Targeting the PI3K/AKT pathway in HR+ HER2- advanced breast cancer

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Integrating PI3K/AKT pathway-targeted agents into practice: How to manage the side effects

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Active management of AEs to optimize benefit of PI3K inhibition

Key learnings from the SOLAR-1 trial of alpelisib in PIK3CA-mutated HR+ HER2- ABC (NCT02437318)

AEs associated with alpelisib

- Hyperglycaemia
- Diarrhoea
- Nausea
- Rash

- Occurred relatively early during treatment
- Were **reversible** and **manageable** with **monitoring, early detection**, and **intervention** (including concomitant medications and dose modifications when needed)
- Were reversible with alpelisib discontinuation

Impact of active AE management in SOLAR-1

Implementation of more-detailed AE management guidance* during the study improved markers of safety:

Fewer discontinuations due to grade ≥3 AEs
(7.9% after active management vs 18.1% previously)

Preventive anti-rash medication resulted in:

Lower incidence and **severity of rash** vs no preventive medication
(Rash incidence any grade, 26.7% vs 64.1%)
and severity, grade 3, 11.6% vs 22.7%)

*The study protocol was amended to improve monitoring and management of hyperglycaemia and skin toxicity after 317 (56.6%) of approximately 560 planned patients had been randomly assigned to receive study treatment.

AE, adverse event; ABC, advanced breast cancer; HR+ HER2-, hormone receptor-positive human epidermal growth factor receptor 2-negative; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene.

Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

AEs leading to discontinuation

Compared with SOLAR-1, improved management of AEs in Cohort A of the BYLieve study (NCT03056755) was associated with a lower discontinuation rate and higher dose intensity of alpelisib[1,2]

SOLAR-1[1]

AEs leading to discontinuation (≥1.5%)	Alpelisib + FULV (n=284)
	All grades, n (%)
Any AE	**71 (25.0)**
Hyperglycaemia	18 (6.3)
Rash	9 (3.2)
Diarrhoea	8 (2.8)
Fatigue	6 (2.1)
Nausea	5 (1.8)

Median relative **dose intensity** for alpelisib in **SOLAR-1** was **82.7%[1]**

BYLieve[2]

AEs leading to discontinuation (≥1.5%)	Prior CDKi + AI (Cohort A) Alpelisib + FULV (n=127)
	All grades, n (%)
Any AE	**26 (20.5)**
Rash	5 (3.9)
Urticaria	2 (1.6)
Colitis	2 (1.6)
Hyperglycaemia	2 (1.6)
Vomiting	2 (1.6)

Median relative **dose intensity** for alpelisib in **BYLieve (Cohort A)** was **89.9%[2]**

AE, adverse event; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; FULV, fulvestrant.

1. André F, et al. *N Engl J Med.* 2019;380:1929–40. 2. Rugo HS, et al. Presented at Virtual ASCO 2020. Abstract 1006. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

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Hyperglycaemia is an on-target effect with PI3K inhibitors

Hyperglycaemia is intrinsically linked to the inhibition of PI3K, a key mediator of insulin signalling and glucose homeostasis[1]

Glucose homeostasis[1]

Normally, the **p110 alpha subunit of PI3K** plays a role in storing **glucose as glycogen** when **insulin levels increase,** which then leads to a

reduction in blood glucose levels

Hyperglycaemia incidence (grade ≥3) with alpelisib was **36.6%** in SOLAR-1[2] and **28.3%** in BYLieve[3]

PI3K inhibitors affect insulin sensitivity and glucose metabolism

Hyperglycaemia[1]

Inhibition of PI3KA blocks glucose uptake by skeletal muscle and adipose tissue and **activates hepatic gluconeogenesis**

Thus, when PI3K is inhibited,

more glucose is released into the blood, leading to **hyperglycaemia**

Patient screening

Before initiating treatment with PI3K inhibitors, patients should be screened for T1D or uncontrolled T2D (FPG >140 mg/dL or HbA_{1c} <6.5%)[2]

HbA_{1c}, glycated haemoglobin; PI3K, phosphatidylinositol 3-kinase; PI3KA, alpha isoform of PI3K; T1D, type 1 diabetes; T2D, type 2 diabetes.

1. Hanker A, et al. *Review Cancer Discov.* 2019;9:482–91. 2. André F, et al. *N Engl J Med*. 2019;380:1929–40. 3. Rugo HS, et al. Presented at Virtual ASCO 2020. Abstract 1006.

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Metformin is considered the standard treatment for hyperglycaemia due to PI3K inhibitors

Management guidance for hyperglycaemia*

Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
1	FPG >ULN to 160 mg/dL or FPG >ULN to 8.9 mmol/L	**No dose adjustment required**	**If FPG is <140 mg/dL, consider metformin** • If FPG is 140–160 mg/dL, start or intensify metformin
2	FPG >160–250 mg/dL or FPG >8.9–13.9 mmol/L	**No dose adjustment required** • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, reduce alpelisib by one dose level	**Start oral antidiabetic treatment (e.g. metformin)** • If FPG keeps rising beyond MTD of metformin, add an insulin sensitizer (e.g. pioglitazone)
3	FPG >250–500 mg/dL or FPG >13.9–27.8 mmol/L	**Discontinue** • If FPG resolves to grade ≤1 within 3–5 days while off alpelisib and on metformin, restart alpelisib and reduce by one dose level • If FPG does not resolve to grade ≤1 within 21 days after antidiabetic treatment, permanently discontinue alpelisib	**Consider consultation with endocrinologist** • Start metformin and add pioglitazone Insulin may be used as rescue medication for 1–2 days
4	FPG >500 mg/dL or FPG ≥27.8 mmol/L	**Discontinue for 24 h,** then: • If grade ≤3, follow specific grade recommendations • If grade 4 persists (with no confounding • factors), permanently discontinue alpelisib	**Consult with endocrinologist** • See grade 3 recommendations; recheck in 24 hours

*Amended management guidance in SOLAR-1 introduced based on recommendations by an advisory board of experts in managing these AESIs.
AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
AE, adverse event; AESI, AE of special interest; FPG, fasting plasma glucose; MTD, maximum tolerated dose; ULN, upper limit of normal.

Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10.

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Prophylaxis for skin toxicities is associated with a positive impact on incidence and severity of rash due to PI3K inhibitors

Management guidance for rash*[1]

Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
1 and 2	<10% BSA with active skin toxicity 10–30% BSA with active skin toxicity	**No dose adjustment required**	**Initiate topical corticosteroid** • Consider adding oral antihistamine to manage symptoms
3	>30% BSA with active skin toxicity	**Interrupt** • Once grade ≤1, resume at the same dose level for first occurrence of rash or at lower dose level in case of second occurrence	**Initiate or intensify topical corticosteroid and oral antihistamine** • Consider low-dose systemic corticosteroid
4	Any % BSA associated with extensive superinfection, with i.v. antibiotics indicated	**Permanently discontinue**	**Treat as medically indicated**

- The most common presentation is **maculopapular rash, with or without pruritus and dry skin**[2]
- **Consultation with a dermatologist** is recommended for better assessment and management of skin toxicity[1]

*Amended management guidance in SOLAR-1 introduced based on recommendations by an advisory board of experts in managing these AESIs.
AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
AE, adverse event; AESI, AE of special interest; BSA, body surface area; i.v., intravenous; MTD, maximum tolerated dose.

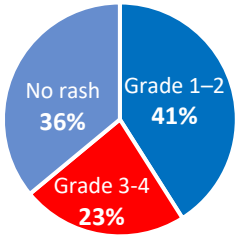
1. Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10. 2. Nunnery SE, Mayer IA. *Ann Oncol.* 2019; 30(Suppl. 10):x21–6.

Impact of prophylaxis with anti-rash medication on incidence and severity of rash in SOLAR-1 and BYLieve (Cohort A)

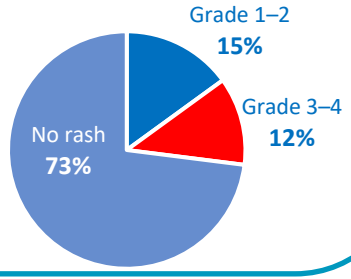
SOLAR-1: Alpelisib + FULV*[1]

Incidence and severity of rash†

✗ **No prophylactic anti-rash** medication before rash onset (n=198)



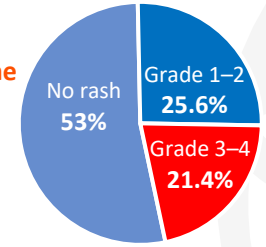
✓ **Prophylactic anti-rash** medication before rash onset (n=86)



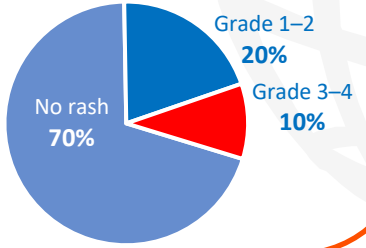
BYLieve: Prior CDKi + AI (Cohort A) - Alpelisib + FULV[2]

Incidence and severity of rash

✗ **No prophylactic antihistamine** before rash onset (n=117)



✓ **Prophylactic antihistamine** before rash onset (n=10)



*Anti-rash medication was administered to 134 patients in the alpelisib group. The most frequently used anti-rash medications were steroids and antihistamines. In total, 86 patients in the alpelisib group received anti-rash medication before the onset of rash with antihistamines being the most frequent treatment (60 of 86 patients; 69.8%). †This grouped term includes the preferred terms rash, dermatitis acneiform, rash papular, dermatitis, rash macular, rash maculopapular, rash generalized, rash pruritic, genital rash and rash pustular.

AE, adverse event; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; FULV, fulvestrant.

1. Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10. 2. Rugo HS, et al. Presented at Virtual ASCO 2020. Abstract 1006.

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Diarrhoea due to PI3K inhibitors is usually mild and manageable using general practice guidelines

Management guidance for diarrhoea*

- Once other causes of diarrhoea are excluded (e.g. infection), some general guidelines should be implemented
- Patients should be encouraged to stay hydrated and have frequent, small meals

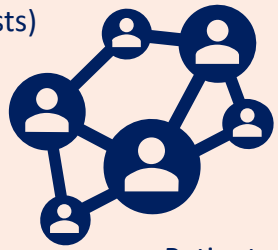
Grade	Criteria	Recommendation for alpelisib dosing	Recommendation for management
1	Increase of <4 stools per day over baseline; mild increase in ostomy output vs baseline	**No dose adjustment required**	**Initiate appropriate medical therapy and monitor as clinically indicated** • Medically manage patients according to local practice guidelines for diarrhoea
2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output vs baseline: limiting instrumental ADL	**Interrupt dose until grade 1 and resume at lower dose level[a]** • Only one dose reduction is permitted; if toxicity reoccurs, permanently discontinue treatment	
3	Increase of 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care ADL		
4	Life-threatening consequences; urgent intervention indicated		

*Amended management guidance in SOLAR-1 introduced based on recommendations by an advisory board of experts in managing these AESIs. [a]Management generally consists of hydration and loperamide. Further interventions may be required for higher-grade diarrhoea, persistent low-grade diarrhoea or diarrhoea with complications such as fever, sepsis, neutropenia, bleeding or dehydration.
AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
ADL, activities of daily living; AE, adverse event; AESI, AE of special interest.

Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10.

An MDT helps to optimize patient assessment and toxicity management

Proactive management of patients receiving PI3K inhibitors using an MDT approach[1–3]



- **Education** of patients and caregivers on possible **side effects** and the importance of **prompt symptom reporting**
- **Frequent monitoring** and early toxicity recognition
- **Active intervention** with supportive care
- **Prophylactic** strategies when available

MDT, multidisciplinary team; PI3K, phosphatidylinositol 3-kinase.

1. Rugo HS, et al. *Ann Oncol.* 2020;31:1001–10. 2. Nunnery SE, Mayer IA. *Ann Oncol.* 2019; 30(Suppl. 10):x21–6. 3. Gallo C. Posted in Faculty Perspectives. May 2020. Available at: http://theoncologypharmacist.com/component/mams/?view=article&artid=18160:the-role-of-the-oncology-nurse-in-an-era-of-novel-therapies-top&secid=15303:faculty-perspectives-pi3k-inhibitors-efficacy-in-hematologic-malignancies-and-management-of-treatment-related-adverse-events-top&catid=&Itemid=0 (Accessed October 2020).