A phase II study of pembrolizumab and eribulin in patients with HR-positive/HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes

KELLY study (KEytruda and EribuLin in Luminal breast cancer)

Sponsor:	Medica Scientia Innovation Research (MedSIR).
Author:	[redacted]
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SIGNATURE PAGE FOR THE STATISTICAL ANALYSIS PLAN

MEDOPP127

Sponsor:	Medica Scientia Innovation Research (MedSIR)
Author:	[redacted]
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Author, signature and date:	[redacted] [redacted]

1. Synopsis

Type of application	Clinical Trial
Sponsor	Medica Scientia Innovation Research (MedSIR) Rambla Cataluña, 2-4, 2D, 08007-Barcelona, Spain Tel.: + 34 93 221 41 35; Fax: + 34 93 299 23 82
Clinical trial title	"A phase II study of pembrolizumab and eribulin in patients with HR-positive/HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes. KELLY study (KEytruda and EribuLin in Luminal breast cancer)."
Protocol number	MEDOPP127
Study Coordinator and Principal Investigator	[redacted]
Expected sites	11
Central Ethics Committee/Institutional Review Board	CEIC Hospital Arnau de Vilanova de Valencia
Name and qualification of the persons in charge of Monitoring	Experior, S.L. C/ Vicente Galmés, 1A; 46139 La Pobla de Farnals (Valencia) Tel.: 902.105.255; Fax: 96.145.21.91
Investigational drug	**Halaven®; Keytruda®**.
Trial phase	II
Objectives	**Primary objective:** • To assess the efficacy -as determined by the clinical benefit rate (CBR) (total number of objective responses plus stable disease for at least 24 weeks) based on RECIST v.1.1- of MK3475 (pembrolizumab) in combination with eribulin in patients with HR-positive/HER2-negative MBC who have previously received an anthracycline and a taxane (for either early or advanced disease), unless contraindicated, and between one to two lines of chemotherapy in the metastatic setting. **Secondary objectives:**

- To determine the CBR based on RECIST v.1.1 in subjects with programmed death ligand-1 (PD-L1) positive tumors.
- To determine the progression-free survival (PFS) based on RECIST v.1.1.
- To determine the PFS based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To determine the overall survival (OS) (OS will be determined at the end of the study).
- To determine the OS in subjects with PD-L1 positive tumors.
- To determine the overall response rate (ORR) based on RECIST v.1.1.
- To determine the ORR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To determine the duration of response (DoR) based on RECIST v.1.1.
- To determine the DoR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To assess the safety and tolerability of MK3475 (pembrolizumab) in combination with eribulin according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

Exploratory objectives:

[redacted]

	[redacted]
[redacted]	[redacted]
Design	Multicenter, open-label, phase II clinical trial.
Primary endpoint	The primary endpoint of this study is to assess the CBR based on RECIST v.1.1.
Study population and total number of subjects	Female patients age ≥ 18 years with advanced HR-positive/HER2-negative breast cancer previously treated with anthracyclines and taxanes. A total of 44 patients will be enrolled into this trial.
Approximate duration of subject participation	All eligible patients will be treated with MK3475 (pembrolizumab) 200 mg on day 1 of each 21-day cycle and eribulin 1.23 mg/m2 (equivalent to eribulin mesylate at 1.4 mg/m2) on days 1 and 8 of every 21-day cycle. Treatment with MK3475 (pembrolizumab) and eribulin will continue based on physician criteria. No maximum duration of treatment is specified. Study follow-up will be performed 12 months after last study dose.
Calendar and estimated completion dates	Recruitment period is planned to be opened for 11 months. The end of study will be 12 months after last study dose or progressive disease experienced in all patients or when the

	trial is terminated by the Sponsor, whichever is earlier. This data point will be considered: • End of Recruitment (LPI) (11 months): August 2018 • Last Patient Last Visit (LPLV): August 2019 • Final Study Report: December 2019

2. Table of contents

3. Abbreviations

AE:	Adverse Event.
AF:	Absolute frequency.
ATC:	Anatomical Therapeutic Chemical.
C1D1:	Cycle 1 Day 1.
CBR:	Clinical benefit rate.
CI:	Confidence Interval.
CR:	Complete Response.
CTCs:	Circulating Tumor Cells.
CTCAE:	Common Terminology Criteria for Adverse Events.
DoR:	Duration of Response.
ECG:	Electrocardiogram.
eCRF:	electronic Case Report Form.
ECOG:	Eastern Cooperative Oncology Group.
ER:	Estrogen Receptor.
EOT:	End Of Treatment.
FDA:	Food and Drug Administration.
HBV:	Hepatitis B Virus.
HCV:	Hepatitis C Virus.
HIV:	Human Immunodeficiency Virus.
HR:	Hormone Receptor.
IC:	Informed Consent.
irRECIST:	immune-related Response Evaluation Criteria in Solid Tumors.
ITT:	Intention To Treat.
LPI:	End of recruitment date.
LPLV:	Last patient last visit.

LVEF:	Left Ventricular Ejection Fraction.
MBC:	Metastatic Breast Cancer.
MEDDRA:	Medical Dictionary for Regulatory Activities.
NA:	Not available.
NCI:	National Cancer Institute.
ORR:	Overall Response Rate.
OS:	Overall Survival.
PD-L1:	Programmed cell Death 1-Ligand.
PFS:	Progression Free Survival.
PR:	Partial Response.
PR:	Progesterone Receptor.
PT:	Preferred Term.
Q1:	First quartile.
Q3:	Third quartile.
RECIST:	Response Criteria In Solid Tumors.
SD:	Stable Disease.
SDev:	Standard Deviation.
SAE:	Serious Adverse Event.
SOC:	System Organ Class.

4. Study objectives and variables

4.1 *Primary objective(s) and primary variable(s)*

Primary objective:

To assess the efficacy -as determined by the CBR (total number of objective responses plus stable disease for at least 24 weeks) based on RECIST v.1.1- of MK3475 (pembrolizumab) in combination with eribulin in patients with HR-positive/HER2-negative MBC who have previously received an anthracycline and a taxane (for either early or advanced disease), unless contraindicated, and between one to two lines of chemotherapy in the metastatic setting.

Primary endpoint:

To determine the CBR based on RECIST v.1.1.

4.2 *Secondary objective(s) and secondary variables*

Secondary objectives:

- To determine the CBR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To determine the PFS based on RECIST v.1.1.
- To determine the PFS based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To determine the OS (OS will be collected at the end of the study).
- To determine the OS in subjects with PD-L1 positive tumors.
- To determine the ORR based on RECIST v.1.1.
- To determine the ORR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To determine the DoR based on RECIST v.1.1.
- To determine the DoR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- To assess the safety and tolerability of MK3475 (pembrolizumab) in combination with eribulin according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

Secondary endpoints:

- CBR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- PFS based on RECIST v.1.1.
- PFS based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- OS (OS will be collected at the end of the study).
- OS in subjects with PD-L1 positive tumors.
- ORR based on RECIST v.1.1.
- ORR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- DoR based on RECIST v.1.1.
- DoR based on RECIST v.1.1 in subjects with PD-L1 positive tumors.
- Safety.

4.3 *Exploratory objective(s) and exploratory variables*

Exploratory objectives:

[redacted]

Exploratory endpoints:

[redacted]

4.4 *Safety evaluation*

The safety evaluation has been included in secondary objective (see 4.2).

4.5 *Determination of sample size*

The accrual objective are 44 patients, with an exact single-stage phase II design. The primary endpoint for this study is the CBR. CBR will be evaluated according to the RECIST criteria v.1.1. The CBR of MK3475 (pembrolizumab) in combination with eribulin will be assessed with the exact binomial test. In designing the trial, a CBR of 30% is deemed to be unacceptable in this patient population [16]. In contrast, a CBR of 50% would be considered to be successful. At least 17 patients with clinical benefit among 39 patients will be adequate to justify the investigation of this strategy in further clinical trials. Considering a drop-out rate of 10%, a sample size of 44 patients will be needed to attain 80% power at nominal level of one-sided alpha of 0.05.

4.6 [redacted]

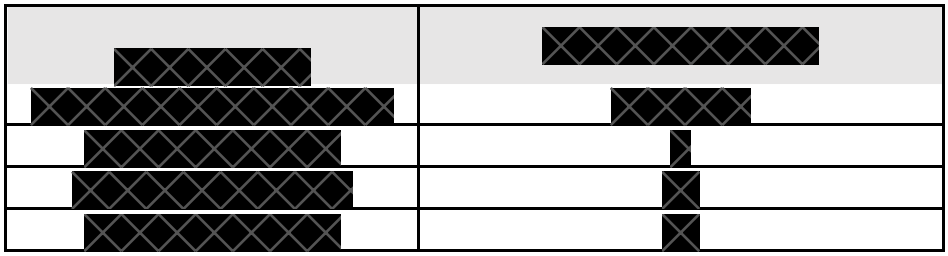
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



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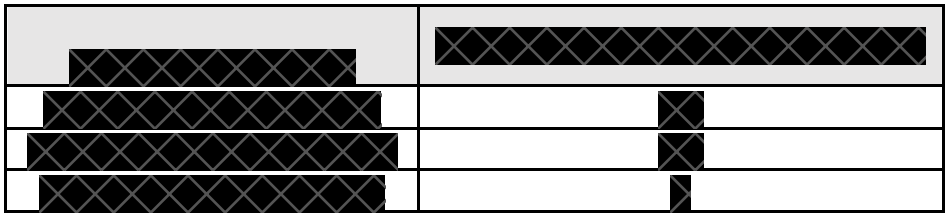

- [redacted]

[redacted]

5. Study populations

The analysis sets will be defined as follows:

Full analysis set

Full analysis set will include all patients that accomplish selection criteria and receive at least one drug exposure.

Per-protocol set

Per-protocol set will include all patients that accomplish selection criteria, receive at least one drug exposure, and receive the protocol required study drug exposure and processing. Criteria for determining the “per protocol” group assignment would be established by the Steering Committee before the statistical analysis begins.

This analysis will only occur if this set differs by ≥ 10% from the full analysis set.

Experior will send a list of protocol deviations (major and minor) to establish the per-protocol set after the close out of data base (see section 5.1).

Intent-to-treat (ITT) set with PD-L1 positive tumors

ITT set will include all patients with PD-L1 positive tumors that accomplish selection criteria and receive at least one drug exposure.

[redacted]

Safety set

The safety set includes patients who receive at least one dose of study medication.

5.1 *Protocol deviations*

Major deviation is defined as a breach that may significantly affect the safety and rights of the trial subjects or the reliability and robustness of the data generated in the clinical trial.

Minor deviation is defined as conditions, practices or processes that indicate a need for improvement but are not expected to harm the rights, safety or well-being of the patients and/or the quality of the data.

Listings of protocol deviations will be reviewed prior to database lock and them will be send to sponsor in the closeout phase.

To determine per protocol set, all major protocol deviations will be check, and a list of exclude patients of the statistical analysis will be established by the Steering Committee.

Data Management unit will review the following protocol deviations according to the data registered in the eCRF:

- Inclusion/exclusion criteria not met.
- Tumor assessments out of window (according to the protocol).
- Visits out of window (according to the protocol).
- Specific evaluations (ECOG, vital signs, hematology, etc.) not performed.
- Prohibited medication administered.
- Adjustments of dose not performed according to the protocol.
- Study treatment interruptions > 21 days.
- Study treatment administration out of window.

Furthermore, Project Manager/CRA will provide a list of major protocol deviations registered during the monitoring visits period.

6. Statistical strategy

Below are detailed the statistical aspects of the data analysis.

6.1 *Primary analysis*

Primary analysis will be based primarily on the Full analysis set and secondarily on the Per protocol analysis set (if applicable, see section 5).

6.1.1 *Summary statistics*

CBR is defined as the number of subjects with complete response (CR), partial response (PR) or stable disease (SD) for at least 24 weeks divided by the number of patients in the analysis set.

CBR= (CR+PR+SD) / Total number of patients

The CBR results will be presented as number and proportion of patients with clinical benefit and 95% CI of the proportion.

6.1.2 *Statistical inference*

- The study will be declared positive in the analysis of CBR if the one-sided p-value estimated in accordance with exact binomial test is ≤ 0.05. With this criterion, we will reach a positive finding if ≥ 17 patients achieve a clinical benefit among 39 patients.
- With this design, there is an 80% power of a positive finding if the true CBR is ≥ 50%. The one-sided type I error is 0.05.

6.2 *Secondary analysis*

Secondary analysis will be performed on full analysis and per-protocol sets. Safety objectives will be based on the safety set. ITT set will be used to analyze the objectives based in subjects with PD-L1 positive tumors.

6.2.1 *Summary statistics*

Efficacy:

- CBR is defined as the number of subjects with complete response (CR), partial response (PR) or stable disease (SD) for at least 24 weeks based on RECIST v.1.1 divided by the number of patients in the analysis set (in subjects with PD-L1 positive tumors). Tumor response will be defined as best response. The CBR results will be presented as number and proportion of patients with clinical benefit and 95% CI of the proportion.
- The radiological PFS is defined as the time from the first dose of treatment until death by any cause or objective tumor progression according to RECIST v.1.1. Patients with

no progression or death will be censored at the date of their last evaluable imaging. PFS censoring rules will follow FDA guidance in 2007 (see Table 1 - Appendix I).

- The first dose of treatment is defined as the minimum date of the first administration of eribulin and/or pembrolizumab.

- The PFS as assessed by investigator is defined as the time from the first dose of treatment until death by any cause or objective tumor progression as assessed by investigator according to RECIST v.1.1. Patients with no progression or death will be censored at the date of their last evaluable imaging. PFS censoring rules will follow FDA guidance in 2007 (see Table 2- Appendix I).

  - oThe first dose of treatment is defined as the minimum date of the first administration of eribulin and/or pembrolizumab.

- The OS is defined as the time from the first dose of treatment until death by any cause or the last date the patient was known to be alive. Patients who are lost to follow-up and the patients who are alive at the date of data cut-off will be censored at the date the patient was last known alive (censoring rules are specified in Table 3 - Appendix I).

  A Kaplan-Meier survival analysis will be carried out to analyse PFS and OS. Number of events, median survival time and the corresponding 95% CI will be provided. Survival curves will be reported.

- The ORR is defined as the number of patients with CR and PR divided by the number of patients in the analysis population. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST v.1.1. ORR will be reported as a proportion with the corresponding 95% CI.

- The DoR is defined as the time from first documented CR or PR until disease progression or death from any cause, according to RECIST v.1.1. In case of the patient first reaching PR and later CR, the duration of CR will be measured and reported separately, starting from the date when first documented and ending when a progressive disease is diagnosed, or the patient dies.

  Patients without PD or death will be censored and patients who has not documented neither CR nor PR response will be considered as not available in the Kaplan Meier analysis.

  Number of events, median survival time, 95% CI of median and survival curves calculated with Kaplan Meier analysis will be provided.

<u>Safety:</u>

- The degree of exposure (dose, duration of treatment, number of patients) will be assessed to determine the degree to which study safety can be assessed. These results will be presented with descriptive statistics (n, NA, mean, standard deviation, median and range).
- Adverse events (AEs) and serious AEs (SAEs) will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term (PT) and by system organ class (SOC). Severity, relationship to study drug (eribulin and pembrolizumab), action taken and outcome will be reported as frequency tables.
- Concomitant medications will be coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating 1st to 4th levels. The results will be reported by frequency tables.
- Deaths and study discontinuations will be described and assessed. It will be reported by frequency tables.

6.2.2 *Statistical inference*

A Kaplan-Meier survival analysis will be performed to analyze PFS, OS and DoR. The number of events and the median survival time with corresponding 95% CI will be provided.

1- and 2-year survival rates with corresponding 95%CI will be calculated.

Comparisons using log rank test or model of Cox proportional hazards multivariate analysis will be used if needed, and P values of 0.05 or less will be considered to indicate statistical significance.

6.3 *Exploratory analysis*

[redacted]

6.3.1 *Summary statistics*

[redacted]

[redacted]

6.4 *Subgroup analysis*

Subgroup analysis for CBR, ORR, PFS, OS and DoR will be performed outside the indications of the study protocol. The following variables will be part of this analysis to explore differences between subgroups of subjects:

- Ki67 ranges (≤ 13% (low), 14-19% (medium), ≥ 20% (high))
- Previous treatment with CDK4/6 inhibitor
- Previous treatment with PI3K inhibitor

The next variables will be used for the PFS, CBR and ORR subgroup analysis:

- Previous treatment with mTOR inhibitor
- ECOG (0 vs. 1)
- Number of organs involved (< 3 organs vs. ≥ 3 organs)
- Number of chemotherapy lines in metastatic setting (1 line vs. 2 lines)
- Endocrine sensitivity. Defined according to either of the following criteria:
    - Relapse that occurred after at least 24 months while the patient was receiving adjuvant endocrine therapy.
    - Progression that occurred after at least 24 weeks while the patient was receiving endocrine therapy in the context of metastatic disease.
- Neutrophil/Lymphocyte, ratio (<3 vs >=3)

6.5 *Statistical methods*

[redacted]

6.6 *Safety analysis*

The safety analysis has been included in secondary analysis (see 6.2.1).

6.7 *Demographic and baseline characteristics*

Demographic and baseline characteristics will be analyzed using the full analysis set.

Descriptive statistics will use for the analysis: continuous variables will be summarized as n, number of not available data (NA), mean, standard deviation (SDev), median, first and third quartiles, minimum and maximum values. For categorical variables frequency tables will be presented (n and %).

Demographic and baseline variables are:

- Age (at the IC signature)
- Race
- Clinically significant disease and surgical interventions (they will be coded with MedDRA)
- Toxic habits
- History of cancer
    - Number of relapses
    - Hormone receptors: ER and PR values
    - Ki67
    - HER2 status
    - Patients treated with anthracyclines, taxanes and antihormone therapy.

- Previous antineoplastic treatment for breast cancer. They will be classified as:
  - Chemotherapy: Antracycline, Taxanes, Capecitabine, Vinorelbine, Other
  - Endocrine therapy: Tamoxifen, Aromatase Inhibitors, Fulvestrant.
  - Target therapy: CDK4/6 inhibitors, ParP inhibitors, mTOR inhibitors.
- Previous procedure for breast cancer (surgery/radiotherapy).
- HIV, HBV, HCV serology.
- Physical examination and ECOG status.
- Vital signs / ECG / LVEF.
- Hematology and coagulation.
- Biochemistry and thyroid function.
- Evolution tables will be presented for laboratory values (hematology, biochemistry, coagulation, thyroid function). Data will be summarized with descriptive statistics for baseline and post-dose values.
- Frequencies for toxicities related to clinically significant laboratory values will be presented (for 2-5 CTCAE grades).

6.8 *Statistical model assumptions*

The proportional hazards assumption in the Cox model will be checked.

6.9 *Transformation of expected variables*

- The CBR is defined as the proportion of subjects who have best overall response of CR, PR or SD (by RECIST v.1.1):

  CBR= (CR+PR+SD)/Total of subjects

- The ORR is defined as the proportion of subjects who have best overall response of CR or PR (by RECIST v.1.1):

  ORR= (CR+PR)/Total of subjects

- The time to progression is defined as the difference between start of study drug (C1D1) and the progression date or death (whichever occurs first) or the last tumor assessment documented.

- The time to death is defined as the difference between start of study drug and the date of death.
- Duration of response (DoR) is defined as the difference between first documented CR or PR and the disease progression date (by RECIST v.1.1) or death.
- Duration of treatment is defined as the difference between the first dose administrated of study drug (eribulin and/or pembrolizumab) and the date of EOT visit. If no date of EOT is available, the last administration of study drug will be used.

6.10 *Handling of missing data*

There is no planned procedure of imputation of missing values in other variables. The analysis will be performed with the available data.

6.11 *Description of the softwares to be used for data analysis*

Statistical programming and analyses will be performed using the R statistical software version 3.1.3.

6.12 *Interim analysis protocol*

No interim analysis is planned.

6.13 *List of tables and figures*

The tables below are an approximated list of the tables and figures that will be shown in the statistical analysis. They will be able to modify as required.

List of tables:

Descriptive statistics for the age at the informed consent signature

Absolute and relative (%) frequencies for the race

Absolute and relative (%) frequencies for significant disease and surgical intervention (registered in medical history).

Absolute and relative (%) frequencies for toxic habits

Descriptive statistics for number of relapses

Absolute and relative (%) frequencies for hormonal receptors (ER, PR) and HER2 status

Descriptive statistics for Ki67

Absolute and relative (%) frequencies for patients treated with anthracyclines, taxanes and antihormone therapy (previous treatments)

Absolute and relative (%) frequencies for patients treated with chemotherapy, endocrine therapy and target therapy.

Absolute and relative (%) frequencies for previous procedure for breast cancer (surgery/radiotherapy)

Absolute and relative (%) frequencies for HIV, HBV HCV

Absolute and relative (%) frequencies for physical examination and ECOG status at screening visit

Descriptive statistics for vital signs, ECG and LVEF at screening visit

Descriptive statistics for laboratory tests (hematology, biochemistry and thyroid function)

Absolute and relative (%) frequencies for toxicities (2 to 5 CTCAE grades) related to clinically significant laboratory values

Absolute and relative (%) frequencies for the best response according to RECIST v1.1 criteria.

Results of CBR (proportion, % and 95% CI)

Results for CBR vs. Ki67 ranges

Results for CBR vs. previous treatment with CDK4/6 inhibitor

Results for CBR vs. previous treatment with PI3K inhibitor

Results for CBR vs. previous treatment with mTOR inhibitor

Results for CBR vs. PD-L1

Results for CBR vs. ECOG

Results for CBR vs. number of organs involved

Results for CBR vs. lines of chemotherapy in metastatic setting

Results for CBR vs. endocrine sensitivity

Results for CBR vs. Neutrophil/Lymphocyte, ratio (<3 vs >=3)

Absolute and relative (%) frequencies for progression disease events and/or deaths

Descriptive statistics for PFS (according to RECIST v1.1 criteria)

Results for PFS (according to RECIST v1.1 criteria) vs. Ki67 ranges

Results for PFS (according to RECIST v1.1 criteria) vs. previous treatment with CDK4/6 inhibitor

Results for PFS (according to RECIST v1.1 criteria) vs. previous treatment with PI3K inhibitor

Results for PFS (according to RECIST v1.1 criteria) vs. previous treatment with mTOR inhibitor

Results for PFS (according to RECIST v1.1 criteria) vs. PD-L1

Results for PFS (according to RECIST v1.1 criteria) vs. ECOG

Results for PFS (according to RECIST v1.1 criteria) vs. number of organs involved

Results for PFS (according to RECIST v1.1 criteria) vs. lines of chemotherapy in metastatic setting

Results for PFS (according to RECIST v1.1 criteria) vs. endocrine sensitivity

Results for PFS (according to RECIST v1.1 criteria) vs. Neutrophil/Lymphocyte, ratio (<3 vs >=3)

Descriptive statistics for PFS (according to investigator criteria)

Results for PFS (according to investigator criteria) vs. Ki67 ranges

Results for PFS (according to investigator criteria) vs. previous treatment with CDK4/6 inhibitor

Results for PFS (according to investigator criteria) vs. previous treatment with PI3K inhibitor

Results for PFS (according to investigator criteria) vs. previous treatment with mTOR inhibitor

Results for PFS (according to investigator criteria) vs. PD-L1

Results for PFS (according to investigator criteria) vs. ECOG

Results for PFS (according to investigator criteria) vs. number of organs involved

Results for PFS (according to investigator criteria) vs. lines of chemotherapy in metastatic setting

Results for PFS (according to investigator criteria) vs. endocrine sensitivity

Results for PFS (according to investigator criteria) vs. Neutrophil/Lymphocyte, ratio (<3 vs >=3)

Descriptive statistics for PFS (according to irRECIST v1.1 criteria)

Descriptive statistics for OS

Results for OS vs. Ki67 ranges

Results for OS vs. previous treatment with CDK4/6 inhibitor

Results for OS vs. previous treatment with PI3K inhibitor

Results for OS vs. PD-L1

Results of ORR (proportion, % and 95% CI) (according to RECIST v1.1 criteria)

Results for ORR vs. Ki67 ranges

Results for ORR vs. previous treatment with CDK4/6 inhibitor

Results for ORR vs. previous treatment with PI3K inhibitor

Results for ORR vs. previous treatment with mTOR inhibitor

Results for ORR vs. PD-L1

Results for ORR vs. ECOG

Results for ORR vs. number of organs involved

Results for ORR vs. lines of chemotherapy in metastatic setting

Results for ORR vs. endocrine sensitivity

Results for ORR vs. Neutrophil/Lymphocyte, ratio (<3 vs >=3)

Results of ORR (proportion, % and 95% CI) (according to irRECIST v1.1 criteria)

Descriptive statistics for DoR

Results for DoR vs. Ki67 ranges

Results for DoR vs. previous treatment with CDK4/6 inhibitor

Results for DoR vs. previous treatment with PI3K inhibitor

Results for DoR vs. PD-L1

Descriptive statistics for dose of study treatment

Descriptive statistics for duration of treatment

Absolute and relative (%) frequencies for adverse events (coded as PT and SOC terms from MedDRA): severity, relationship to study drugs, action taken and outcome

Absolute and relative (%) frequencies for concomitant medication (coded using ATC)

Absolute and relative (%) frequencies for deaths and discontinuations

List of figures

Kaplan-Meier curves for PFS (according to RECIST v1.1 criteria) and subgroups

Kaplan-Meier curves for PFS (according to investigator criteria) and subgroups

Kaplan-Meier curves for PFS (according to irRECIST v1.1 criteria)

Kaplan-Meier curves for OS and subgroups

Kaplan-Meier curves for DoR and subgroups

7. References

1. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL (http://www.R-project.org/).

2. Guidance for Industry: Clinical Trail Endpoints the Approval of Cancer Drugs and Biologics (May 2007).

Appendix I

Table 1. Censoring rules for PFS

Situation	Date of progression or censoring	Outcome
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions); Or	Progressed
Death before first progression disease assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
No progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation for toxicity or other reason*	Date of last radiological assessment of measured lesions	Censored
Death or progression after more than one missed visit *	Date of last radiological assessment of measured lesions	Censored

* In accordance with these criteria death after the end of treatment visit will be considered as censored with the date of last radiological assessment of measured lesions.

Table 2. Censoring rules for PFS as assessed by investigator.

Situation	Date of progression or censoring	Outcome
No baseline assessment	Randomization + 1 day	Censored
Progression documented* between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Investigator's claim of progression*	Scheduled visit (or next scheduled visit if between visits)	Progressed
Treatment discontinuation for toxicity or other reason **	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first progression disease assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death after an extended lost-to-followup time (two or more missed assessments)**	Last visit with adequate assessment	Censored

* In addition to the progressions confirmed by radiological criteria, also the progressions evaluated by the investigator, without a radiological image confirming them, will be considered as PFS events.

** In accordance with these criteria death after the end of treatment visit will be considered as censored with the date of last adequate assessment.

Table 3. Censoring rules for OS

Situation	Date of death or censoring	Outcome
Death during study follow-up	Date of death	Death
The patient is alive at last follow-up	Date of last follow-up	Censored