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

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Targeting the PI3K/AKT pathway in HR+ HER2- advanced breast cancer: Rationale and drug development

Prof. Fabrice André

Director of Research
Gustave Roussy
Villejuif, France

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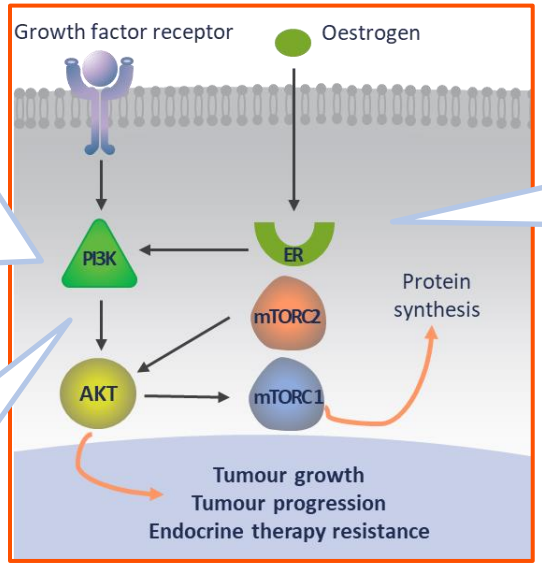
The PI3K/AKT pathway is a key intracellular signalling system driving cellular growth and survival

Activation of the PI3K/AKT pathway plays a role in tumour proliferation and endocrine resistance in breast cancer, making it an attractive therapeutic target[1]

- **PI3Ks** consist of a **p85 regulatory subunit** and a **p110 catalytic subunit with 4 isoforms** (alpha, beta, delta, and gamma)[2,3]
- The different PI3K isoforms have divergent roles in normal and oncogenic signalling[3]

- **PI3K** plays an important role in cell survival, proliferation, growth and glucose metabolism[3]



- There is **cross-talk** between the **ER** and **PI3K pathway**[2]

Adapted from Nunnery S, et al. 2020.[4]

AKT, protein kinase B; ER, oestrogen receptor; mTORC; mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

1. Ciruelos Gil EM. *Cancer Treat Rev.* 2014;40:862–71. 2. Vasan N, et al. *Ann Oncol.* 2019;30(Suppl. 10):x3–11. 3. Thorpe LM, et al. *Nat Rev Cancer.* 2015;15:7–24.
4. Nunnery SE, Mayer IA. *Drugs.* 2020;80:1685–97.

PIK3CA mutations are the most common mechanism of PI3K/AKT pathway activation

About 30–40% of patients with HR+ HER2- advanced breast cancer have PIK3CA mutations[1,2]

The efficacy of **pan-PI3K inhibitors** (buparlisib and pictilisib) in HR+ breast cancer is **restricted by dose-limiting toxicities**[1]

More selective **isoform-specific inhibitors** of **PI3K**, such as alpelisib, target **PI3KCA**[1]

Development of PI3KCA inhibitors is expected to **expand the therapeutic window** of PI3K inhibitors in HR+ advanced breast cancer[1]

AKT, protein kinase B; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PI3K, phosphatidylinositol 3-kinase; PIK3CA; phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene.

1. Rugo HS, et al. *Am Soc Clin Oncol Educ Book.* 2016;35:e40–54. 2. Presti D, Quaquarini E. *Cancers.* 2019;11:1242.

Clinical development of taselisib in advanced breast cancer was halted after modest efficacy data from SANDPIPER

Phase III SANDPIPER study: Taselisib + FULV in post-menopausal women with HR+ HER2- PIK3CA-mutant advanced breast cancer (NCT02340221)[1]

Modest efficacy[1–3]

- **2 months** survival benefit with taselisib + FULV vs placebo + FULV
- Median **PFS** was **7.4** and **5.4** months, respectively; HR=0.70, p=0.0037

Challenging toxicity[1–3]

- AEs led to more **taselisib discontinuations** (**17%** vs **2%**) and **dose reductions** (**37%** vs **2%**), vs placebo
- Most common grade ≥3 AEs with taselisib + FULV were diarrhoea (12%), hyperglycaemia (10%), colitis (3%) and stomatitis (2%)

- Although taselisib is targeted against PIK3CA, dose-limiting AEs may arise due to its off-target action on **delta** and **gamma** isotopes[3]

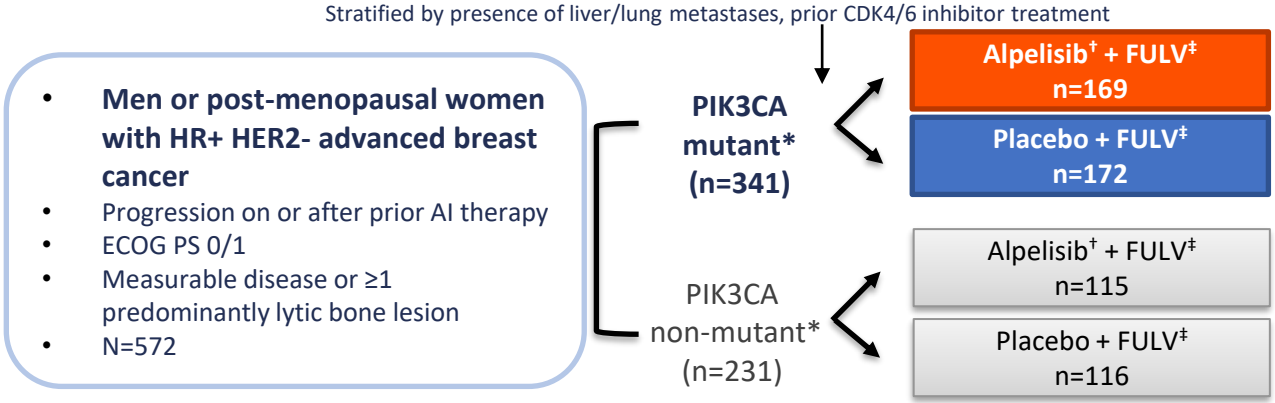
AE, adverse event; FULV, fulvestrant; HR, hazard ratio; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA; phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene.

1. Baselga J, et al. *J Clin Oncol.* 2018;36(Suppl. 18):LBA1006. 2. FierceBiotech, Adams B.ASCO: Roche punts taselisib after weak data, severe side effects. June 2018. Available at: www.fiercebiotech.com/biotech/asco18-roche-punts-taselisib-after-weak-data-severe-side-effects (accessed October 2020). 3. MedPage Today, Smith M. PI3K inhibitor has mixed results in advanced breast cancer. June 2018. Available at: https://www.medpagetoday.com/meetingcoverage/asco/73239 (accessed October 2020). Clinical trials listed by their identifiers at: ClinicalTrials.gov (accessed October 2020).

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 PIK3CA-mutant cohort (locally assessed)
- **Secondary endpoints including:** ORR, clinical benefit and safety

*By tumour tissue; †300 mg PO QD; ‡500 mg IM on days 1 and 15 of first 28-day cycle, then on Day 1 in subsequent cycles.
AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; FULV, fulvestrant; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IM, intramuscular injection; ORR, overall response rate; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene; 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 efficacy results

Treatment with alpelisib + FULV prolonged PFS in patients with PIK3CA-mutated, HR+ HER2- advanced breast cancer, who had received previous endocrine therapy

Median duration of follow-up (randomization to data cutoff) was **20.0 months** (range, 10.7–33.3)

mPFS with alpelisib + FULV was **11.0 months** (95% CI, 7.5–14.5)

mPFS with placebo was **5.7 months** (95% CI, 3.7–7.4)

HR=0.65 (95% CI, 0.50–0.85, p<0.001)

ORR and **CBR** were greater with alpelisib + FULV vs placebo + FULV **(26.6% vs 12.8%)** and **(61.5% vs 45.3%)**, respectively

CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4 and 6; CI, confidence interval; FULV, fulvestrant; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; ORR, overall response rate; mPFS, median progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene.

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 efficacy results

The primary endpoint for the prior CDK4/6 inhibitor + AI group was met* with 50.4% of patients alive without disease progression at 6 months[1,2]

Endpoint	Cohort A (CDK4/6 inhibitor + AI group) (n=121)
Primary endpoint: Patients alive without disease progression at 6 months	**50.4%** (n=61, 95% CI, 41.2–59.6)
Secondary endpoints: Median PFS	**7.3 months** (n=72 [59.5%] with event); 95% CI, 5.6–8.3
ORR	**17.4%** (95% CI, 11.1–25.3)
CBR	**45.5%** (95% CI, 36.4–54.8)

*Lower bound of 95% CI was >30%.

AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4 and 6; CI, confidence interval; ORR, overall response rate; PFS, progression-free survival.

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.

Investigational agents targeting PI3K/AKT in advanced breast cancer

Several new isoform-specific PI3K and AKT inhibitors are in clinical development

Developmental agent	Mechanism of action	Trial	Patients	Recruitment status
GDC-0077	Alpha-specific PI3K inhibitor	NCT03006172 Open-label, phase I dose-escalation study of **GDC-0077 monotherapy** and **GDC-0077 + ET + palbociclib**	Locally advanced or metastatic PIK3CA-mutant solid tumours	Recruiting
		NCT04191499 Randomized, double-blind, placebo-controlled, phase II/III study of **GDC-0077 + ET + palbociclib** vs placebo + ET + palbociclib	Locally advanced or metastatic PIK3CA-mutant, HR+ HER2- breast cancer	Recruiting
Copanlisib	Alpha- and delta-specific PI3K inhibitor	NCT02705859 (Panther) Phase Ib/II open-label, single-arm, adaptive multi-centre study of **copanlisib + trastuzumab**	Pre-treated recurrent or metastatic HER2+ breast cancer	Recruiting
Capivasertib[1]	Inhibitor of three AKT isoforms (AKT1/AKT2/AKT3)	NCT01992952 (FAKTION) Randomized, double-blind, placebo-controlled, phase II study of **capivasertib + fulvestrant** vs placebo + fulvestrant	Postmenopausal women with AI-resistant HR+ HER2- advanced breast cancer	Active, not recruiting
Ipatasertib	Inhibitor of three AKT isoforms (AKT1/AKT2/AKT3)	NCT03337724 (IPATunity130) Randomized, double-blind, placebo-controlled, phase II/III study of **ipatasertib + paclitaxel** vs placebo + paclitaxel	Locally advanced or metastatic PIK3CA/AKT1/PTEN-altered, triple-negative or HR+ HER2- breast cancer	Recruiting

AKT, protein kinase B; AI, aromatase inhibitor; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha protein coding gene; PTEN, phosphatase and tensin homologue.

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

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