Poster 422

Emily J. Gallagher
Emily.Gallagher@mssm.edu

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 (ABC) treated with alpelisib (ALP)

Emily J. Gallagher, MD, PhD[1]; Heather Moore, PharmD[2]; Mario E. Lacouture, MD[3]; Susan F. Dent, MD[2]; Azeez Farooki, MD[3]; Marcus D. Goncalves, MD, PhD[4]; Claudine Isaacs, MD[5]; Abigail Johnston, JD, MA[6]; Dejan Juric, MD[7]; Zoe Quandt, MD[8]; Laura Spring, MD[7]; Brian Berman, MD, PhD[9]; Melanie Decker, MS, PharmD[10]; Gabriel N. Hortobagyi, MD, FACP[11]; Benjamin Kaffenberger, MD[12]; Bernice Y. Kwong, MD[13]; Timothy Pluard, MD[14]; Ruta Rao, MD[15]; Lee Schwartzberg, MD, FACP[16]; Michael S. Broder, MD, MSHS[17]

[1]Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA; [2]Duke Cancer Institute, Duke University, Durham, NC, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Weill Department of Medicine, Weill Cornell Medicine, New York, NY, USA; [5]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA; [6]Surviving Breast Cancer, 305 Pink Pack, Miami, FL, USA; [7]Massachusetts General Hospital Cancer Center, Department of Medicine, Harvard Medical School, Boston, MA, USA; [8]School of Medicine, University of California, San Francisco, CA, USA; [9]Center for Clinical and Cosmetic Research, Aventura, FL, USA; [10]Woodland Memorial Hospital, Woodland, CA, and Kaiser Permanente, Sacramento, CA, USA; [11]Department of Breast Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA; [12]Wexner Medical Center, The Ohio State University, Columbus, OH, USA; [13]Stanford University School of Medicine, Stanford, CA, USA; [14]St. Luke's Hospital Koontz Center for Advanced Breast Cancer, Kansas City, MO, USA; [15]Rush Hematology, Oncology and Cell Therapy, Rush University Medical Center, Chicago, IL, USA; [16]West Cancer Center, Memphis, TN, USA; [17]PHAR, Beverly Hills, CA, USA.

Scan to obtain:
- Poster
- Supplementary Material

Visit the web at: https://bit.ly/GallagherQC12

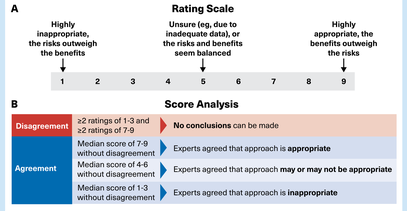
BACKGROUND

- **Alpelisib** is a PI3Kα inhibitor and degrader approved with fulvestrant for the treatment of patients with HR+, HER2–, *PIK3CA*-mutated ABC[1,2]
- Hyperglycemia and rash are expected adverse events (AEs) resulting from alpelisib treatment; management of these AEs remain a challenge for physicians and patients[3,4]
- Currently available management guidance is primarily based on clinical trial experience, which is not necessarily reflective of real-world patients[2,5]
- The Delphi panel method is a systematic, validated approach to organize consensus from experts based on real-world experience in the absence of definitive evidence[6,7]
- The **purpose** of this study is to provide practical recommendations for optimizing prevention and management of hyperglycemia and rash in patients taking alpelisib based on expert consensus from an integrated Delphi panel

METHODS

- Two RAND (RAND Corporation)/University of California at Los Angeles (UCLA) modified Delphi panels were conducted, focusing on the management of hyperglycemia and rash in patients, respectively, with HR+, HER2– ABC treated with alpelisib
- Ten experts were recruited to participate in each panel, representing a diverse range of backgrounds/expertise
- A structured questionnaire was developed for each panel based on a summary of current evidence on (a) mechanism of action of hyperglycemia and rash associated with alpelisib in patients with HR+, HER2– ABC, (b) risk factors for developing these AEs, and (c) management strategies, in collaboration with panelists (full list of evidence reviewed is available in **Suppl Table 1** and **Suppl Table 2**, via the QR code)
- The Delphi process involved 2 rounds for both panels; at each round, experts were asked to review the evidence and rate the appropriateness of clinical interventions for hyperglycemia or rash on hypothetical patient scenarios in the structured questionnaire (rating form) using a scale of 1 (highly inappropriate) to 9 (highly appropriate; **Figure 1A**)
- The median scores and dispersion from the final rating form were used to classify the data into 3 levels of panel agreement or a single level of disagreement (**Figure 1B**)
  - Levels of agreement were used to develop consensus recommendations and treatment algorithms

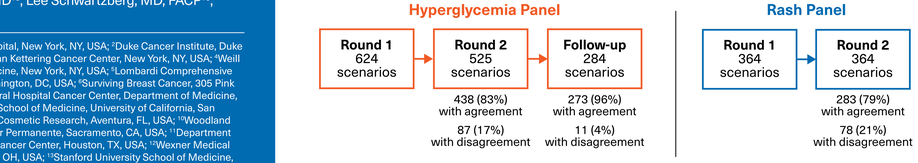
Figure 1. Rating scale (A) for scenarios on questionnaires and (B) score analysis for each panel



RESULTS

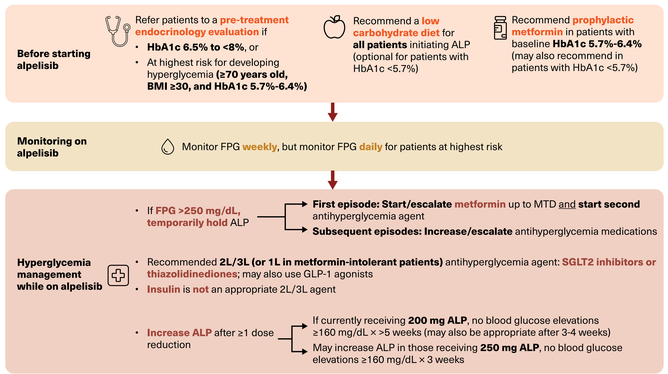
- Each panel was composed of 10 experts: 4 oncologists, 4 endocrinologists (hyperglycemia panel) or 4 dermatologists (rash panel), 1 clinical pharmacist, and 1 patient advocate; no expert participated in more than 1 panel
- The Delphi panel process with outcomes are summarized in **Figure 2**

Figure 2. Delphi process and outcomes



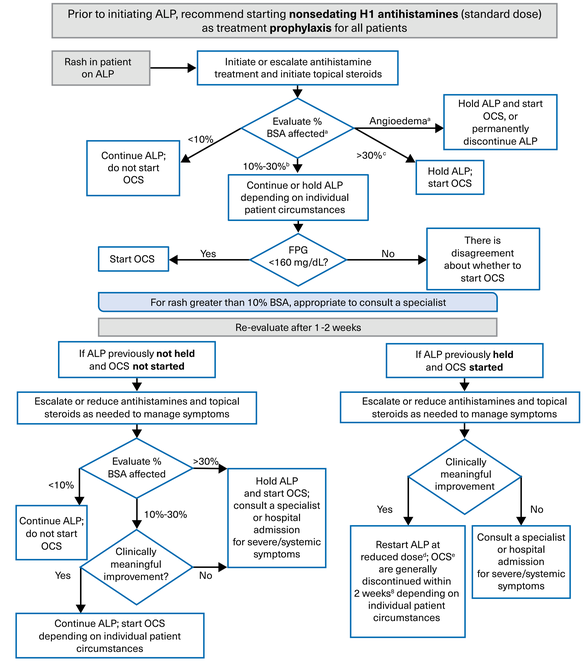
- Consensus recommendations per areas of agreement for each panel are summarized on **Figure 3**, **Figure 4**, and **Figure 5;** areas of disagreement for which consensus could not be reached are summarized on **Table 1**

Figure 3. Consensus recommendations per areas of agreement—Hyperglycemia panel[a]



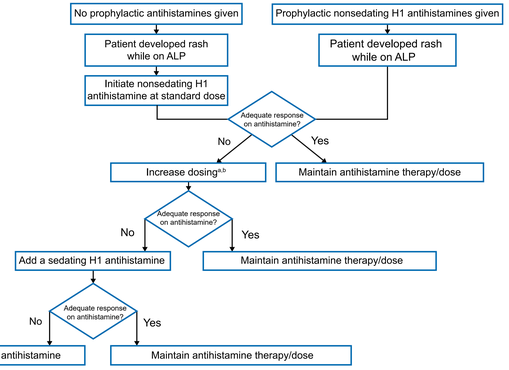
1L, first line; 2L, second line; 3L, third line; ALP, alpelisib; BMI, body mass index; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; MTD, maximum tolerated dose; SGLT2, sodium-glucose cotransporter-2.
[a]Consensus recommendations presented here are based on available data at the time of poster submission; a complete list of recommendations and treatment algorithm will be published separately once finalized.

Figure 4. Consensus recommendations and treatment algorithm for managing rash associated with alpelisib per areas of agreement—Rash panel



ADL, activities of daily living; ALP, alpelisib; BSA, body surface area; FPG, fasting plasma glucose; OCS, oral corticosteroids.
[a]Documented by an allergist and/or dermatologist. Defined as swelling in the deep layers of the skin, often seen with urticaria (hives). Angioedema most often occurs in soft tissues such as the eyelids, mouth, or genitals.[8] 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.[2] The only way to ascertain impact on ADLs is by asking the patient or caregiver; [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]First dose reduction to 250 mg and the second dose reduction to 200 mg. No further dose reductions typically considered; [e]Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving the prednisone equivalent of 20 mg or more daily for 4 or more weeks.[11-13]

Figure 5. Consensus recommendations for use of antihistamines to manage rash in patients receiving alpelisib—Rash panel



ALP, alpelisib.
[a]Adding a sedating H1 antihistamine to standard dose nonsedating H1 is also appropriate, but escalating nonsedating H1 antihistamines is preferred over adding sedating antihistamines. [b]Cetirizine can be increased to 40 mg/day, levocetirizine can be increased to 15 mg/day, loratadine can be increased to 20 mg/day, and fexofenadine can be increased to 360 mg/day.

Table 1. Areas of disagreement[a]

Hyperglycemia Panel	Rash Panel
• Prophylactic use of metformin and a second antidiabetic agent in patients at highest risk of developing hyperglycemia (eg, ≥70 years old, BMI ≥30, HbA1c 5.7%-6.4%)	• Need for a dermatology consultation for patients experiencing rash covering <10% BSA
• Holding alpelisib in patients who had diabetes at baseline, regardless of whether they received prophylactic metformin, and present with FPG >160 mg/dL-250 mg/dL at first episode of hyperglycemia	• Administering topical corticosteroids in patients presenting with any % BSA rash and angioedema
• Reduce dose of alpelisib (versus holding it) for patients with FPG >250 mg/dL	• Initiating OCS in patients with FPG ≥160 mg/dL, who present for the first time with rash covering (a) 10%-30% BSA or (b) any % BSA limiting instrumental ADLs

ADLs, activities of daily living; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; OCS, oral corticosteroids.
[a]Areas of disagreement presented here are based on available data at the time of poster submission.

CONCLUSIONS

- These expert recommendations provide practical, easy-to-implement guidance on prevention and management of hyperglycemia and rash related to treatment with alpelisib
- Areas of disagreement identified per the Delphi approach emphasize the need for additional studies to further refine management guidance
- Expert recommendations presented here are based on the panelists' personal experience treating patients with alpelisib; further empirical, prospective evidence is needed to determine the relationship between these recommendations and patient outcomes

Acknowledgments

The authors thank Mary Lou Smith, JD, MBA, Research Advocacy Network, for her contributions to this publication.

Medical editorial assistance was provided by Casandra M. Monzon, PhD, of Healthcare Consultancy Group, LLC, and funded by Novartis Pharmaceuticals Corporation

This study is sponsored by Novartis Pharmaceuticals Corporation.

Presented at ASCO Quality Care Symposium; September 30 – October 1, 2022; Chicago, Illinois & online.

Disclosures

Emily J. Gallagher: Consulting or advisory role with Novartis, Seattle Genetics, and SynDevRx; **Heather Moore:** Consulting or advisory roles with Novartis, Eli Lilly, Daiichi Sankyo, AstraZeneca, and Seattle Genetics; **Mario E. Lacouture:** Consulting or advisory roles with Novocure, Janssen Research & Development, Roche, AstraZeneca, Genentech, Seattle Genetics, Lutris, Novartis, OnQuality Pharmaceuticals, Deciphera, Apricity Health, Relay Therapeutics, La Roche-Posay, Incyte, Tyra Biosciences, and Innovaderm; other relationship and stock/other ownership interests with Oncoderm (immediate family member), honoraria with Novartis, AstraZeneca, Deciphera, Seattle Genetics/Astellas, Novocure, Janssen, Roche/Genentech, Apricity Health, OnQuality Pharmaceuticals, Relay Therapeutics, RBC Consultants, MJH Associates, L'Oreal, Innovaderm, Nanology, Tyra Biosciences, Incyte, Lutris, and La Roche-Posay; research funding to author from US Biotest, Lutris, Pierrean, Novocure; research funding to institution from AstraZeneca/MedImmune, Columbia University, National Jewish Health, and Novartis; an uncompensated relationship with Oncoderm; and an Open Payments link at https://openpaymentsdata.cms.gov/physician/302897/summary; **Susan F. Dent:** Consulting or advisory roles with Novartis and AstraZeneca; **Azeez Farooki:** Consulting or advisory roles with Novartis; stock or other ownership interests in Johnson and Johnson; **Marcus D. Goncalves:** Consulting or advisory roles with Scorpion Therapeutics; stock or other ownership interests in Faeth Therapeutics; honoraria from Novartis, Pfizer, Scorpion Thera, and BridgeBio; patents, royalties, and other intellectual property with Weill Cornell Medicine; **Claudine Isaacs:** Consulting or advisory roles with Pfizer, Genentech/Roche, Novartis, Puma Biotechnology, Seattle Genetics, Sanofi/Aventis, Eisai, Ion Solutions, bioTheranostics, and AstraZeneca/MedImmune; patents, royalties, and other intellectual property with McGraw Hill Publishing, Wolters Kluwer, and Elsevier; other relationship with Side-Out Foundation; research funding to institution from Tesaro, Merck, and Seattle Genetics; **Abigail Johnston:** No interests to disclose; **Dejan Juric:** Consulting or advisory roles with Novartis, EMD Serono, Eisai, Genentech, Ipsen, Syros Pharmaceuticals, MapKure, Vibliome Therapeutics, Petra Pharma, Relay Therapeutics, Silverback Therapeutics, and PIC Therapeutics; stock and other ownership interests in Relay Therapeutics, PIC Therapeutics, and Vibliome Therapeutics; research funding to institution from Novartis, Genentech, Takeda, Eisai, EMD Serono, Placon, Amgen, Syros Pharmaceuticals, InventisBio, Infinity Pharmaceuticals, Takeda, and Pfizer; **Zoe Quandt:** Consulting or advisory role with Novartis; **Laura Spring:** Consulting or advisory roles with Novartis, Aveo, and Puma; research funding to institution from Merck and Phillips; **Brian Berman:** Consulting or advisory roles with Berg, Sensus, Aviva, Pulse, Sinaomics, Lemonex, Medkwound, Almirall, and Minolabs; speakers' bureau with Sensus and Almirall; travel, accommodations, and expenses from Berg; stock and other ownership interest in Berg; research funding to institution from Sinaomics; **Melanie Decker:** Honorarium with Phar, LLC; **Gabriel N. Hortobagyi:** Consulting or advisory role and research funding to institution from Novartis (unrelated to this abstract); **Benjamin Kaffenberger:** Honorarium with Novartis; consulting or advisory roles with Eli Lilly, Novartis, and Novocure; research funding from Dermatology Foundation, Biogen, ImfaRx, Eli Lilly, and Onquality; patents, royalties, or other intellectual property with ZitGenius; expert testimony for Emory Healthcare; **Bernice Y. Kwong:** Consulting or advisory roles with Oncoderm and Novartis; **Timothy Pluard:** Consulting or advisory roles with Pfizer, Macrogenics, Genentech, Seattle Genetics, Novartis, H3 Biomedicine, AstraZeneca/Daiichi Sankyo, and Gilead Sciences; speakers' bureau with Genentech/Roche, Novartis, Seattle Genetics, and Gilead Sciences; research funding to institution from Seattle Genetics, Zymeworks, HiberCell, Pfizer, H3 Biomedicine, GRAIL/HWA Pharmaceutical, G1 Therapeutics, Olema Pharmaceuticals, Dantari, AstraZeneca/Daiichi Sankyo, Orinove, and Sanofi; **Ruta Rao:** Consulting or advisory roles with Novartis, AstraZeneca, Puma Biotechnology, Genentech/Roche, Seattle Genetics, and Immunomedics; **Lee Schwartzberg:** Employment, leadership, and stock or other ownership in OneOncology; speakers' bureau with Seagen, Merck, and Pfizer; **Michael S. Broder:** Relationships with Amgen, Bristol-Myers Squibb, Boston Scientific, Celgene, Dompe US, Eisai, Genentech, GRAIL, Greenwich Biosciences, Innovation and Value Initiative, Novartis, Otsuka, PHRMA Foundation, Prothena, Sanofi, Sunovion, Veana Therapeutics, Ackea Therapeutics, Biomarin, Exact Sciences, Genzyme, Jazz Pharmaceuticals, Mirum Pharmaceuticals, Recordati, Regeneron, and Takeda.

References

1. Fritsch C, et al. *Cancer Res.* 2018;78(13 suppl):Abstract 3934 [poster].
2. Piqray [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.
3. Drullinsky PR, et al. *Breast Cancer Res Treat.* 2020;181(2):233-248.
4. Andre F, et al. *N Engl J Med.* 2019;380(20):1929-1940.
5. Rugo HS, et al. *Ann Oncol.* 2020;31(10):1001-1010.
6. Dalkey NC. RAND Corp, RM-5888-PR; 1969.
7. Nasa P, et al. *World J Methodol.* 2021;11(4):116-129.
8. Zuberbier T, et al. *Allergy.* 2009;64(10):1427-1443.
9. American Academy of Allergy, Asthma, and Immunology, 2022. https://www.aaaai.org/conditions-treatments/allergies/skin-allergy. Accessed September 8, 2022.
10. National Cancer Institute, Common Terminology Criteria for Adverse Events, Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed August 15, 2022.
11. Reference[d] with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prevention and Treatment of Cancer-Related Infections V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed August 30, 2022. **To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.**
12. Halani S, et al. *CMAJ.* 2020;192:E1306-1308.
13. Roux A, et al. *Med Mal Infect.* 2019;44:185-198.