% of metastatic breast cancer cases, activate the phosphatidylinositol 3-kinase (PI3K) pathway involved in cell growth and survival. Inhibitors like alpelisib improve outcomes but are limited by on-target toxicity, notably hyperinsulinaemic hyperglycaemia. While metformin is first-line therapy, shared gastrointestinal side effects such as diarrhoea can limit its use. No standardised guidelines exist for managing hyperglycaemia when metformin is contraindicated or ineffective.

**Method**

We describe three patients with PIK3CA-mutated metastatic breast cancer who developed alpelisib-induced hyperglycaemia, despite near-normal baseline glycaemia. We explore their shared features, key differences in presentation, and the tailored approaches required to achieve euglycaemia.

**Results**

The onset of hyperglycaemia varied between patients, ranging from 4 weeks to 33 months after initiation of PIK3CA inhibitor therapy. One patient required multiple glucose-lowering agents, including empagliflozin, linagliptin, and gliclazide in addition to metformin. On commencement of an SGLT2 inhibitor, all patients achieved adequate glycaemic control and were able to maintain alpelisib dose intensity. Based on this clinical experience and a review of the literature, we propose a practical management algorithm for PI3K inhibitor–induced hyperglycaemia (Figure 1).

**Conclusion**

Effective management of alpelisib-induced hyperglycaemia requires endocrine strategies that avoid hyperinsulinaemia, which may otherwise diminish the drug’s anti-oncogenic effect. While metformin remains the preferred first-line agent, SGLT2 inhibitors are promising adjunctive second-line options. Given the high disease burden in this population, pragmatic strategies are essential to optimise cancer outcomes and preserve quality of life.

**Figure 1. Proposed baseline assessment and management of PI3K inhibitor induced hyperglycaemia**

