Optimizing Treatment Outcome in Patients Treated with Piqray (Alpelisib)

GLOBAL SPEAKER

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EXPERT PANELIST

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Prof Lee Soo Chin chaired a "Meet-The-Experts round table discussion" on the optimization of treatment outcomes with Piqray (alpelisib) at Regent Hotel Singapore on 13 October 2022, along with guest speakers Joyce O'Shaughnessy from the USA and Dr Yap Yoon Sim from Singapore. Dr Wong Seng Weng and Dr Samuel Ow joined them as expert panellists.

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Multidisciplinary Approach to Optimize Treatment Outcomes in Patients Treated with Alpelisib by Dr Joyce O'Shaughnessy

Dr Joyce presented the common adverse events associated with alpelisib which included hyperglycaemia, diarrhoea, nausea, decreased appetite and maculopapular rash as well as the recommendations published by Rugo H et al (2022) on managing these adverse events, particularly diarrhoea, hyperglycaemia, and rash related to alpelisib[1]

Alpelisib-induced Hyperglycaemia

Hyperglycaemia is an expected "off-target" effect of PI3K inhibitor as PI3K plays a key role in glucose homeostasis

INCIDENCE[2]

65% of patients — treated with alpelisib plus fulvestrant experienced any-grade hyperglycaemia

37% of patients — treated with alpelisib plus fulvestrant had grade ≥3 hyperglycaemia

RATE OF TREATMENT DISCONTINUATION[2]

18 patients (6.3%) — treated with alpelisib plus fulvestrant discontinued treatment due to hyperglycaemia

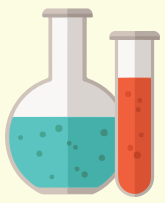
TIME-TO-ONSET OF GRADE ≥2 HYPERGLYCAEMIA[2]

Median

15 days

after starting alpelisib

RISK FACTORS FOR HYPERGLYCAEMIA



Laboratory tests

- FPG ≥100mg/dL (5.6 mmol/L) or HBA1c ≥5.7% (39 mmol/mol)*
- HDL-C <35mg/dL (0.9 mmol/L) and/or triglycerides >250mg/dL (2.82 mmol/L)
- Optional: Fructosamine 230 µM or GA ≥13.35%

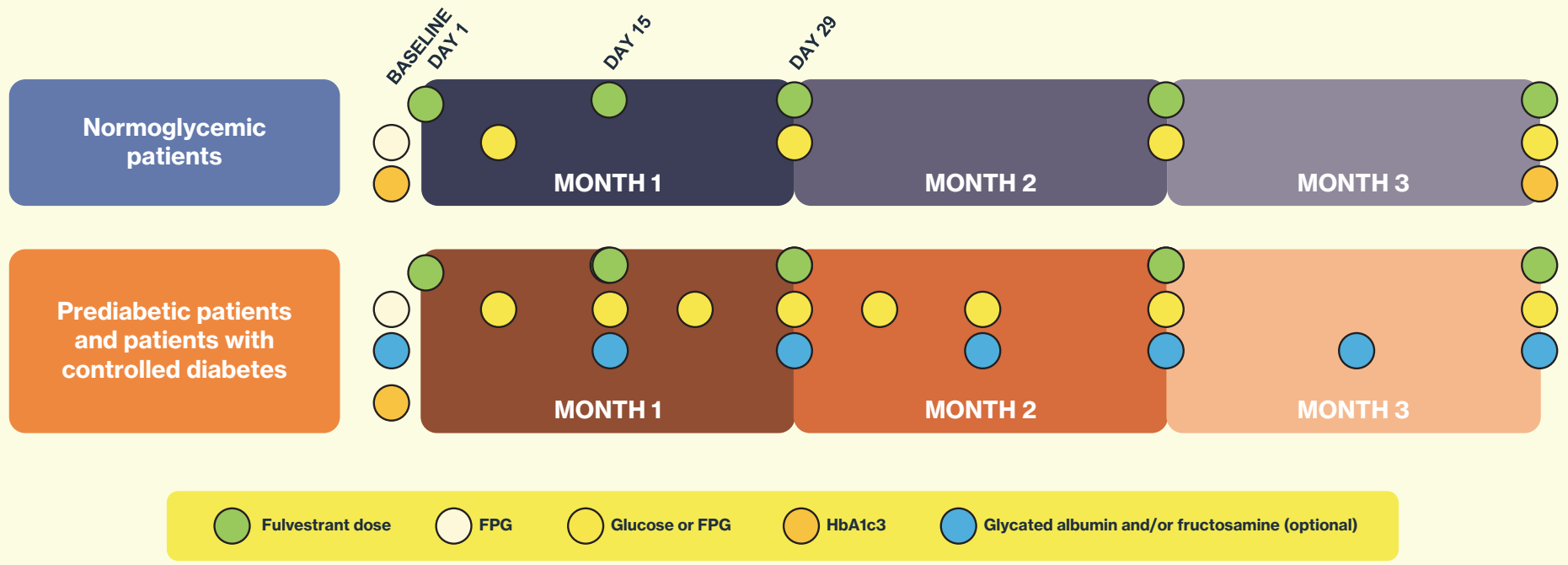
Medical history/comorbidities

- BMI 25 kg/m^2 or 23 kg/m^2 for Asian Americans
- Ethnicity: African American, Latino, Native American, Asian American, Pacific Islander
- Hypertension (BP ≥140/90 mmHg or on treatment for hypertension)
- Prior history of gestational DM, PCOS or glucose intolerance to acute stress such as glucocorticoids
- Conditions associated with insulin resistance e.g. acanthosis nigricans
- Family history of type II DM in first- or second-degree relative

Monitoring during treatment

Prior to initiation, assess patients thoroughly and educate patients on symptoms of hyperglycaemia

Monitoring schedule



Recommendations for prevention

- Optimise blood glucose prior to initiation of alpelisib
  - Do not initiate alpelisib if HbA1c ≥ 6.5% at baseline
  - Alpelisib can be initiated in patients with well-controlled type II DM (HbA1c ≤ 7% at baseline
- Individualise glycaemic targets based on patients' prognosis and QoL considerations
- Counsel prediabetes patients who are overweight or obese to lose weight. High risk patients should also adopt healthier lifestyles
- Initiate home fasting blood glucose monitoring 1x/day or home continuous interstitial glucose monitoring one week before starting alpelisib. Counsel patients to contact their doctor if their fasting blood glucose is consistently >160mg/dL
- Consult an endocrinologist or an oncologist with experience managing PI3K-associated hyperglycaemia on monitoring and detecting hyperglycaemia early in at-risk patients

Management

- Further lifestyle modifications such as >12 hours (overnight) of daily consecutive fasting or low carbohydrate meals (<100g)
- In cases of significant hyperglycaemia, consider dose reduction or treatment interruption of alpelisib
- Consider antihyperglycaemic medication if necessary
  - Start metformin 500mg OD before dinner and optimise as necessary
  - Add another antihyperglycaemic agent, preferably that do not affect the PI3K pathway such as acarbose or SGLT2 inhibitors

Rash

INCIDENCE[2]	RATE OF TREATMENT DISCONTINUATION[2]	TIME-TO-ONSET OF ALPESILIB-ASSOCIATED RASH[2]	PRESENTATION OF ALPESILIB-ASSOCIATED RASH
35.6% of patients treated with alpelisib plus fulvestrant experienced any grade rash **9.9%** treated with alpelisib plus fulvestrant had grade ≥3 hyperglycaemia	**9** patients (3.2%)	Around **12** days after starting alpelisib	Frequently appears on the torso and extremities Usually accompanied with significant percentage increases in blood eosinophil levels

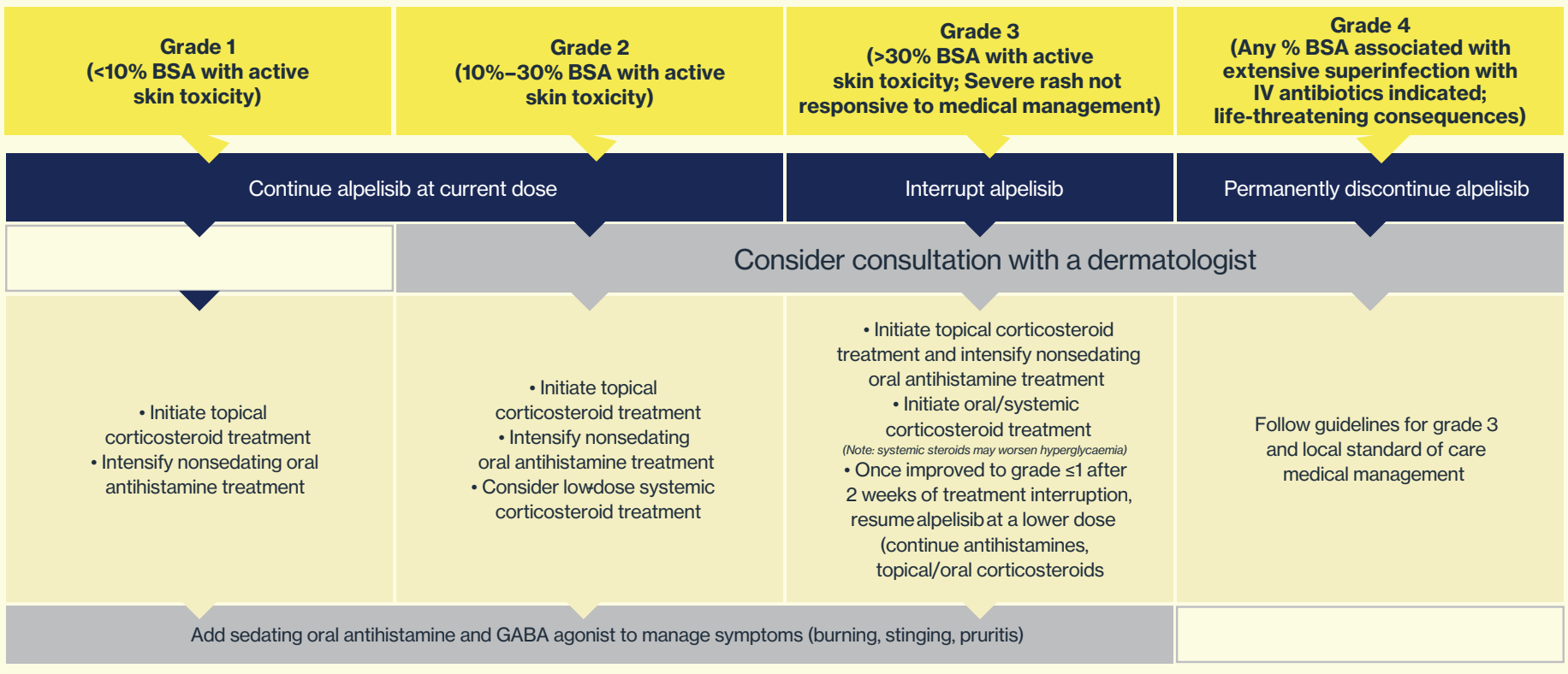
Recommendations for prevention

- Prescribe prophylactic non-sedating antihistamines OD for first 8 weeks then taper off, to reduce frequency and severity of rash
- Advise to avoid unprotected sun exposure and irritant products (containing alcohol, salicyclic acid, ammonium lactate, urea, topical retinoids or benzoyl peroxide)

Monitoring during alpelisib treatment

- Check skin lesions/rash, early symptoms of PI3K inhibitors associated skin toxicity includes pruritis, dry skin, tightness or burning sensation which may present before rash

Management



Diarrhoea

INCIDENCE[2]	TIME-TO-ONSET OF GRADE 2/3 DIARRHOEA[2]	TIME TO IMPROVEMENT[2]
58% of patients treated with alpelisib plus fulvestrant experienced any grade diarrhoea **7%** treated with alpelisib plus fulvestrant had grade ≥3 diarrhoea	Median: **46** days after starting alpelisib	Median: **18** days (by ≥1 grade in patients with grade ≥3 diarrhoea)

Management

- Monitor frequency of bowel movements
- Advise patients to remain hydrated
- Eat frequent, small meals
- Prescribe antidiarrheal medication
- Advise urgent treatment
- For grade 3-4 diarrhoea, interrupt alpelisib until recover to grade 1. Consider hospital admission for IV hydration and antibiotics. Increase loperamide frequency to every 2 hours (maximum dose of 16mg/day)[1]

Long-term Clinical Benefits of Alpelisib in PIK3CA HR + HER2– ABC by Dr Yap Yoon Sim

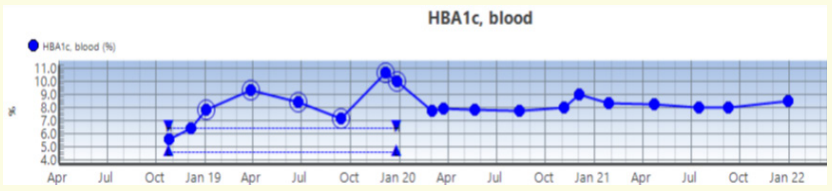
Case studies

Case Study 1

49 year old post-menopausal patient started on fulvestrant and alpelisib 300mg OD in April 2021, but developed grade1 diarrhoea and mucositis after 4 days. After 8 days, she developed generalised grade 1 then 3 rash with 1 episode of fever. She was rechallenged with 150mg after dose interruption and resolution of symptoms, and started on prophylactic steroid mouthwash and antihistamines. However, after a few hours of dosing, developed fever and widespread rash and discontinued permanently.

Case Study 2

Patient with HR+ HER2- diagnosed for 21 years (currently 65 years old) was heavily pre-treated and was enrolled in a clinical study of a compound in addition to alpelisib (study is now discontinued). Patient started on alpelisib 200mg OD and developed Grade 1 and grade 2 hyperglycaemia after the first two cycles. HBA1c creeped up from 5.6% to 9.0% after 6 months.

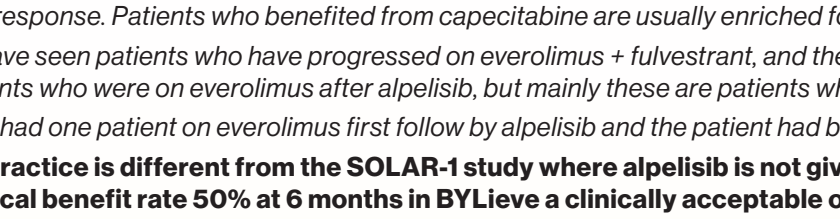


She started on metformin with diabetic diet but was unable to tolerate higher doses of metformin due to diarrhoea. Empagliflozin was added then later discontinued. Patient continued on metformin only with dose reduction of alpelisib to 100mg OD in Feb 2020. Patient maintained on glipizide 5mg OM and metformin XR 750mg OM.

Patient had achieved partial response after 12 months and response maintained after 4 years, and remains fit and well.

Case Study 3

59 year old patient with metastatic HR+ HER2- breast cancer de novo, with liver and bone metastases, previously progressed on multiple lines of therapies: letrozole, ribociclib, weekly paclitaxel and capecitabine. Breast biopsy specimen showed *E545K PIK3CA* mutation and TP53, MET missense mutations. Fulvestrant and alpelisib was started in July 2021 (alpelisib was started at 200mg as patient was 43kg and had deranged LFTs).



Fasting glucose increased and remained elevated despite increasing dose of metformin to 1g BD and diabetic diet. Baseline HbA1c 5.4% increased to 8.5% in November 2021, and subsequently patient was referred to endocrinologist who started her on metformin 500mg BD and linagliptin 5mg OM

Patient had partial response after 3 months of treatment, but eventually disease progressed after 9 cycles of treatment

Overall experience

- Tolerability to alpelisib varies
- Multidisciplinary care may be necessary for optimal management of alpelisib AEs. Patient selection is important
- Response to alpelisib may be independent of prior receipt/response to chemotherapy, although PFS may be poorer in heavily pre-treated patients with aggressive features

Expert Panel Q&A

What is the longest patient you had treated with alpelisib and the lowest dose that was maintained at?

Dr O'Shaughnessy: *The longest duration was 2 years in a HR+, HER2-, heavily pretreated patient and was borderline obese (no diabetes). Patient started on alpelisib 300mg and required metformin. Patient lost 30-35 lbs, and alpelisib dose was reduced to 200mg, and had good disease control. I believe that patients who have progressed on capecitabine having benefitted from MAPK pathway blockade usually have enriched PIK3CA in ctDNA and would benefit from alpelisib. When patients progressed from successful blockade of PI3K pathway would lead to re-sensitization of the oestrogen pathway in some patients particularly in patients with bone or lung mets*

What is your treatment preference in the management of hyperglycaemia?

Dr Ow: *It depends on the healthcare system that you are in, and in public healthcare system (in Singapore), it may be difficult to get access to an endocrinologist urgently. I would usually triage patients at the beginning of the treatment, and will do OGTT and HbA1c to assess the patient's baseline characteristics. I would not give alpelisib to patients who are diabetics. Close monitoring of glucose control is required in the early weeks, and I would involve dieticians and diabetic nurses early on in the treatment*

What would be your choice of partner if patients had fulvestrant before?

Dr O'Shaughnessy: *If patients had fulvestrant in the past (e.g. 1-2 regimens ago), I would go back to fulvestrant. If patient had progressed on fulvestrant + CDK4/6 inhibitor, and wants to switch to alpelisib, I am more inclined to continue with fulvestrant and discontinue CDK4/6 inhibitor. In the BYLieve trial[3], the cohort of patients who had letrozole + alpelisib had a 50% clinical benefit rate, so letrozole could be an alternative but I would generally stick to fulvestrant to ensure complete blockage of the oestrogen receptor.*

What is your experience of patients who had a PI3K mutation, what is the response for patients on everolimus followed by alpelisib or vice versa?

Dr O'Shaughnessy: *I have seen benefit in both ways (everolimus and then alpelisib, or vice versa). Patients who do well with alpelisib generally have long natural history of breast cancer. All oncologists have the experience of recycling the available agents, e.g. 1L CDK4/6i + AI, then on alpelisib, and on progression or intolerability, would use everolimus and there are patients who benefit on this. It depends on which pathway is in control at the moment. Some bone-only patients may also just benefit from tamoxifen-only and get 6-9 months of response. Patients who benefited from capecitabine are usually enriched for PI3K and would benefit from alpelisib*

Dr Yap: *I have seen patients who have progressed on everolimus + fulvestrant, and then had multiple lines of chemotherapy, also benefitted from alpelisib afterwards. I have not had many patients who were on everolimus after alpelisib, but mainly these are patients who could not tolerate alpelisib*

Dr Wong: *I had one patient on everolimus first follow by alpelisib and the patient had better disease control on alpelisib*

Real-life practice is different from the SOLAR-1 study where alpelisib is not given in the first line setting and in SOLAR-1 only 5-6% have been exposed to CDK4/6i. Is the clinical benefit rate 50% at 6 months in BYLieve a clinically acceptable outcome for real-life practice? How would treatment choice be affected with the availability of newer agents such as antibody-drug conjugates?

Dr Joyce: *I believe that 50% success rate is clinically beneficial. Pre-clinically, the key mechanism to CDK4/6 resistance is PI3K mutation, therefore it makes sense for patients who progressed on CDK4/6 if they have PI3K mutation to go on alpelisib. I tend to optimize oral therapy as long as possible before using systemic agents. These newer antibody-drug conjugate agents would be a therapy option but may not overtake oral agents*

Conclusion

Alpelisib is the only PI3K-inhibitor approved for PI3K-mutant metastatic breast cancer in patients with endocrine sensitivity, who have failed first line CDK4/6 inhibitors. Alpelisib toxicities include hyperglycaemia, rash and diarrhoea which are manageable and can be overcome in some patients with proper management and/or prophylaxis treatment

"In my experience, putting in the effort to use alpelisib is worth the trouble if the patients respond. The toxicities can be overcome in some patients. They may still respond even after having progressed on other treatments, including those that were refractory to multiple lines of chemotherapy"

"This drug has some toxicities just like other drugs. With familiarity and experience, along with the tips to manage hyperglycaemia, rash and diarrhoea, they are all very manageable. Today's sharing from the experts also highlighted that once you get over the initial difficult period of managing side effects and dose adjustments, alpelisib is fairly easy to use and patients can enjoy good and long disease control"

Abbreviations

AE, adverse events; AI, aromatase inhibitor; BMI, body mass index; BSA, body surface area; DM, diabetes mellitus; FPG, fasting plasma glucose; LFT, liver function test; OD, once a day; OGTT, oral glucose tolerance test; OM, once a day in the morning; PCOS, polycystic ovary syndrome; SGLT2, Sodium-glucose transport protein 2

References

1. Rugo H et al. The Breast. 2022;61:156-167.
2. Rugo H et al. Ann Oncol. 2020;31:1001-1010
3. Rugo H et al. Cancer Res. 2021;81(4_suppl): PD2-07

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