Alpelisib (Piqray®) plus fulvestrant for *PIK3CA*-mutated, hormone receptor–positive (HR+) advanced breast cancer

General information [1]

Drug description	Indication
Alpelisib is a α-specific class-I phosphatidylinositol-3-kinase ($PI_3K\alpha$) inhibitor	Alpelisib is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR+, human epidermal growth factor receptor 2 (HER_2)-negative, locally advanced or metastatic breast cancer with a PIK_3CA mutation after disease progression following endocrine therapy as monotherapy.

Current treatment [2]

- **NICE guidelines** for managing HR+, HER_2- advanced breast cancer recommend the following treatments:
  - **Endocrine therapy or chemotherapy:**
    - Offer endocrine therapy as a first-line treatment for the majority of patients with HR+ advanced breast cancer.
    - Offer chemotherapy as first-line treatment for patients with HR+ advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.
    - For patients with HR+ advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy.
  - **Endocrine therapy:**
    - Offer an aromatase inhibitor (either non-steroidal or steroidal) to:
      - postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
      - postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.
    - Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
    - Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.
    - Offer tamoxifen as first-line treatment to men with HR+ advanced breast cancer.
  - **Chemotherapy:**
    - On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.
    - Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.
    - For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:
      - first line: single-agent docetaxel
      - second line: single-agent vinorelbine or capecitabine
      - third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).
  - **Other second-line treatments:**
    - Everolimus: Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced HR+, HER_2- breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor. Everolimus is recommended only if the company provides it with the discount agreed in the patient access scheme.
    - Fulvestrant: Fulvestrant is not recommended within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy. Post-menopausal women currently receiving fulvestrant within its licensed indication as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer whose cancer has relapsed on or after adjuvant antioestrogen therapy, or who have disease progression on anti-oestrogen therapy, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.
  - **Other third-line treatments:**
    - Eribulin: Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
      - it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)
      - the company provides eribulin with the discount agreed in the patient access scheme.

Regulatory status

EMA [1]	FDA [3]
Approval status for this indication: On 28 May 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Piqray®. Date of issue of marketing authorisation valid throughout the European Union: **27/07/2020** The **full indication** is: Piqray® is indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with HR+, HER2-negative, locally advanced or metastatic breast cancer with a PIK3CA mutation after disease progression following endocrine therapy as monotherapy. **Other indications**: none ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 24 May, 2019 the FDA approved Piqray® (alpelisib) tablets, to be used in combination with the FDA-approved endocrine therapy fulvestrant, to treat postmenopausal women, and men, with HR+, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer (as detected by an FDA-approved test) following progression on or after an endocrine-based regimen. **Other indications**: none

Costs

56 Piqray® tablets 150 mg = € 3,200.00 (ex-factory price) [4].
According to the dosing regimen of the SOLAR-1 trial, one month of alpelisib treatment would cost € 3,200.00 + costs for co-administration of fulvestrant.

Posology [5]

Alpelisib should be co-administered with fulvestrant. The recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter.

Warnings and precautions [6]

In patients treated with alpelisib, the following can occur:

- Severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock
- Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS), erythema multiforme (EM), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS); in the SOLAR-1 study, SJS and EM were reported in 0.4% and 1.1% of the patients, respectively.
- Severe hyperglycemia (including ketoacidosis)
- Severe pneumonitis (including acute interstitial pneumonitis and interstitial lung disease)
- Severe diarrhea (including dehydration and acute kidney injury)
- When administered to a pregnant woman, alpelisib can cause fetal harm.

Study characteristics [5, 7, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
SOLAR-1 NCT02437318	572 (a total of 341 patients had *PIK3CA*-mutated disease[1])	**oral alpelisib** at a dose of **300 mg** plus **fulvestrant** (500-mg intramuscular injection on days 1 and 15 of cycle1 and on day 1 of subsequent 28-day cycles)	**placebo** plus **fulvestrant**	PFS	randomized, double-blind, placebo-controlled, phase 3 trial, ongoing[2]	PIK3CA	Novartis Pharmaceuticals	Link

Efficacy (I vs. C)

Cohort with *PIK3CA*-mutated cancer:
Median PFS:11.0 months (95% CI, 7.5 to 14.5) vs. 5.7 months (95% CI, 3.7 to 7.4); HR for progression or death, 0.65; 95% CI, 0.50 to 0.85; p<0.001).
% of patients with PFS at 12 months: 46.3% vs. 32.9%
Overall response: 26.6% vs. 12.8%,
Overall response among patients with measureable disease: 35.7% vs. 16.2%
Clinical benefit: 61.5% vs. 45.3%); **Clinical benefit among patients with measurable disease:** 57.1% vs. 44.1%

Safety (I vs. C)

Grade 3 AEs: n=183/284 (64.4%) vs. n=87/287 (30.3%)
Grade 4 AEs: n=33/284 (11.6%) vs. n=15/287 (5.2%)
SAEs: n=99/284 (34.9%) vs. n=48/287 (16.7%)

[1] Including 169 who were assigned to receive alpelisib plus fulvestrant and 172 who were assigned to receive placebo plus fulvestrant
[2] Solar-1 trial is ongoing until 12/2020

OS in the PIK3CA mutant cohort (months, 95% CI): 40.6 (32.2-NE) vs. 31.2 (26.8-NE); HR (95% CI) 0.77 (0.56-1.06); p=0.06 **QoL**: NR **Cohort without *PIK3CA*-mutated cancer** **Median PFS**: 7.4 months (95% CI, 5.4 to 9.3) vs. 5.6 months (95% CI, 3.9 to 9.1); HR for progression or death, 0.85; 95% CI, 0.58 to 1.25; posterior probability of true HR <1.00, 79.4%; **% of patients with PFS at 12 months:** 28.4% vs. 22.2%	**Death[3]:** n=7/284 (2.5%) vs. n=12/287 (4.2%). A total of 5 vs. 8 patients died from underlying breast cancer. **Discontinuation[4]:** n=71/284 (25.0%) vs. n=12/287 (4.2%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	-	OS: +9.4	0.77 (0.56-1.06)	HR ≤0.70 AND gain ≥9 months	4	+40.5% grade 3-4 AEs	NA	+1/-1[5]	4
Adapted	NC	2a	-	OS: +9.4	0.77 (0.56-1.06)	HR >0.75 OR gain <4 months	1	+40.5% grade 3-4 AEs, +18.2 % SAEs +20.8% discontinuation	NA	-1[6]	0

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[7]	yes[8]	unclear

First published: 05/2020
Last updated: 12/2020

Abbreviations: AE=adverse event, AJ=adjustment, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EM=erythema multiforme, DRESS=drug reaction with eosinophilia and systemic symptoms, EMA=European Medicines Agency, ER=oestrogen receptor, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HER2=human epidermal growth factor receptor 2, HR+=hormone receptor-positive, HR=hazard ratio, Int.=intention, MG=median gain, n=number, NA=not available, NC=not curative, NE=not evaluable, NICE=National Institute for Health and Care Excellence, NR= not reported, SAE=serious adverse event, SCARs=severe cutaneous adverse reactions, SJS= Stevens-Johnson Syndrome, ST=standard treatment, TEN= toxic epidermal necrolysis, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life

References:

1. European Medicines Agency (EMA). Medicines. Piqray. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/piqray.
2. National Institute for Health Research. Alpelisib in combination with fulvestrant for advanced HR positive, HER2-negative breast cancer in men and postmenopausal women [Available from: www.io.nihr.ac.uk/wp-content/uploads/2017/12/9191-Alpelisib-fulvestrant-for-breast-cancer.pdf.
3. U.S. Food and Drug Administration (FDA). FDA approves first PI3K inhibitor for breast cancer [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-pi3k-inhibitor-breast-cancer.
4. Österreichischer Apotheker-Verlag. Warenverzeichnis Online [Available from: https://warenverzeichnis.apoverlag.at/.
5. European Medicines Agency (EMA). Piqray: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/piqray-epar-product-information_en.pdf.

[3] During the trial (including during the 30-day postintervention safety period)
[4] Permanent discontinuation due to AE(s)
[5] Upgrade one level due to a long-term plateau in the PFS curve, and there is >10% improvement in PFS at 1 year & downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.
[6] Downgrade one level due to >10% increased grade ≥3 toxicities/downgrade 1 level if the medicine ONLY leads to improved PFS (mature data shows no OS advantage) and QoL assessment does not demonstrate improved QoL.
[7] Trial is ongoing, not all predefined outcomes reported (yet).
[8] Industry-funded; the trial was designed and overseen by a steering group of medical oncology experts, including representatives from the trial sponsor.

6. U.S. Food and Drug Administration (FDA). Piqray. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212526s001lbl.pdf.
7. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med 2019;380:1929-40.
8. U.S. National Library of Medicine. ClinicalTrials.gov. Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment. (SOLAR-1) [Available from: https://clinicaltrials.gov/ct2/show/study/NCT02437318.