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

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# PI3K/AKT inhibitors: What are the key adverse events?


## Dr Judy King

Consultant Medical Oncologist
Royal Free London NHS Foundation Trust
London, UK


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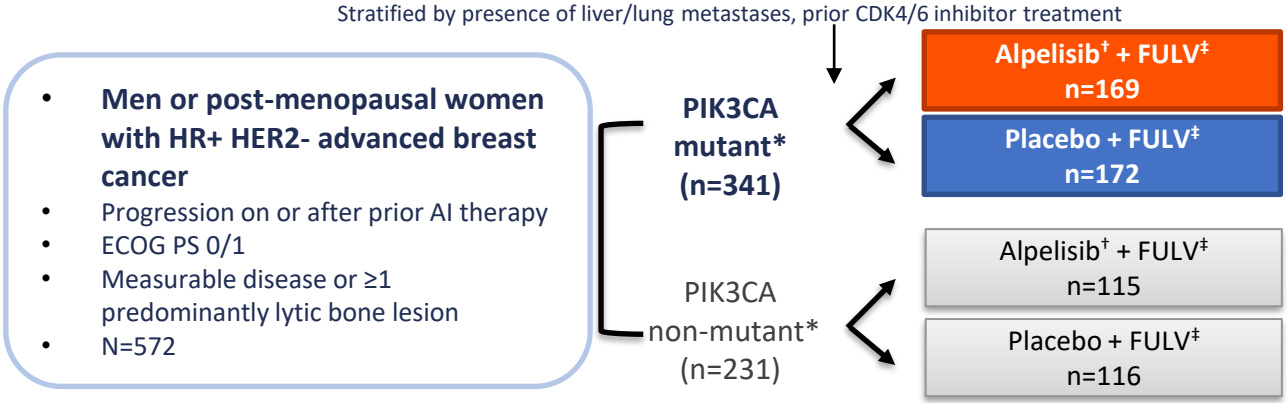
# SOLAR-1 study design

## Alpelisib + fulvestrant for men and women with HR+ HER2- advanced breast cancer

- International, randomized, double-blind phase III study (NCT02437318)




- **Primary endpoint:** PFS in PIK3A-mutant cohort (locally assessed)
- **Secondary endpoints including:** ORR, clinical benefit and safety

*By tumour tissue; †300mg PO QD; ‡500mg IM on Days 1, 15 of first 28-day cycle, then on Day 1 in subsequent cycles.
AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ECOG PS, Eastern Cooperative Oncology Group performance status; FULV, fulvestrant; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; PFS, progression free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA, alpha isoform of PI3K, PO, orally; QD, once daily.

André F, et al. *N Engl J Med.* 2019;380:1929–40. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

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# SOLAR-1 safety results in overall patient population

## The most frequent grade 3 or 4 AEs were hyperglycaemia, rash and diarrhoea[1]

### Most common adverse events (AEs)

| AE | Placebo + FULV (n=287) | Alpelisib + FULV (n=284) |
|---|---|---|
| **All-grade AEs in ≥30% of patients in any group (%)** | | |
| Hyperglycaemia | 9.8 | 63.7 |
| Diarrhoea | 15.7 | 57.7 |
| Nausea | 22.3 | 44.7 |
| Decreased appetite | 10.5 | 35.6 |
| Rash | 5.9 | 35.6 |
| **Grade 3 and 4 AEs in ≥5% of patients in any group (%)** | | |
| Hyperglycaemia | 0.7 | 36.6 |
| Rash | 0.3 | 9.9 |
| Maculopapular rash | 0.3 | 8.8 |
| Diarrhoea | 0.3 | 6.7 |

- AEs were generally reversible and with the exclusion of hyperglycaemia, were mostly low grade
- Overall, **AE-related discontinuation** of alpelisib occurred in **25%** of patients
- Most frequent AEs (**≥2%**) leading to discontinuation of apelisib were:
  - **Hyperglycaemia** (an on-target effect of alpelisib), **6.3%**
  - **Rash, 3.2%**
  - **Diarrhoea, 2.8%**
  - **Fatigue, 2.1%**

AE, adverse events; FULV, fulvestrant.

André F, et al. *N Engl J Med.* 2019;380:1929–40.

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# BYLieve study design

## Alpelisib + FULV in PIK3CA-mutated HR+ HER2- advanced breast cancer after CDK4/6 inhibitor + AI (Cohort A)

- International, open-label, 3-cohort, non-comparative phase II study (NCT03056755)

- **Men or pre/post-menopausal women with PIK3CA mutant* HR+ HER2- advanced breast cancer**
- Immediate prior treatment with:
  - CDK4/6 inhibitor and ET
  - Systemic CT or ET
- ECOG PS ≤2
- Measurable disease or ≥1 predominantly lytic bone lesion

→ Cohort A: Prior CDK4/6 inhibitor + AI
Alpelisib† + FULV‡
n=121

**Current presented results**

→ Cohort B: Prior CDK4/6 inhibitor + FULV
Alpelisib† + letrozole§
minimum n=112

→ Cohort C: Prior AI then CT or ET
Alpelisib† + FULV‡
minimum n=112

- **Primary endpoint:** proportion of patients alive without disease progression at 6 months (RECIST v1.1)
- **Secondary endpoints (in each cohort) include:** PFS, ORR, CBR, OS and safety

*Centrally confirmed; †300 mg PO QD; ‡500 mg IM on days 1 and 15 of first 28-day cycle, then on day 1 in subsequent cycles; §Men in letrozole cohort and premenopausal women received goserelin 3.6 mg SC Q28D or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression.

AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4 and 6; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FULV, fulvestrant; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IM, intramuscular; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene; PO, orally; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous.

Rugo HS, et al. *J Clin Oncol.* 2020;38(Suppl. 15):1006. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

# BYLieve Cohort A safety results

## The most frequent AEs were diarrhoea, hyperglycaemia and nausea[1,2]

| **All-grade AEs** (in >25% of patients) | **Cohort A: Prior CDK4/6 inhibitor + AI (safety set*) (n=127)** (% of patients) |
|---|---|
| Diarrhoea | 59.8 |
| Hyperglycaemia | 58.3 |
| Nausea | 45.7 |
| Fatigue | 29.1 |
| Decreased appetite | 28.3 |
| Rash | 28.3 |
| Stomatitis | 26.8 |

- The most **frequent grade ≥3 AEs** included **hyperglycaemia (28.3%), rash (9.4%)**, and diarrhoea **(5.5%)**
- Overall, **AEs** leading to **discontinuation** occurred in **20.5%** of patients
- The most **frequent AEs** leading to **discontinuation** were **rash (3.9%), colitis, hyperglycaemia, urticaria, and vomiting** (**1.6%** each)

*The safety set included all patients who had at least one dose of study treatment.
AE, adverse event; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6.

1. Rugo HS, et al. *J Clin Oncol.* 2020;38(Suppl. 15):1006. 2. Rugo HS, et al. Presented at Virtual ASCO 2020. Abstract 1006.

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# GDC-0077 phase Ia dose-escalation study

## Study: GDC-0077 as monotherapy or combination therapy with ET and palbociclib in PIK3CA-mutated advanced breast cancer (NCT04191499)

**Study details** (single-agent arm)

- **GDC-0077 monotherapy** administered 6, 9, or 12 mg PO QD in 28-day cycles until intolerable toxicity or disease progression

**Patients** (at study cut-off: 29 March 2019)

- **N=20 pts** (19 with HR+ breast cancer, 1 with colorectal cancer)
- 19 pts had received ≥2 prior lines of therapy for metastatic disease
- **GDC-0077 MTD was established at 9 mg QD**

**Safety results** (single-agent arm)

The most frequent TRAEs in ≥3 (15%) patients:

| | | | |
|---|---|---|---|
| **Hyperglycaemia (70%)** | **Diarrhoea (40%)** | **Decreased appetite and vomiting (20% each)** | **Alopecia, fatigue, nausea and decreased weight (15% each)** |

- **30%** of patients required **dose reductions** because of **AEs**
- Median **duration of treatment** was **5.3 months**
- All patients ultimately discontinued treatment due to disease progression

AE, adverse event; ET, endocrine therapy; HR+, hormone receptor positive; MTD, maximum tolerated dose; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene; PO; orally; QD, once-daily; TRAE, treatment-related AE.

Juric D, et al. *Cancer Res.* 2020;80(Suppl. 4):OT1-08-04. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

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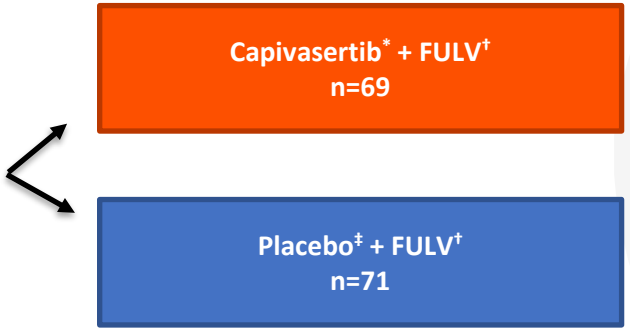
# FAKTION study design

## Capivasertib + FULV after relapse or progression on AI in HR+ HER2- advanced breast cancer

- Randomized, double-blind, placebo-controlled study (NCT01992952)

  - **Post-menopausal women with HR+ HER2- metastatic or unresectable locally advanced breast cancer**
  - Prior therapy with PD or relapse on adjuvant AI in metastatic setting
  - Maximum 3 previous lines ET and 1 line CT for metastatic breast cancer
  - ECOG PS 0–2
  - Measurable disease or non-measurable disease
  - Controlled T2D allowed
  - N=140




- **Primary endpoint:** PFS in overall population
- **Secondary endpoints including:** safety, ORR, CBR and OS

*Capivasertib BID 4 days on/3 days off from cycle 1, day 15; †500 mg (day 1) every 28 days (+ loading dose on day 15 of cycle 1); ‡ Placebo BID 4 days on/3 days off from cycle 1, day 15.
AI, aromatase inhibitor; BID, twice-daily; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FULV, fulvestrant; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; T2D, type 2 diabetes.

Jones R, et al. *Lancet Oncol.* 2020;21:345–57. Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

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# FAKTION safety results

## The most common grade 3–4 AEs with capivasertib were hypertension, rash and diarrhoea

| AE | Placebo + FULV (n=71) | Capivasertib + FULV (n=69) |
|---|---|---|
| **Grade 1 and 2 AEs in ≥50% of patients in any group (%)** | | |
| Diarrhoea | 31 | 67 |
| Hypertension | 63 | 59 |
| Fatigue | 54 | 57 |
| Nausea | 51 | 55 |
| Hypertriglyceridaemia | 28 | 52 |
| **Grade 3 and 4 AEs in ≥3% of patients in any group (%)** | | |
| Hypertension | 24 | 32 |
| Rash | 0 | 20 |
| Diarrhoea | 4 | 14 |
| Infection | 3 | 6 |
| Fatigue | 4 | 1 |

### Dose reductions and discontinuations

- More than **one third (41%)** of patients required **at least one dose reduction**; 3 patients subsequently stopped capivasertib because of toxicity
- An additional 5 patients (8%) stopped capivasertib without previous dose reduction
- Eight (12%) patients **discontinued capivasertib** due to AEs – most common reasons were **rash (n=6)** and **diarrhoea (n=3)**
- The pattern of AEs observed with capivasertib was consistent with other PI3K/AKT inhibitors

AE, adverse event; AKT, protein kinase B; FULV, fulvestrant; PI3K, phosphatidylinositol 3-kinase.

Jones R, et al. *Lancet Oncol.* 2020;21:345–57.

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