SEQUence of Endocrine therapy in advanced Luminal Breast cancer (SEQUEL-Breast)
A phase 2 study on fulvestrant beyond progression in combination with alpelisib for PIK3CA-mutated, hormone-receptor positive HER2 negative advanced breast cancer.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON54330

Source
ToetsingOnline

Brief title
SEQUEL-Breast trial

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer; HR positive/HER2 negative breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center
Source(s) of monetary or material Support: BOOG,Novartis

Intervention

Keyword: Breast cancer, HR positive/HER2 negative, Metastatic, Progression on fulvestrant

Outcome measures

Primary outcome

- to determine Progression-free survival (PFS), defined as time from study enrollment to disease progression or death from any cause, with censoring when fulvestrant and alpelisib are stopped and another treatment is initiated without confirmed disease progression.

Secondary outcome

- to determine *on treatment* Progression-free survival (PFS), defined as time from study enrollment to disease progression or death from any cause, with censoring when fulvestrant and alpelisib are stopped earlier than disease progression;

- to determine the Objective Response Rate, described as complete response (CR) or partial response (PR);

- to determine the Clinical Benefit Rate, described as stable disease (SD), PR, or CR;

- to determine the Duration of Response (DoR);

- to evaluate safety and tolerability;

- to determine timing and severity of alpelisib-induced hyperglycaemia;

- to determine risk factors for alpelisib-induced hyperglycaemia;

- to assess Quality of Life (QoL);

- to evaluate Patient Reported Outcome Measures (PROMs);

- to compare PFS in patients with the 11 most frequent activating PIK3CA

mutations with PFS in patients with unselected activating PIK3CA mutations

(including rare mutations);

- to determine Overall Survival (OS);

- to determine pharmacokinetics of alpelisib.

Study description

Background summary

In the pivotal SOLAR-1 study alpelisib, a PI3K α-specific inhibitor, added to fulvestrant led to a median progression free survival (PFS)-benefit of 5.3 months (11.0 vs. 5.7 months; HR 0.65; 95% CI, 0.50- 0.85; p<0.001) compared to fulvestrant monotherapy in patients with PIK3CAmutated, hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer (Andre et al , 2019). In this study men and postmenopausal women were included who relapsed or progressed on or after adjuvant or palliative treatment with an aromatase inhibitor (AI) and had not received fulvestrant previously. Only ~ 6% of the patients had already received a Cyclin-Dependent Kinase 4/6-(CDK4/6) inhibitor. Around half of the patients was treated in first and the other half in second line.
In the current phase 2 study we will investigate the efficacy of the combination of fulvestrant and alpelisib directly after progression on 1st or 2nd line therapy with fulvestrant with or without a CDK 4/6 inhibitor in patients with HR+HER2- advanced breast cancer with tumors harboring an activating PIK3CA mutation. Primary endpoint is PFS. The aim is to determine a clinically meaningful median PFS of at least six months.

Study objective

In the current phase 2 study we will investigate the efficacy of the combination of fulvestrant and alpelisib directly after progression on 1st or 2nd line therapy with fulvestrant with or without a CDK 4/6 inhibitor in patients with HR+HER2- advanced breast cancer with tumors harboring an activating PIK3CA mutation. Primary endpoint is PFS. The aim is to determine a clinically meaningful median PFS of at least six months.

Study design

phase 2 study

Intervention

Alpelisib 300mg once daily (may be reduced to 1dd250 or 1dd200mg in case of toxicity) + fulvestrant 300mg 1x/four weeks.

Study burden and risks

Since extensive pre-clinical and clinical studies have been performed, effect and possible toxicities of alpelisib are rather predictable. The toxicities are described in the protocol.
There is growing experience with toxicity management from previous and ongoing clinical studies. Data from these studies show that common toxicities are generally manageable by common clinical practices. Furthermore, alpelisib does not inhibit PIK3CA-pathway irreversibly and half-time is only 8-9 hours, so if severe toxicity were to occur, the effects will likely be reversible within days. In our opinion, the burden and risks are justified by the potential benefits. We consider the risk of partaking in the study to be low, especially since the treatment given in the study is also commercially available for this population, and applied. Hence, patients participating in the study will not be subject to any additional risk. Patients in the study will be carefully assessed for any toxicities, and given instructions on how to seek medical support when necessary.
The potential benefit (PFS increase) justifies these risks for this group of patients with advanced breast cancer, status after two lines of systemic treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Adult women and men (>= 18 years of age) with proven diagnosis of adenocarcino-ma of the breast with locoregional recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated
* Estrogen receptor (ER) expression >10% and/or progesterone receptor (PR) expression >10% breast cancer based on local la-boratory results. Tumor must be HER2- as defined by ASCO-CAP guidelines
* Patients must have progressed on fulvestrant as a preceding treatment line (as first or second line therapy)
* Previous treatment with a CDK4/6 inhibitor in the advanced setting
* The presence of an activating PIK3CA mutation
* Evaluable disease* as defined per RECIST v.1.1
* Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 or 2

Exclusion criteria

* Patients with advanced, symptomatic, visceral spread, who are at risk of life-threatening complications in the short term
* Known active uncontrolled or symptomatic CNS metastases, carcinomatous

meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth
* Prior treatment with an PI3K /AKT/mTOR inhibitor
* Prior treatment with chemotherapy in the advanced setting
* (prior) use of oral SERD in any setting
* Type 1 diabetes or uncontrolled type 2 diabetes (Hba1C > 68 mmol/mol)
* Clinically significant, uncontrolled heart disease and/or recent cardiac events

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-06-2022
Enrollment:	130
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Piqray
Generic name:	Alpelisib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	09-03-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-03-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	12-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-004191-33-NL
ClinicalTrials.gov	NCT05392608
CCMO	NL78749.031.21