Poster 15

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Updated Expert Consensus Recommendations for Managing Hyperglycemia and Rash in Patients With *PIK3CA*-Mutated, Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2–) Advanced Breast Cancer Treated With Alpelisib

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CONCLUSIONS

- This practical guidance, based on experts' recommendations and clinical experience, combined with emerging clinical trial evidence, may help address the challenges that healthcare practitioners encounter with managing AEs of alpelisib in their routine practice
- Although the management of AEs of alpelisib can be guided using these recommendations, further studies are needed to establish their effect on patient outcomes
- Areas of disagreement identified in this study emphasize a need for further evidence to guide clinical decision making

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INTRODUCTION

- Alpelisib is an alpha-selective phosphatidylinositol-3-kinase inhibitor and degrader approved, in combination with fulvestrant, for the treatment of patients with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)-mutated hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC)[1,2]
- Hyperglycemia and rash are challenging but expected adverse events (AEs) with alpelisib treatment[3,4]
- Current management guidelines for hyperglycemia and rash are based primarily on experience from clinical trials, whose populations may not necessarily represent real-world patients; therefore, detailed guidance remains lacking in certain aspects
- The Delphi panel method is a systematic and validated approach to establishing consensus from experts based on real-world experience[5,6]
- The objective of this study is to provide practical recommendations to optimize prevention and management of hyperglycemia and rash in patients receiving alpelisib
- Preliminary expert consensus guidance has been previously presented[7]; here, we present final recommendations following the completion of the study

METHODS

- Two RAND Corporation/University of California Los Angeles (UCLA) modified Delphi panels were assembled, one focusing on the management of hyperglycemia, and the other focusing on the management of rash, in patients with HR+, HER2– ABC treated with alpelisib
- Each panel comprised 10 experts representing a broad range of backgrounds and expertise, including 4 oncologists, a clinical pharmacist, and a patient advocate; the hyperglycemia panel included 4 endocrinologists whereas the rash panel included 4 dermatologists
  – No expert participated in both panels
- For each panel, a structured questionnaire was developed, in collaboration with the panelists, based on the summary of evidence from literature review on the mechanism of action, risk factors, and management strategies for hyperglycemia and rash
  – A list of reviewed publications is included in **Supplementary Tables 1** and **2**
- Experts from each panel reviewed the evidence and rated the appropriateness of clinical interventions for hyperglycemia or rash per hypothetical scenarios in the structured questionnaire in two rounds of review, using a scale of 1 to 9 (highly inappropriate, wherein risks outweigh the benefits, to highly appropriate, wherein benefits outweigh the risks)
- Median scores and dispersion from the final rating form were used to classify the data into three levels of panel agreement or a single level of disagreement (**Figure 1**)
  – The consensus statements and treatment algorithms were developed based on the level of agreement

Figure 1. Rating scale score analysis for each panel

Score Analysis		
Agreement	Median score of 7-9 without disagreement	Experts agree that the approach **is appropriate**
	Median score of 4-6 without disagreement	Experts agree that the approach **may or may not be appropriate**
	Median score of 1-3 without disagreement	Experts agree that the approach **is inappropriate**
Disagreement	≥2 ratings of 1-3 and ≥2 ratings of 7-9	**No conclusions** can be made

RESULTS

Expert Agreement

- Experts in the hyperglycemia panel reviewed 624 scenarios for Round 1 and 525 scenarios for Round 2, reaching agreement in 83% of the scenarios for Round 2
  – Experts decided that portions of the questionnaire needed to be revised, necessitating a follow-up panel, in which agreement was met in 96% of 284 scenarios
- Experts in the rash panel reviewed 364 scenarios in each round, reaching agreement in 79% of scenarios for Round 2

Consensus Recommendations per Areas of Agreement

- Expert consensus recommendations for pre-alpelisib initiation and for fasting blood glucose (FBG) monitoring while on alpelisib therapy are summarized in **Figure 2**
- Algorithms for hyperglycemia management are shown in **Figures 3** and **4**, and the algorithms for rash management are summarized in **Figures 5** and **6**
- Areas of disagreement are shown in **Supplementary Table 3**

Figure 2. Recommendations for (A) pre-alpelisib initiation and (B) FBG monitoring during alpelisib treatment

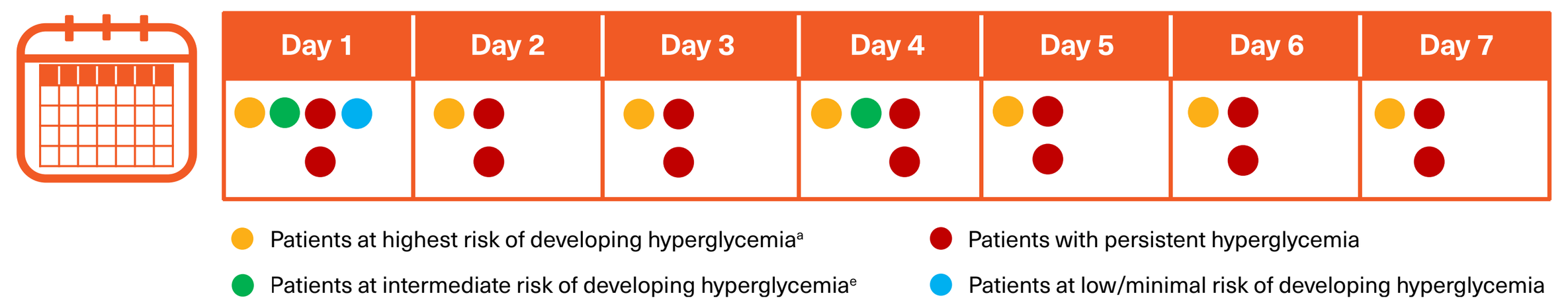
A. Alpelisib pre-initiation recommendations

Pre-treatment endocrinology evaluation for patients:
- At highest risk for developing hyperglycemia[a]
- With type 2 diabetes mellitus and/or HbA1c 6.5%-<8.0%

Dietary changes
- A low-carbohydrate diet[b] in all patients
- A ketogenic diet[c] and/or pre-treatment fasting[d] may be considered

Prophylactic metformin
(short-acting or extended-release) is recommended for patients with baseline HbA1c 5.7%-6.4%, and it may be appropriate for patients with HbA1c <5.7%

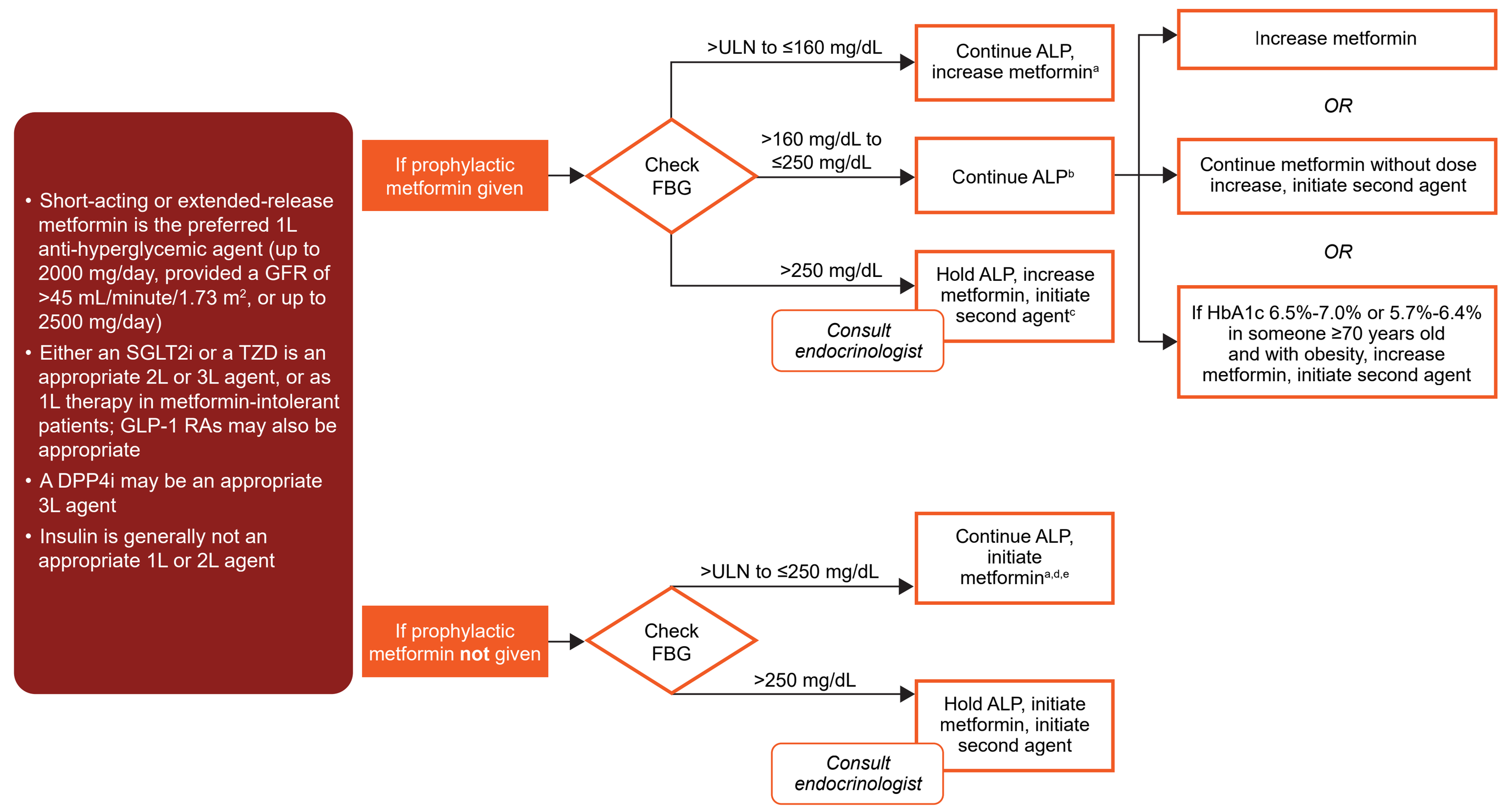
B. Weekly FBG monitoring schedule during alpelisib treatment:



Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Patients at highest risk of developing hyperglycemia[a]
Patients at intermediate risk of developing hyperglycemia[e]
Patients with persistent hyperglycemia
Patients at low/minimal risk of developing hyperglycemia

BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin.
[a]≥70 years old, with obesity (BMI ≥30 kg/m²), HbA1c 5.7%-6.4%.
[b]Maximum 60-130 g/day.
[c]Total carbohydrate intake of <50 g/day.
[d]>12 hours of food restriction prior to dosing alpelisib daily.
[e]With obesity (BMI ≥30 kg/m²) and HbA1c 5.7%-6.4%.

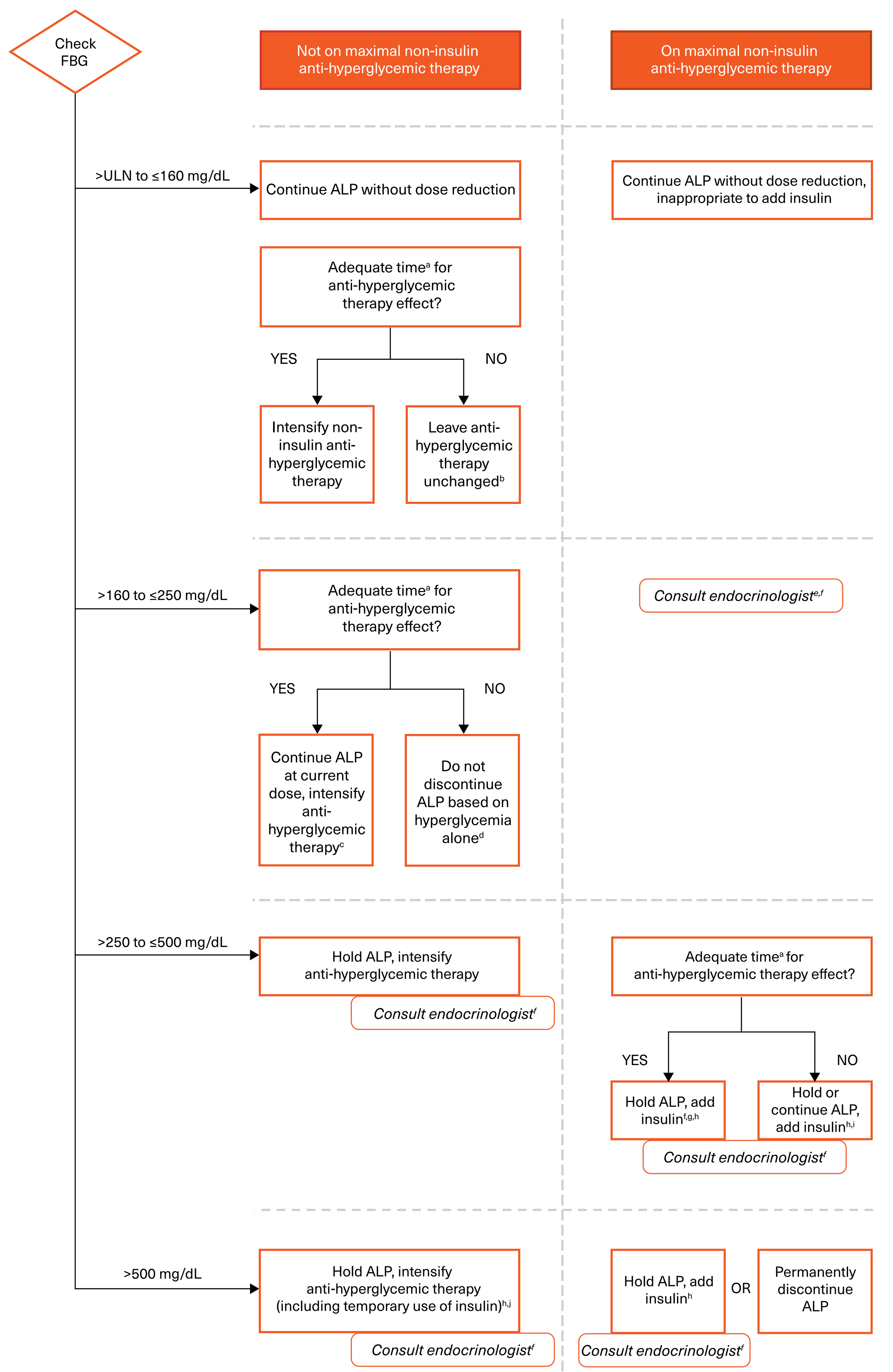
Figure 3. Consensus treatment algorithm for the management of the first episode of hyperglycemia associated with alpelisib



• Short-acting or extended-release metformin is the preferred 1L anti-hyperglycemic agent (up to 2000 mg/day, provided a GFR of >45 mL/minute/1.73 m², or up to 2500 mg/day)
• Either an SGLT2i or a TZD is an appropriate 2L or 3L agent, or as 1L therapy in metformin-intolerant patients; GLP-1 RAs may also be appropriate
• A DPP4i may be an appropriate 3L agent
• Insulin is generally not an appropriate 1L or 2L agent
If prophylactic metformin given
Check FBG
>ULN to ≤160 mg/dL
Continue ALP, increase metformin[a]
>160 mg/dL to ≤250 mg/dL
Continue ALP[b]
>250 mg/dL
Hold ALP, increase metformin, initiate second agent[c]
Consult endocrinologist
Increase metformin
OR
Continue metformin without dose increase, initiate second agent
OR
If HbA1c 6.5%-7.0% or 5.7%-6.4% in someone ≥70 years old and with obesity, increase metformin, initiate second agent
If prophylactic metformin not given
Check FBG
>ULN to ≤250 mg/dL
Continue ALP, initiate metformin[a,d,e]
>250 mg/dL
Hold ALP, initiate metformin, initiate second agent
Consult endocrinologist

1/2/3L, first/second/third-line; ALP, alpelisib; DPP4i, dipeptidyl peptidase 4 inhibitor; FBG, fasting blood glucose; GFR, glomerular filtration rate; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycosylated hemoglobin; MTD, maximum tolerated dose; SGLT2i, sodium-glucose co-transporter 2 inhibitor; TZD, thiazolidinedione; ULN, upper limit of normal.
[a]In certain circumstances (eg, select patients who continue to have HbA1c <8.0% or those who are asymptomatic and intolerant to metformin), it may be appropriate to continue ALP without initiating or changing metformin dose.
[b]It may also be appropriate to temporarily hold ALP (with the intent to restart at same dose) and increase metformin in certain high-risk patients (eg, HbA1c >5.7%).
[c]If FBG >250 to ≤500 mg/dL, it may also be appropriate to hold or dose reduce ALP without first holding and continue metformin without a dose increase (metformin not at MTD) while simultaneously initiating a second agent.
[d]With the goal of titrating to maximum dose of 2000 mg/day within 1 week.[8]
[e]If FBG >ULN to ≤250 mg/dL, it may also be appropriate to either (1) continue ALP while simultaneously initiating metformin and a second agent or, (2) hold ALP while simultaneously initiating metformin and a second agent in certain high-risk patients (eg, HbA1c ≥6.5%).

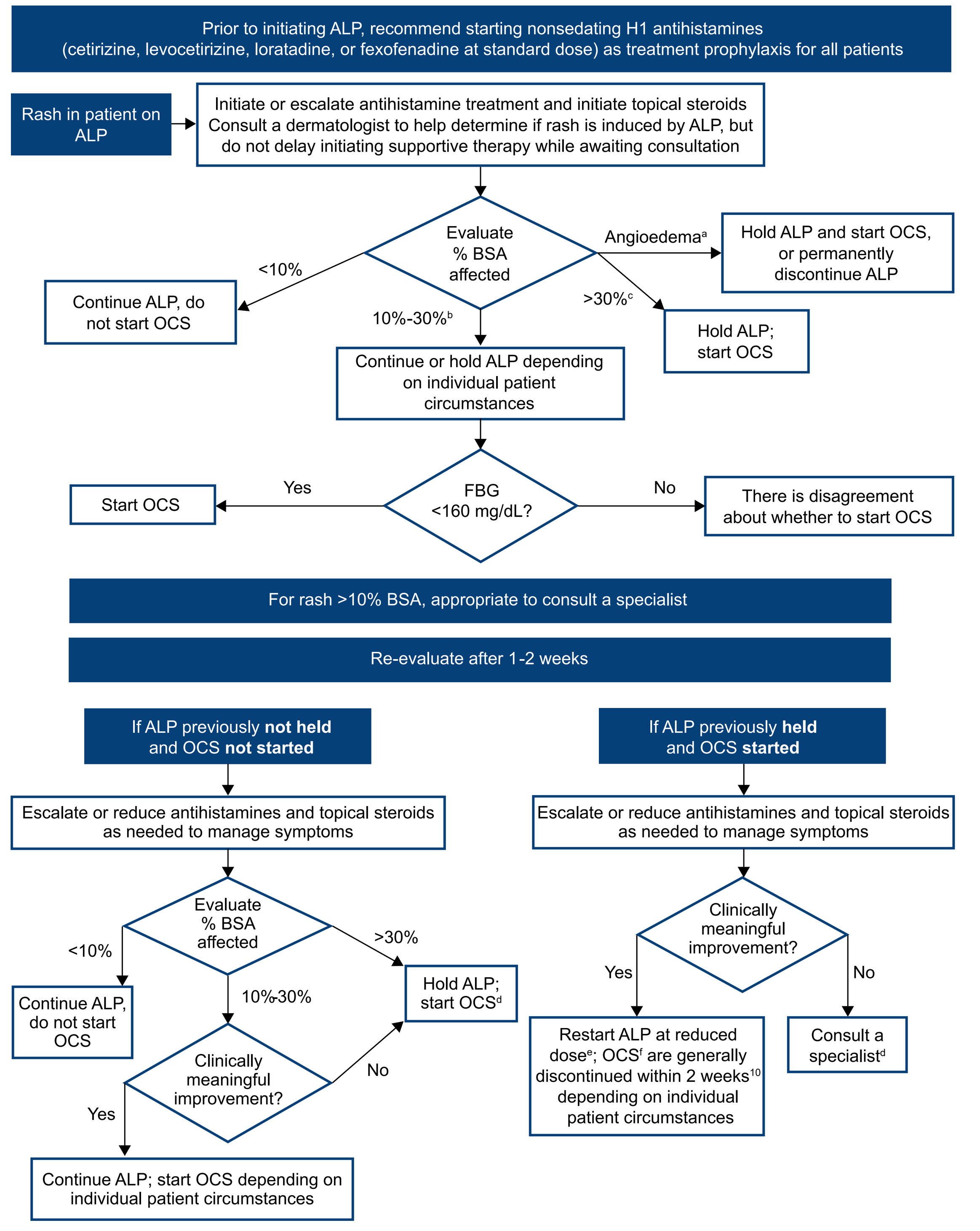
Figure 4. Consensus treatment algorithm for the management of subsequent episodes of hyperglycemia associated with alpelisib



Check FBG
Not on maximal non-insulin anti-hyperglycemic therapy
On maximal non-insulin anti-hyperglycemic therapy
>ULN to ≤160 mg/dL
Continue ALP without dose reduction
Adequate time[a] for anti-hyperglycemic therapy effect?
YES
NO
Intensify non-insulin anti-hyperglycemic therapy
Leave anti-hyperglycemic therapy unchanged[b]
Continue ALP without dose reduction, inappropriate to add insulin
>160 to ≤250 mg/dL
Adequate time[a] for anti-hyperglycemic therapy effect?
YES
NO
Continue ALP at current dose, intensify anti-hyperglycemic therapy[c]
Do not discontinue ALP based on hyperglycemia alone[d]
Consult endocrinologist[e,f]
>250 to ≤500 mg/dL
Hold ALP, intensify anti-hyperglycemic therapy
Consult endocrinologist[f]
Adequate time[a] for anti-hyperglycemic therapy effect?
YES
NO
Hold ALP, add insulin[f,g,h]
Hold or continue ALP, add insulin[h,i]
Consult endocrinologist[f]
>500 mg/dL
Hold ALP, intensify anti-hyperglycemic therapy (including temporary use of insulin)[h,j]
Consult endocrinologist[f]
Hold ALP, add insulin[h]
OR
Permanently discontinue ALP
Consult endocrinologist[f]

ALP, alpelisib; FBG, fasting blood glucose; DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; PI3K, phosphatidylinositol-3-kinase; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; ULN, upper limit of normal.
[a]2 weeks for metformin, 2 days for SGLT2i, 1 week for DPP4i, 6 weeks for TZDs, and 1 week for GLP-1 RA.
[b]It may also be appropriate to intensify non-insulin anti-hyperglycemic therapy depending on the specific circumstances.
[c]It may be appropriate to consult an endocrinologist to assist with intensifying anti-hyperglycemic treatments. It may also be appropriate to temporarily hold ALP and intensify anti-hyperglycemic treatment.
[d]It may be appropriate to continue ALP either with or without intensifying anti-hyperglycemic therapy, or to temporarily hold ALP and intensify anti-hyperglycemic therapy.
[e]It may be appropriate to give insulin, depending on individual circumstances. It may also be appropriate to either continue or hold ALP.
[f]Or have the patient evaluated in the emergency department if circumstances warrant it.
[g]It may also be appropriate to continue ALP and add standing insulin.
[h]Insulin may reverse catabolic weight loss caused by sustained hyperglycemia. Exercise caution on the use of insulin when holding ALP. Holding ALP may likely cause hyperglycemia to resolve and adding insulin may lead to hypoglycemia.
[i]Depending upon individual patient circumstances. Insulin can achieve rapid control of hyperglycemia but carries the potential risk of PI3K pathway stimulation.[9]
[j]It may also be appropriate to permanently discontinue ALP depending on the patient's clinical status.

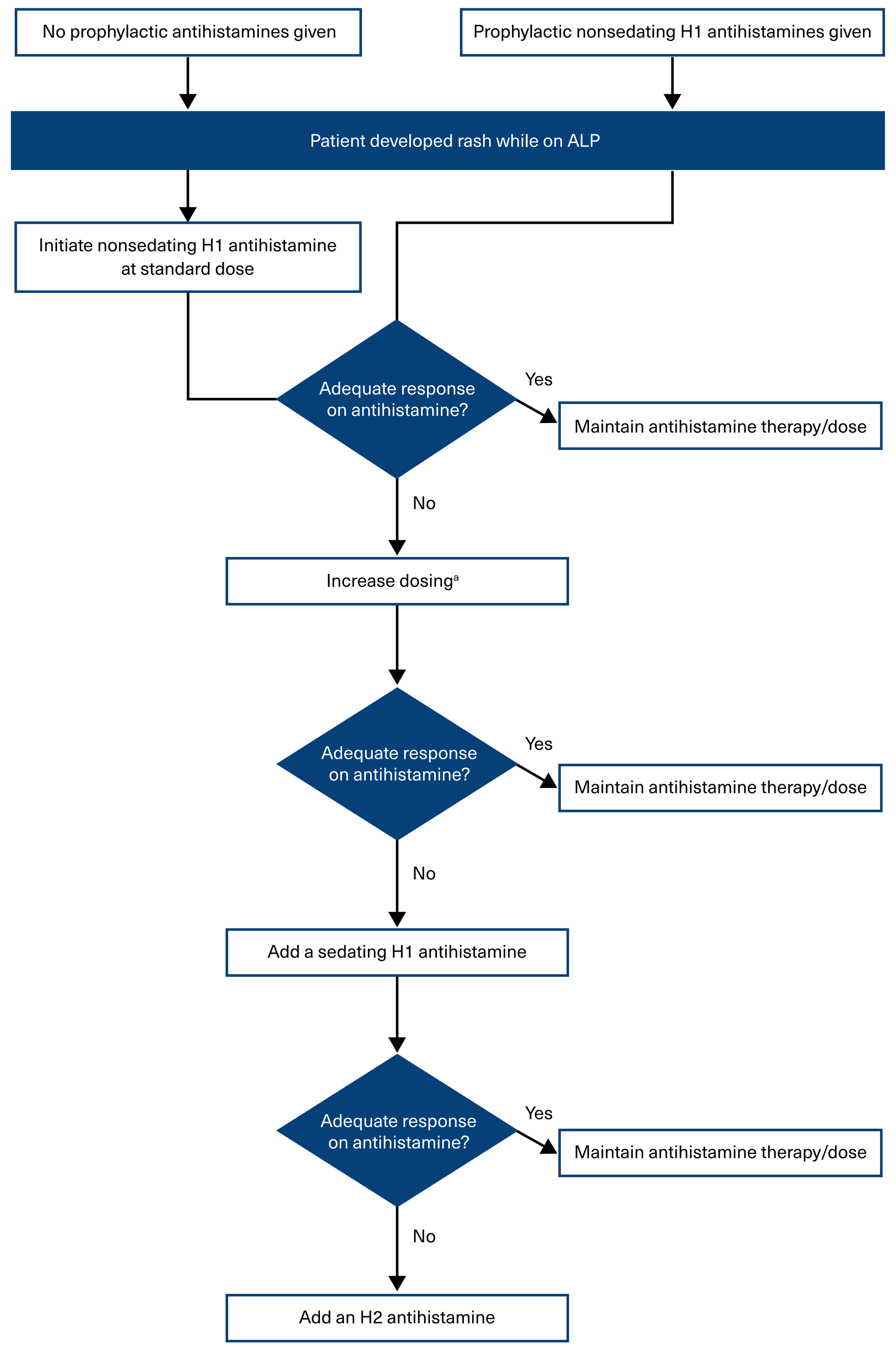
Figure 5. Consensus treatment algorithm for managing rash associated with alpelisib[7]



Prior to initiating ALP, recommend starting nonsedating H1 antihistamines (cetirizine, levocetirizine, loratadine, or fexofenadine at standard dose) as treatment prophylaxis for all patients
Rash in patient on ALP
Initiate or escalate antihistamine treatment and initiate topical steroids Consult a dermatologist to help determine if rash is induced by ALP, but do not delay initiating supportive therapy while awaiting consultation
Evaluate % BSA affected
<10%
Continue ALP, do not start OCS
10%-30%[b]
Continue or hold ALP depending on individual patient circumstances
Angioedema[a]
Hold ALP and start OCS, or permanently discontinue ALP
>30%[c]
Hold ALP; start OCS
FBG <160 mg/dL?
Yes
Start OCS
No
There is disagreement about whether to start OCS
For rash >10% BSA, appropriate to consult a specialist
Re-evaluate after 1-2 weeks
If ALP previously not held and OCS not started
Escalate or reduce antihistamines and topical steroids as needed to manage symptoms
Evaluate % BSA affected
<10%
Continue ALP, do not start OCS
10%-30%
>30%
Hold ALP; start OCS[d]
Clinically meaningful improvement?
Yes
No
Continue ALP; start OCS depending on individual patient circumstances
If ALP previously held and OCS started
Escalate or reduce antihistamines and topical steroids as needed to manage symptoms
Clinically meaningful improvement?
Yes
No
Restart ALP at reduced dose[e]; OCS[f] are generally discontinued within 2 weeks[10] depending on individual patient circumstances
Consult a specialist[d]

ADLs, activities of daily living; ALP, alpelisib; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; FBG, fasting blood glucose; OCS, oral corticosteroids.
[a]If angioedema persists or reoccurs, it is appropriate to permanently discontinue ALP and consult a specialist (which can include a dermatologist or allergist) or seek hospital admission for severe or systemic symptoms.
[b]Or if it covers >30% BSA but produces only mild symptoms, or if it limits instrumental ADLs (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc) regardless of BSA affected. Descriptors are consistent with CTCAE v5.0.[11]
[c]With moderate or severe symptoms, or if it limits self-care ADLs (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden) regardless of BSA affected.
[d]Consult a specialist (such as a dermatologist or allergist) or hospital admission for severe or systemic symptoms.
[e]First dose reduction to 250 mg and the second dose reduction to 200 mg. No further dose reductions typically considered.
[f]For patients receiving the prednisone equivalent of ≥20 mg daily for ≥4 weeks, consider prophylaxis against *Pneumocystis jirovecii* pneumonia.[12,13]

Figure 6. Consensus recommendations for the use of antihistamines to manage rash in patients receiving alpelisib[7]



No prophylactic antihistamines given
Prophylactic nonsedating H1 antihistamines given
Patient developed rash while on ALP
Initiate nonsedating H1 antihistamine at standard dose
Adequate response on antihistamine?
Yes
Maintain antihistamine therapy/dose
No
Increase dosing[a]
Adequate response on antihistamine?
Yes
Maintain antihistamine therapy/dose
No
Add a sedating H1 antihistamine
Adequate response on antihistamine?
Yes
Maintain antihistamine therapy/dose
No
Add an H2 antihistamine

ALP, alpelisib.
[a]Adding a sedating H1 antihistamine to standard dose nonsedating H1 antihistamine is also appropriate, but escalating nonsedating H1 antihistamines is preferred over adding sedating antihistamines.

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