NCT number: NCT03284957

# STATISTICAL ANALYSIS PLAN

**A phase 1/2 study for safety, efficacy, pharmacokinetic and pharmacodynamics evaluation of SAR439859, administered orally as monotherapy, then in combination with palbociclib in postmenopausal women with estrogen receptor-positive advanced breast cancer**

**SAR439859-TED14856**

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## TABLE OF CONTENTS

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AESI: | adverse event of special interest |
| AI: | aromatase inhibitor |
| ALT: | alanine aminotransferase |
| aPTT: | activated partial thromboplastin time |
| AST: | aspartate aminotransferase |
| ATC: | anatomical, therapeutic and chemical |
| BUN: | blood urea nitrogen |
| CDK4/6i: | CDK4/6 inhibitor |
| CTCAE: | Common Terminology Criteria for Adverse Events |
| ECOG: | Eastern Cooperative Oncology Group |
| eCRF: | electronic case report form |
| HLGT: | high-level group term |
| HLT: | high-level term |
| HRQL: | health-related quality of life |
| ICR: | Independent Central Review |
| IMP: | investigational medicinal product |
| INR: | international normalized ratio |
| LLT: | lower-level term |
| MDRD: | modification of diet in renal disease |
| MedDRA: | Medical Dictionary of Regulatory Activities |
| MRD: | minimal residual rate |
| mTORi: | mTOR inhibitor |
| NCI: | National Cancer Institute |
| PgR: | progesterone receptor |
| PI3Ki: | PI3K inhibitor |
| PS: | performance status |
| PT: | preferred term |
| RBC: | red blood cell |
| SAP: | statistical analysis plan |
| sCr: | serum creatinine |
| SERD: | selective estrogen receptor down-regulator |
| SERM: | selective estrogen receptor modulator |
| SOC: | system organ class |
| TEAE: | treatment-emergent adverse event |
| TTP: | time to progression |
| WBC: | white blood cells |
| WHO-DD: | World Health Organization-Drug Dictionnary |

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN

This is an open-label, non-comparative, dose escalation and dose expansion, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PDy) evaluation study of SAR439859 administered orally as monotherapy (Parts A and B), in combination with palbociclib (Parts C and D), in combination with alpelisib (Parts F and G), in combination with everolimus (Parts H and I) and in combination with abemaciclib (Parts J and K). SAR439859 is given once daily or twice daily to postmenopausal women with estrogen receptor (ER) positive advanced breast cancer.

The duration of the study for a participant will include a period for screening of up to 4 weeks. The cycle duration is 28 days. Participants will continue study treatment until disease progression, unacceptable toxicity, participant wish to stop the study, or any other reason, whichever comes first.

The study will be performed in ten parts divided in 5 arms:

- Arm 1 - SAR439859 monotherapy
  - Part A: escalation phase
  - Part B: expansion phase
- Arm 2 - SAR439859 in combination with palbociclib:
  - Part C: escalation phase
  - Part D: expansion phase
- Part E: Cancelled
- Arm 3 - SAR439859 in combination with alpelisib
  - Part F: safety run-in phase
  - Part G: expansion phase
- Arm 4 – SAR439859 in combination with everolimus
  - Part H: escalation phase
  - Part I: dose expansion phase
- Arm 5 – SAR439859 in combination with abemaciclib
  - Part J: escalation phase
  - Part K: dose expansion phase

Enrollment of participants in Parts B, C, F, H and J will be initiated after completion of dose escalation in Part A, and identification of MTD/RD, and can be conducted in parallel. Participants' entry criteria in Parts B, C and D are slightly different with regards to prior anticancer therapy. At the sites enrolling participants in any study part, when a selected participant is potentially eligible for Parts B and C or D, priority will be given to Parts C and D.

Approximately 251 participants will be enrolled overall from up to 40 sites.

### 1.1.1 Arm 1 - SAR439859 as monotherapy

#### *1.1.1.1 Part A - Escalation phase with SAR439859 as monotherapy*

Three to 6 participants will be treated at each dose level depending on DLTs observed in the first 3 participants. If one of the first 3 evaluable participants experiences DLT during Cycle 1, this cohort will be expanded with a total of up to 6 participants. If less than 1 out of 3 participants or less than 2 out of 6 participants experienced a DLT at a given DL, the dose escalation will proceed to the next DL.

**Table 1 - SAR439859 dose levels in Part A**

| Dose Level (DL)[a] | SAR439859 (mg) |
|---|---|
| *DL(-1) QD* | *10 once daily* |
| DL1 QD | 20 once daily |
| *DL1bis QD* | *50 once daily* |
| DL2 QD | 100 once daily |
| *DL2bis QD* | *150 once daily* |
| DL3 QD | 200 once daily |
| DL 4 QD | 400 once daily |
| DL4 bis BID | 200 twice daily |
| DL5 | 600 once daily |
| DL5 bis BID | 300 twice daily |

*a* Additional intermediate or higher dose levels can be tested after agreement between Sponsor and investigators (study committee)
A BID schedule of administration may be added during the study. The starting dose will be a DL of the same dose intensity as the highest cleared DL with QD Schedule. Other Schedules of administration may be added during the study.

In addition, depending on $^{18}$FES-PET scan results at DL1 and DL2, the intermediate dose levels (DL1bis and DL2bis) could be explored. From these two DLs, DL1bis and DL2bis, the next DLs (DL2 and DL3 respectively) should not be skipped.

At subsequent dose levels (≥DL3), other intermediate or higher dose levels may be tested based on safety, $^{18}$FES-PET scan results (if all participants have >90% inhibition of the target) and PK parameters upon recommendation from the Study Committee.

The second and third participants of a given cohort can only be enrolled when the first participant will have received at least one week of SAR439859 without DLT. The enrollment of the next DL may not proceed before at least 3 participants treated at the current DL have been followed for at least one cycle (ie, 28 days) and are evaluable for DLT assessment.

Participants who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT must be replaced.

The dose escalation will stop when the maximum administered dose (MAD) is reached, MAD being defined as the dose at which ≥33% (2 participants out of up to 6) of evaluable participants have experienced a DLT at Cycle 1.

Although the dose escalation is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations should also be considered for the dose escalation and the dose selection decisions, as well as any other relevant information, upon recommendation from the Study Committee.

The recommended dose (RD) for the expansion phase will be primarily based on safety data, but also on target saturation, PK and PK/PDy data. If the MTD cannot be determined in the absence of DLT at the MAD, PK after repeated administration, level of inhibition of target occupancy measured by $^{18}$FES-PET imaging and PK/PDy on ER occupancy as well as any other relevant information, will also be taken into account to select the RD and for the decision to expand the study to Parts B, C and D. The RD should be potentially at least 2 dose levels above the dose level showing >90% of inhibition of the target on $^{18}$FES-PET scan at this dose level, unless there are DLTs at this dose, in which case the RD could be any dose where >90% inhibition was reached.

The twice a day (BID) regimen will be explored on 6 DLT-evaluable participants at the dose level providing the same dose intensity as the highest cleared QD dose level (600 mg): 300 mg taken two times a day 12 hours apart (ie, 2x300 mg ± 1 hour). Other doses such as 200 mg taken two times a day 12 hours apart may be explored. In that case, 6 DLT-evaluable participants will be enrolled at this dose level.

***Pilot food effect***

A pilot food effect will be assessed by PK sampling after drug administration with a moderate fat breakfast (see Appendix E) on Day 3 of Cycle 1 in all participants treated in Part A. All other dosing in Part A will be taken in fasted condition. If results from the QD dosing regimen allow conclusions to be drawn, this will not be implemented for other dosing regimen (eg, BID) that are explored.

#### *1.1.1.2 Part B - Expansion phase with SAR439859 as monotherapy*

When the dose escalation ends for the QD regimen, the RD will be proposed by the Study Committee for the expansion part (Part B) and a total of 78 participants will be treated at this RD. An interim analysis based on objective response rate (ORR), after the treatment of 45 participants is planned to decide, based on preset criteria, if the recruitment of planned additional participants is justified. If results in Part A with the BID dosing regimen are of interest in terms of safety, PK, exposure, preliminary efficacy and any other relevant information such as data from patients treated with the QD regimen, and warrants further investigation, a BID regimen could be tested in an additional expansion subpart with a total of 56 patients treated at the recommended BID regimen from Part A. In that case, an interim analysis based on ORR (by RECIST v1.1) would be planned when 29 patients are treated to decide, based on preset criteria, if the recruitment of planned total patients is justified.

### 1.1.2 Arm 2 - SAR439859 in combination with palbociclib

#### *1.1.2.1 Part C - Escalation phase with SAR439859 in combination with palbociclib*

It is expected to assess two SAR439859 dose levels starting from one dose level below the RD fixed in Part A (RD[A-1]) and then SAR439859 RD[A], using a 3+3 standard dose escalation design with palbociclib given at fixed dose. An additional BID dose could be tested assuming that BID monotherapy in Part A indicates a benefit compared to the RD given QD. The Study Committee will decide on whether to escalate (or not) to the next dose level in combination with palbociclib during Study Committee meeting on the basis of their knowledge of the whole safety profile, and PK results.

**Table 2 - SAR439859 and palbociclib dose levels in Part C**

| Dose levels (DL)[a] | SAR439859 | Palbociclib[b] |
|---|---|---|
| DL1 QD | DL RD(A – QD)-1 | 125 mg |
| DL2 QD | RD(A – QD) | 125 mg |
| DL3 BID | RD(A – BID) | 125 mg |

*a* Lower dose, intermediate dose levels and a BID dose regimen can be tested after agreement between Sponsor and Investigators (study committee)

*b* Oral route once daily with food for 21 days followed by 7 days off therapy to comprise a complete cycle of 28 days. Lower dose (eg, 100 mg, 75 mg) can be proposed depending on tolerance

Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations should also be considered for the dose escalation and the dose selection decisions, as well as any relevant information, upon recommendation from the Study Committee.

#### *1.1.2.2 Part D - Expansion phase with SAR439859 in combination with palbociclib*

When the dose escalation phase (Part C) ends, at least one RD will be proposed by the study committee for the expansion cohort (Part D) and approximately 28 participants will be treated at each selected RD (from Part C). Intra-patient dose escalation or re-escalation of any study drug is not allowed. The study committee will review preliminary data (eg, safety, efficacy and PK) of each selected RD.

### 1.1.3 Arm 3 - SAR439859 in combination with alpelisib

#### *1.1.3.1 Part F - Safety run-in phase with SAR439859 in combination with alpelisib*

SAR439859 200 mg QD dose level will be assessed in combination with alpelisib at a fixed (standard) dose of 300 mg per alpelisib label according to incidence of DLTs and PK results. Additional dose levels of SAR439859 (eg, 300 mg QD, or 400 mg QD or 100 mg BID, or 200 mg BID etc.) with alpelisib could be explored if needed based on the safety and PK results from the 200 mg dose level testing with 300 mg alpelisib. Lower dose of alpelisib (eg, 250 mg or 200 mg) could be explored from Cycle 1 Day 1 based on the PK results and safety profile from the initial combination of SAR439849 200 mg and alpelisib 300 mg on the first 3 to 6 participants in Part F.

Based on the preliminary safety profile as well as PK and preliminary antitumor activity data, the Study Committee will decide whether to test additional SAR439859 dose levels in the feasibility study part and expand the alpelisib combination to Part G, or not.

**Table 3 - SAR439859 and alpelisib dose levels in Part F[a]**

| Dose levels (DL)[b] | SAR439859 | Alpelisib Standard dose[c] | Alpelisib Reduced dose[d] |
|---|---|---|---|
| DL1 QD | 200 mg | 300 mg | |
| DL2 QD | 200 mg | | 250 mg |
| DL3 QD | 200 mg | | 200 mg |

*a* In Part F (and G), Cycle 1 is defined as a 28-day cycle with 3 days of pretreatment with alpelisib single-agent for PK assessment followed by a 25-day treatment cycle with SAR439859 and alpelisib. Following cycles will also continue to be 28 days.
*b* Lower dose, intermediate dose levels and a BID dose regimen can be tested after agreement between Sponsor and the study committee
*c* Oral route, once daily with food.
*d* Lower dose (e.g., 250 mg, 200 mg) can be proposed depending on tolerance

Up to 6 DLT-evaluable participants could be treated at the already established SAR439859 dose of 200 mg when given in combination with other drugs, in order to confirm this dose when administered in combination with alpelisib. Lower dose levels of alpelisib and/or other dose levels of SAR439859 could be considered for testing in Part F if this established dose is not confirmed.

A decision to continue to dose expansion study part (Part G) will be based on DLTs observed for at least 1 cycle duration of all evaluable participants, and PK results from Part F combination. Intra-patient dose escalation or re-escalation of any study drug is not allowed

1. If none or one of the first 3 evaluable participants experiences DLT(s) during Cycle 1, the cohort will be expanded to include an additional 3 participants for a total of 6 participants.

    a) In the second set of 3 participants (ie, 6 participants altogether), if none or one DLT is experienced among the 6 participants (ie, 0/6 or 1/6), the doses of the combination are adequate for further testing in Part G.
    b) In the second set of 3 participants (ie, 6 participants altogether), if two or more DLTs are experienced among the 6 participants (ie, ≥2/6), the doses of the combination are NOT adequate for further testing in Part G. In this case, other dose levels of alpelisib and/or SAR439859 could be considered in Part F, or Part F can be stopped.

2. If 2 or more of the first 3 evaluable participants experience DLT(s), lower dose of alpelisib dose and/or other dose levels of SAR439859 will be considered or a decision to stop Part F can be made.

Although the confirmation of SAR439859 dose when given in combination with alpelisib will be guided by safety evaluation during Cycle 1, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose selection/confirmation decision (ie, expansion of a given dose level), as well as any relevant information such as PK and anti-tumor activity data that may need additional participants, upon recommendation from the study committee.

Participants who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLTs must be replaced.

As a rule, the combination feasibility study part will stop when the MAD, dose at which ≥33% of evaluable participants have experienced DLTs at Cycle 1, is reached.

#### *1.1.3.2 Part G - Expansion phase with SAR439859 in combination with alpelisib*

When the safety run-in (Part F) completes, based on safety, PK and efficacy data, RD of amcenestrant for the combination therapy will be confirmed by Study Committee for expansion cohort (Part G), and approximately 34 participants will be treated at the SAR439859 confirmed RD from Part F agreed by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

### 1.1.4 Arm 4 - SAR439859 in combination with everolimus

#### *1.1.4.1 Part H - Dose-escalation with SAR439859 in combination with everolimus*

SAR439859 200 mg QD dose level will be assessed in combination with everolimus at a fixed (standard) dose of 10 mg per everolimus label according to incidence of DLTs and PK results. Additional dose levels of SAR439859 (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with everolimus could also be explored if needed, based on the safety and PK results of everolimus in this dose escalation study.

Based on the preliminary safety profile as well as PK and preliminary antitumor activity data, the Study Committee will decide whether to test additional SAR439859 dose levels in the safety run-in phase, and expand the everolimus combination to Part I, or not.

**Table 4 - SAR439859 and everolimus dose levels in Part H[a]**

| Dose levels (DL) | SAR439859[b] | Everolimus (QD) |
|---|---|---|
| DL1 QD | 200 mg | 5 mg[c] |
| DL 2 QD | 200 mg | 10 mg[d] |

*a* In Part H (and I), Cycle 1 is defined as a 28-day treatment cycle of SAR439859 and everolimus. Following cycles will also continue to be 28 days.
*b* Lower dose, intermediate dose levels and BID dose regimen can be tested after agreement between Sponsor and Study Committee
*c* Oral route, once daily (QD) with or without food.
*d* Lower dose everolimus, 5 mg QD (every day) or 5 mg QOD (every other day) can be proposed depending on tolerance

Six (6) to 12 evaluable participants will be treated with already established RP2D of SAR439859 dose of 200 mg QD when given in combination with 2 dose levels of everolimus: 5 mg QD and 10 mg QD. Dose escalation decision will be based on DLT(s) observed for at least 1 cycle duration (ie, 28 days) in a following way:

- If 1 of the first 3 evaluable participants who were treated with SAR439859 200 mg QD and everolimus 5 mg QD experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional participants at the same dose level of everolimus and amcenestrant to the total of 6 participants.
- If 0 of the first 3 participants or less than 2 out of 6 participants treated at SAR439859 200 mg QD with 5 mg everolimus QD experienced DLT(s), dose escalation will proceed to the next dose level of everolimus (ie,10 mg QD) and SAR439859 200 mg QD by adding 3 participants at this new combination dose level, to the total of 6 or 9 participants
- If 1 of the first 3 evaluable participants treated with SAR439859 200 mg QD and everolimus 10 mg QD experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional participants to total of 9 or 12 participants in dose escalation study.

The second and third participants of a given cohort can only be enrolled when the first participant will have received 1 week of SAR439859 and everolimus without experiencing DLT(s).

The enrollment at the next dose level of everolimus may not proceed to 10 mg QD dose level before at least 3 participants treated with amcenestrant 200 mg QD and everolimus initial dose level (5 mg QD) have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLTs' assessment.

Participants who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT(s) must be replaced.

As a rule, the dose escalation will stop when the MAD, dose at which ≥33% (2 participants out of up to 6) of evaluable participants have experienced a DLT at Cycle 1, is reached. The MTD is defined as the highest dose level at which no more than 1 participant of a maximum of 6 evaluable participants experienced DLT(s). The MTD is one dose level below the MAD or the highest dose tested if MAD is not reached. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose escalation, dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any relevant information, upon recommendation from the study committee.

#### *1.1.4.2 Part I - Expansion phase with SAR439849 in combination with everolimus*

When the dose-escalation study (Part H) completes, based on safety, PK and preliminary antitumor activity data, RD of everolimus for the combination therapy will be proposed by Study Committee for expansion cohort (Part I); approximately 12 participants will be treated at the RD from Part H selected by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

### 1.1.5 Arm 5 - SAR439859 in combination with abemaciclib

#### *1.1.5.1 Part J - Dose-escalation with SAR439859 in combination with abemaciclib*

SAR439859 200 mg QD dose level will be assessed in combination with abemaciclib at a fixed (standard) dose of 150 mg BID (twice daily) per abemaciclib label according to incidence of DLTs and PK results. Additional dose levels of SAR439859 (eg, 300 mg QD, or 400 mg QD, or 100 mg BID, or 200 mg BID etc.) with abemaciclib could be explored if needed based on the safety and PK results from this dose escalation study.

Based on the preliminary safety profile, PK and preliminary antitumor activity data, the Study Committee will determine the recommended dose (RD) of abemaciclib in combination with amcenestrant 200 mg QD, and/or expand this combination to Part K, or not.

**Table 5 - SAR439859 and abemaciclib dose levels in Part J[a]**

| Dose levels (DL) | SAR439859[b] | Abemaciclib (BID) |
|---|---|---|
| DL1 QD | 200 mg QD | 100 mg BID[c] |
| DL 2 QD | 200 mg QD | 150 mg BID[d] |

*a* In Part J (and K), Cycle 1 is defined as a 28-day treatment cycle of SAR439859 and abemaciclib. Following cycles will also continue to be 28 days.
*b* Lower dose, intermediate dose levels and BID dose regimen can be tested after agreement between Sponsor and Study Committee
*c* Oral route, twice daily (BID) with or without food.
*d* Lower doses of abemaciclib, 50 mg BID can be proposed depending on tolerance

Six (6) to 12 evaluable participants will be treated with already established RP2D of SAR439859 dose of 200 mg QD when given in combination with 2 dose levels of abemaciclib: 100 mg BID and 150 mg BID. Dose escalation decision will be based on DLT(s) observed for at least 1 cycle duration (ie, 28 days) in a following way:

- If 1 of the first 3 evaluable participants who were treated with SAR439859 200 mg QD and abemaciclib 100 mg BID experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional participants at the same dose level of abemaciclib and SAR439859 to the total of 6 participants.
- If 0 of the first 3 participants or less than 2 out of 6 participants treated at amcenestrant 200 mg QD with abemaciclib 100 mg BID experienced DLT(s), dose escalation will proceed to the next dose level of abemaciclib (ie,150 mg BID) and SAR439859 200 mg QD by adding 3 participants at this new combination dose level, to the total of 6 or 9 participants

- If 1 of the first 3 evaluable participants treated with amcenestrant 200 mg QD and abemaciclib 150 mg BID experienced DLT(s) during Cycle 1, this cohort will be expanded with 3 additional participants to total of 9 or 12 participants in dose escalation study.

The second and third participants of a given cohort can only be enrolled when the first participant will have received 1 week of SAR439859 and abemaciclib without experiencing DLT(s).

The enrollment at the next dose level of abemaciclib may not proceed to 150 mg BID dose level before at least 3 participants treated with SAR439859 200 mg QD and abemaciclib initial dose level (100 mg BID) have been followed for at least 1 cycle duration (ie, 28 days) and are evaluable for DLTs' assessment.

Participants who discontinue study treatment prematurely before the end of DLT observation period for any reason other than DLT(s) must be replaced.

As a rule, the dose escalation will stop when the MAD, dose at which ≥33% (2 participants out of up to 6) of evaluable participants have experienced a DLT at Cycle 1, is reached. The MTD is defined as the highest dose level at which no more than 1 participant of a maximum of 6 evaluable participants experienced DLT(s). The MTD is one dose level below the MAD or the highest dose tested if MAD is not reached. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

Although the dose escalation process is guided by the safety evaluation during Cycle 1 of treatment, cumulative or irreversible toxicities observed after subsequent administrations will also be considered for dose escalation, dose selection decisions (ie, expansion of a given dose level, intermediate dose levels), as well as any relevant information, upon recommendation from the study committee.

#### *1.1.5.2 Part K - Expansion phase with SAR439859 in combination with abemaciclib*

When the safety run-in phase (Part J) completes, based on safety, PK and preliminary antitumor activity data, RD for the combination will be proposed by Study Committee for expansion cohort (Part K) and approximately 20 participants will be treated at RD from Part J selected by the Study Committee. Intra-patient dose escalation or re-escalation of any study drug is not allowed.

## 1.2 OBJECTIVES

### 1.2.1 Primary objective

#### *1.2.1.1 Part A and C*

The primary objective of the two dose escalation parts A and C is to assess the incidence rate of dose-limiting toxicity (DLT) and to determine the maximum tolerated dose (MTD) as well as the recommended dose (RD) of SAR439859 administered as monotherapy (Part A), then in combination with palbociclib (Part C), to postmenopausal women with estrogen receptor (ER)-positive and human epidermal growth factor receptor (HER2)-negative advanced breast cancer.

#### *1.2.1.2 Part B*

The primary objective of the expansion part B is to assess antitumor activity using objective response rate (ORR) according to response evaluation criteria in solid tumors (RECIST) v1.1 at the SAR439859 RD administered as monotherapy to postmenopausal women with ER-positive and HER2-negative advanced breast cancer.

#### *1.2.1.3 Part D, G, I and K*

The primary objective of the expansion parts D, G, I and K is to characterize the overall safety profile of SAR439859 administered in combination with palbociclib, with alpelisib, with everolimus and with abemaciclib respectively.

#### *1.2.1.4 Part F*

The primary objective of the safety run-in past F is to confirm the RD of SAR439859 in combination with alpelisib in postmenopausal women with ER positive, HER2 negative and PIK3CA-mutated advanced breast cancer.

#### *1.2.1.5 Part H and J*

The primary objective of the dose-escalation phases H and J is to assess the incidence rate of DLT and determine the recommended dose of SAR439859 in combination with everolimus, and in combination with abemaciclib in postmenopausal women with ER positive, HER2 negative advanced breast cancer respectively.

### 1.2.2 Secondary objectives

The secondary objectives are:

- To characterize the overall safety profile of SAR439859 administered as monotherapy (arm #1 Parts A and B ), in combination with palbociclib (arm #2 Part C) and in combination with alpelisib (arm #3 Part F), everolimus (arm #4 Part H) and abemaciclib (arm #5 Part J).
- To characterize the PK profile of SAR439859 administered as monotherapy (arm#1), or in combination in each study arms, as well as the PK profile of palbociclib, alpelisib, everolimus and abemaciclib in the appropriate treatment arm.
- To evaluate the antitumor activity using ORR according to RECIST v1.1 of SAR439859 administered as monotherapy (arm #1 Part A), in combination with palbociclib (arm #2 Part C and D), in combination with alpelisib (arm #3 Part F and G), in combination with everolimus (arm #4 Parts H and I), and in combination with abemaciclib (arm #5 Parts J and K), the clinical benefit rate (CBR) defined as complete response [CR], partial response [PR] and stable disease [SD] ≥24 weeks, and progression-free survival (PFS) in each treatment arm.
- To evaluate the ORR and CBR (CR, PR and SD ≥24 weeks) in dose expansion of each study treatment arm according to the estrogen receptor 1 (ESR1) gene mutational status (mutant and wild type) at baseline and during treatment.

- To evaluate the time to first tumor response (CR or PR) in dose expansion of each study treatment arm.
- To evaluate residual ER availability with positron emission tomography (PET) scan [(18)F] fluoroestradiol ($^{18}$F-FES) uptake with increasing doses of SAR439859 (arm #1 Part A).
- To assess the food effect on PK of SAR439859 (arm #1 Part A).
- To assess potential induction/inhibition effect of SAR439859 on cytochrome P450 (CYP) 3A using 4b-OH cholesterol (arm #1 Parts A and B).

### 1.2.3 Exploratory objectives

The exploratory objectives are:

- To evaluate PK/pharmacodynamic (PD) relationships.
- To evaluate target engagement: confirm the ER degradation with re-biopsy of the tumor at recommended dose arms #1, #4, and #5 (Part B, H, I, J and K).
- To evaluate other breast cancer biomarkers in tumor over time such as Ki67, Bcl-2, PgR, ER, and tumor gene expression profiles in arms #1, #3, #4, and #5 (Part A, B, F, G, H, I, J and K). In arm #5 (parts J and K), Cyclin D1 protein expression will be evaluated too, at baseline and over time.
- To assess the extent of metastases with FDG- PET/CT during dose escalation (arm #1 Part A).
- To evaluate change of cfDNA alterations from screening to progression of disease during Parts B, C, D, F, G, H, I, J, K. The percentage of participants with cfDNA alterations will be provided over time to characterize the biological evolution of the disease in each participant. The association of these alterations with clinical outcomes will also be provided.

## 1.3 DETERMINATION OF SAMPLE SIZE

It is anticipated that up to approximately 251 participants will be enrolled into the study. The actual sample size will vary depending on DLTs observed, number of dose levels (DLs) actually explored and the other potential schedules to be tested.

### 1.3.1 Arm 1 - SAR439850 in monotherapy

#### *1.3.1.1 Part A - Dose escalation phase with SAR439859 in monotherapy*

The sample size calculation for Part A is based on different simulated scenarios, it is anticipated that approximately 25 DLT-evaluable participants will enter the monotherapy dose escalation part (Part A) of the study in QD and 12 DLT-evaluable participants may enter the monotherapy dose escalation phase (Part A) in BID regimen.

#### *1.3.1.2 Part B - Expansion phase with SAR439859 in monotherapy*

For Part B, the sample size calculation is based on the primary endpoint (ie, ORR). The following assumptions were used:

- Null hypothesis: ORR ≤10%
- Alternative hypothesis: ORR ≥20%
- A two-stage Simon's Minimax design at a one-sided 5% significance level for QD regimen
- A two-stage Simon' Minimax design at a one-sided 10% significance level if BID regimen is tested.

Based on the above assumptions, a total of 78 participants are needed to achieve 80% power for the study.

### 1.3.2 Arm 2 - SAR430959 in combination with palbociclib

#### *1.3.2.1 Part C - Dose escalation phase with SAR439859 in combination with palbociclib*

For Part C, it is anticipated that approximately 12 DLT-evaluable participants will be required to establish the MTD and preliminary RD of SAR439859 when administered in combination with palbociclib.

#### *1.3.2.2 Part D - Expansion phase with SAR438959 in combination with palbociclib*

For Part D, it is anticipated that approximately 28 participants will be treated in an expansion phase at the selected RD (as per study committee recommendation) of SAR439859 with palbociclib in order to further assess the safety, tolerability and PK profiles of each RD and to explore preliminary antitumoral activity.

### 1.3.3 Arm 3 - SAR439859 in combination with alpelisib

#### *1.3.3.1 Part F - Safety run-in phase with SAR439859 in combination with alpelisib*

For Part F, it is anticipated that approximately up to 6 DLT-evaluable participants will be required to confirm the RD of SAR439859 when administered in combination with alpelisib.

#### *1.3.3.2 Part G - Expansion phase with SAR439859 in combination with alpelisib*

For Part G, it is anticipated that approximately 34 participants will be treated in an expansion phase at the selected RD(s) (as per study committee recommendation) of SAR439859 with alpelisib in order to further assess the safety, tolerability and PK profiles of each RD and to and for preliminary exploration of antitumoral activity.

### 1.3.4 Arm 4 - SAR439859 in combination with everolimus

#### *1.3.4.1 Part H - Dose-escalation with SAR439859 in combination with everolimus*

It is anticipated that approximately up to 12 DLT-evaluable participants will be required to confirm the RD of SAR43859 when administered in combination with everolimus.

#### *1.3.4.2 Part I - Expansion phase with SAR439859 in combination with everolimus*

It is anticipated that approximately 12 participants will be treated in an expansion phase at the selected RD (as per study committee recommendation) of SAR439859 with everolimus.

### 1.3.5 Arm 5 - SAR439859 in combination with abemaciclib

#### *1.3.5.1 Part J - Dose-escalation with SAR439859 in combination with abemaciclib*

It is anticipated that approximately up to 12 DLT-evaluable participants will be required to confirm RD of SAR43859 when administered in combination with abemaciclib.

#### *1.3.5.2 Part K - Expansion phase with SAR439859 in combination with abemaciclib*

It is anticipated that approximately 20 participants will be treated in an expansion phase at the selected RD (as per study committee recommendation) of SAR439859 with abemaciclib.

## 1.4 STUDY PLAN

The complete study plan is presented in Section 1.1 of the amended protocol 09.

## 1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

In the definition of the DLT-evaluable population, FDG PET/CT is not taken into account contrary to what can be seen in amended protocol 03.

In secondary efficacy endpoints, the objective response rate based on the ESR1 status (mutated or wild type) will also be assessed by investigators/local radiologists for Parts B and D, however in amended protocol 04 it is mentioned only for Part B. Similarly, the clinical benefit rate based on the ESR1 status (mutated or wild type) will also be assessed for Part B and D, which does not appear in the amended protocol 04.

## 1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This is an amended SAP. This is version 3 of the SAP.

**Table 6 - Statistical analysis plan statistical changes**

| SAP version number | Rationale | Description of statistical changes |
|---|---|---|
| 2 | Inclusion of BID regimen | Total sample size updated to 224<br>• sample size part A update: +12 patients<br>• sample size part B update: +56 patients<br>Number of sites updated to 50<br>Dose levels table of Part A for SAR439859 updated to add:<br>• DL4 bis BID: 200 mg twice daily<br>• DL5 bis BID: 300 mg twice daily<br>Design of Part B updated with addition of BID part with 56 patients and an interim analysis at 29 patients treated with BID regimen<br>Dose levels table of Part C for SAR439859 updated to add:<br>• DL3 BID: RD(A-BID)<br>18FES-PET/CT scan time window detailed for BID |
| | New Biomarker to explore | Additional biomarker evaluated in exploratory objectives: Bcl-2 |
| | No analysis planned | Removal of Allred Score and H score in disease characteristics |
| | Clarification on evaluable response definition | A SD response has to be assessed at least 42 days after the first IMP administration to be considered evaluable |
| | Provide details on non-progression rate at 24 weeks | Additional details on Progression Free Survival useful for derivation of non-progression rate at 24 weeks |
| | No analyses by cycle | For laboratory safety variables and vital signs:<br>• remove sentence regarding assignment of measurements performed on 2nd day of last cycle |
| | Clarification of PK variables | |
| | Correction on efficacy population definition | Removal of the 42 days after IMP condition for non-evaluability |
| | Specification of subgroups of interest | Updates on prognostic factors for subgroup analyses |
| | Correction on population of analysis for relative change from baseline in tumor size | Safety population replaced by response-evaluable population |
| | Details on Progression-free survival analysis | Censoring rules added |
| 3 | New combinations have been added in the study | Analyses related to arms 3 (Part F and G), 4 (Parts H and I) and 5 (Parts J and K) have been added |
| | Include flexibility in case more than one RD is selected for Part D | Update the design of Part D |
| | BID regimen will not be explored further | BID wording removed from all parts, apart from part A |
| | Maximize the sample size used for the analyses within each arm to provide more robust estimates | More details provided on strategies for pooled analyses |
| | Align the cut off strategy because of several arms | Cut off definitions updated per protocol definitions |

| SAP version number | Rationale | Description of statistical changes |
|---|---|---|
| 3 | Make more relevant assessment of prior anti-cancer therapies | Clean prior anti-cancer therapies analyses |
| | Clarify clinical benefit rate definition | Update the clinical benefit rate definition with clarified details |
| | Explain pharmacodynamic variables | Details are provided for mutational profiling in circulating free DNA |
| | Explain pharmacogenetic variables | Details are provided to clarify the focus on specific genes |
| | Clarify survival analysis | Non-progression rate at 24 weeks has been included in more general progression free survival analysis |
| | Clarification of PK variables | Accumulation ratio for Ctrough added |
| | | Normalized 4β-hydroxycholesterol ratio added |
| | Make more relevant deaths analyses | Replace few tables planned by SOC and PT, by an overview table |

# 2 STATISTICAL AND ANALYTICAL PROCEDURES

As a general convention, dose-escalation part or dose-escalation phase are indifferently used through the document. In the same way, expansion part or expansion phase will be indifferently used through the document.

All analyses described in this SAP will be done separately for each arm and by part:

- Arm 1
  - Pooled efficacy and safety analyses, including participants treated at dose levels strictly above 20 mg during the dose-escalation of SAR439859 in monotherapy (Part A) and all participants treated in Part B, dose expansion of SAR439859 in monotherapy, will also be provided. Dose levels strictly above 20 mg have been selected based on the pharmacodynamic effect ($^{18}$FES-PET) observed in Part A.
- Arm 2:
  - Pooled efficacy and safety analyses, including participants treated at the RD during the dose escalation with SAR439859 in combination with palbociclib (Part C) and all participants treated in Part D, dose expansion of SAR439859 in combination with palbociclib, will also be provided.
- Arm 3:
  - Pooled efficacy and safety analyses, including participants treated at the RD during the safety run-in with SAR439859 in combination with alpelisib (Part F) and all participants treated in Part G, dose expansion of SAR439859 in combination with alpelisib, will also be provided.
- Arm 4:
  - Pooled efficacy and safety analyses, including participants treated at the RD during the safety run-in with SAR439859 in combination with everolimus (Part H) and all participants treated in Part I, dose expansion of SAR439859 in combination with everolimus, will also be provided.
- Arm 5:
  - Pooled efficacy and safety analyses, including participants treated at the RD during the safety run-in with SAR439859 in combination with abemaciclib (Part J) and all participants treated in Part K, dose expansion of SAR439859 in combination with abemaciclib, will also be provided.

For dose-escalation parts and safety run-in parts, analyses will be performed by dose level, and overall for dose expansion or pooled analyses.

Definition of cut-off date analyses according to cut-off date as per protocol:

1. In each study arm dose escalation (Parts A, C, H and J) and safety run-in (Part F), the first COD will be done at the end of the first cycle of the last participant treated in the given cohort study part in order to have at least the first cycle evaluable for all participants for determination of the MTD and for the RD.

2. The COD for each study arm (dose escalation and dose expansion combined), for primary analysis, will be at each study arm's last participant in + 12 months.
3. The final study COD will be performed when the last study arm will have reached its COD (ie, last participant in + 12 months)
4. In addition, for all study parts, informal analyses could be performed on as needed basis during the study to support further development of the compound and regulatory requirements.

After the final COD, ongoing participant s will receive study therapy until disease progression, occurrence of an unacceptable toxicities, whichever is earlier, and they will only be followed for study treatment administration, SAEs, study treatment-related AEs and AEs leading to study treatment discontinuation.

The study data will be analyzed and reported in one Clinical Study Report (CSR) per arm, based on data at the COD of each study arm.

## 2.1 ANALYSIS ENDPOINTS

### 2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value or measurement taken up to the date and time of the first dose of study treatment irrespective of the treatment. This definition applies for all variables unless otherwise specified.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with summary statistics in the safety and efficacy sections (Section 2.4.6 and Section 2.4.5).

***Demographic characteristics***

Demographic variables include race (White, Black, Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, Not reported, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), age in years ([18-64],[65-84], ≥85), weight (kg), eastern cooperative oncology group (ECOG) performance status (PS) at baseline and menopausal status (pre-menopausal versus post-menopausal).

***Medical or surgical history***

Medical or surgical history includes relevant history of previous or associated pathologies other than the tumor.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

***Disease characteristics at diagnosis***

The following disease characteristics at initial diagnosis will be described:

- Time from initial diagnosis of breast cancer to first study treatment administration (in years),
- Histology (diagnosis type as collected in eCRF),
- Disease Location,
- Histopathology type,
- Stage of the disease,
- HER2 status,
- ER status,
- PgR status.

***Disease characteristics at study entry***

The following disease characteristics at study entry will be described:

- Extent of the disease (metastatic, locally advanced)
- Number of organ(s) involved
- Type of organ(s) involved
- Type of disease: visceral metastases only (ie, any organ except bone and lymph nodes), bone metastases only, lymph nodes only, both bone and visceral metastases, both bone metastases and lymph nodes, both lymph nodes and visceral metastases, bone and visceral metastases and lymph nodes.

***Prior anticancer therapies***

- Prior anti-cancer therapies

  Prior anti-cancer treatments are collected by regimen in the eCRF. The following variables will be collected/derived:

  - Intent of prior anti-cancer therapy according to the following categories: neoadjuvant only, adjuvant only, advanced only, both neoadjuvant and adjuvant, both neoadjuvant and advanced, both adjuvant and advanced, neoadjuvant and adjuvant and advanced.
  - Time from last relapse/progression to first IMP administration (months)
  - Number of prior lines of treatment in advanced setting descriptive statistics (min and max) and by class 0, 1, 2, ≥3. A line of therapy in the advanced setting consists of a single agent, combination or a sequential therapeutic strategy with several drugs, given until a PD is documented. It corresponds to a regimen in advanced setting.
  - Intent of the last prior anti-cancer therapy according to the following categories: De novo metastatic, Neoadjuvant or adjuvant, advanced.
  - Endocrine resistance status according to the following categories:
    - Primary resistance, defined as relapse <24 months after the start of adjuvant hormonotherapy, for participant s without advanced hormonotherapy treatment; progression <6 months after the start of the last prior advanced hormonotherapy, for participant s with advanced hormonotherapy treatment.

  - Secondary resistance, defined as relapse ≥24 months after the start and <12 months after the end of adjuvant hormonotherapy, for participant s without advanced hormonotherapy treatment; progression ≥6 months after the start of the last prior advanced hormonotherapy, for participant s with advanced hormonotherapy treatment.
  - Sensitive, defined as relapse ≥12 months after the end of adjuvant hormonotherapy and treatment-naïve in advanced hormonotherapy.
- Type of prior anticancer therapy in neoadjuvant setting (targeted therapy, hormonotherapy, chemotherapy, immunotherapy or other as collected in eCRF),
- Type of prior anticancer therapy in adjuvant setting (targeted therapy, hormonotherapy, chemotherapy, immunotherapy or other as collected in eCRF),
- Time from start of adjuvant therapy to relapse in adjuvant setting (years),
- Time from end of adjuvant therapy to relapse in adjuvant setting (years) (Treatment-free interval),
- Duration of adjuvant therapy (years),
- Among participants with prior adjuvant hormonotherapy,
  - Number of participant s with relapse <24 months after the start of adjuvant hormonotherapy,
  - Number of participant s with relapse ≥24 months after the start and <12 months after the end of adjuvant hormonotherapy,
  - Number of participant s with relapse ≥12 months after the end of adjuvant hormonotherapy.
- Type of prior anticancer therapy in advanced setting (targeted therapy, hormonotherapy, chemotherapy, immunotherapy or other as collected in eCRF),
- Reason for discontinuation of the last prior line in advanced setting,
- Best response to the last prior line in advanced setting,
- Time to progression of last prior line in advanced settings (ie, start date of the first drug within the last prior line of treatment up to last progression) (months)
- Duration of last prior line in advanced settings (last line end date - last line start date + 1) (months)
- Among prior hormonotherapy:
  - Number of participant s with intent: neoadjuvant only, adjuvant only, advanced only, both neoadjuvant and adjuvant, both neoadjuvant and advanced, both adjuvant and advanced, neoadjuvant and adjuvant and advanced,
  - Number of prior hormonotherapy-based lines in advanced setting descriptive statistics (min and max) and by category (0, 1, 2 or ≥3),
  - Type of prior hormonotherapy in neoadjuvant or adjuvant settings and Type of prior hormonotherapy in advanced settings:
    - Aromatase inhibitors (AIs)
    - SERM (eg, Tamoxifen)
    - SERD (eg, Fulvestrant)
    - Other

- Among prior chemotherapy:
  - Number of participant s with intent: neoadjuvant only, adjuvant only, advanced only, both neoadjuvant and adjuvant, both neoadjuvant and advanced, both adjuvant and advanced, neoadjuvant and adjuvant and advanced,
  - Number of prior chemotherapy lines in advanced setting descriptive statistics (min and max) and by category (0, 1, 2 or ≥3)
  - Type of prior chemotherapy in neoadjuvant or adjuvant settings and Type of prior chemotherapy in advanced settings:
    - Anthracyclines
    - Taxanes
    - Capecitabine
    - Other
- Among prior targeted therapy:
  - Number of participant s with intent: advanced only, neoadjuvant and advanced, adjuvant and advanced, neoadjuvant and adjuvant and advanced,
  - Number of prior targeted-based lines in advanced setting descriptive statistics (min and max) and by category (0, 1, 2 or ≥3
  - Type of prior targeted therapy in neoadjuvant or adjuvant settings and Type of prior targeted therapy in advanced settings:
    - Anti-HER2
    - CDK4/6 inhibitors (CDK4/6i)
    - mTOR inhibitors (mTORi)
    - PI3K inhibitors (PI3Ki)
    - PARP inhibitors
    - Other
- Among prior immunotherapy:
  - Number of participant s with intent: neoadjuvant only, adjuvant only, advanced only, both neoadjuvant and adjuvant, both neoadjuvant and advanced, both adjuvant and advanced, neoadjuvant and adjuvant and advanced,
  - Number of prior immunotherapy lines in advanced setting descriptive statistics (min and max) and by category (0, 1, 2 or ≥3),
  - Type of prior immunotherapy in neoadjuvant or adjuvant settings and Type of prior targeted therapy in advanced settings:
    - Anti PD-1
    - Anti PD-L1
    - Other
- Prior anti-cancer therapies in combination with endocrine therapy
  - Type of prior endocrine-based combinations in advanced settings:
    - CDK4/6i + AIs
    - CDK4/6i + SERD
    - AIs + SERD

- AIs + SERM
- PI3Ki + SERD
- mTORi + AIs
- mTORi + SERD
- Other

- Prior surgery: number (n, %) of participant s with any prior surgery related to breast cancer, type of procedure (Preferred Term) and time from the last surgery to the first IMP date (months).
- Prior radiotherapy: number (n, %) of participant s with any prior radiotherapy related to breast cancer, intent, intent of last prior radiotherapy, time from the last radiotherapy to the first IMP date (months) overall and by intent (curative and palliative) and location of prior radiation therapy by intent.

Any technical details related to computation, dates, and imputation for missing dates are described Section 2.5.

### 2.1.2 Prior or concomitant medications

All medications taken from the signed informed consent date up to the first study treatment administration and until the end of the study are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD), using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used from the date of informed consent until first study treatment administration. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the participant concomitantly to the study treatment from first administration to the last administration + 30 days.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

### 2.1.3 Efficacy endpoints

#### *2.1.3.1 Primary efficacy endpoint(s)*

The primary efficacy endpoint for expansion part B is the Objective Response Rate (ORR) and will be estimated by dividing the number of participants achieving confirmed complete response (CR) or partial response (PR) by the number of participants from the analysis population.

The response will be defined according to RECIST v1.1 (see Appendix C) and will be assessed at baseline and then every 2 cycles. Antitumoral response information, ie, category of response such as CR, PR, stable disease (SD) as best response, or progressive disease, will be determined by Independent Central Review (ICR) in Part B in participants with evaluable disease (RECIST v1.1). Furthermore, a PR or a CR must be confirmed on a second examination done at least

4 weeks apart, in order to confirm the antitumoral response. In addition to investigators/ local radiologists' assessments, copies of all imaging sets will be systematically collected for the purpose of ICR in Part B only.

A SD response has to be assessed at least 42 days after the first IMP administration to be considered as evaluable.

Of note, the BOR for each participant will also be summarized according to ICR (Part B).

#### *2.1.3.2 Secondary efficacy endpoint(s)*

##### *2.1.3.2.1 Objective response rate*

The objective response rate will be assessed by investigators/local radiologists for each arm of the study as a secondary endpoint of the study.

Of note, for each part of the study, the BOR for each participant will also be summarized according to investigator assessments.

The objective response rate in participants based on their ESR1 status (mutated or wild type) will also be assessed by investigators/local radiologists and also based on ICR for Part B.

##### *2.1.3.2.2 Relative change from baseline in tumor size*

Relative change from baseline in tumor size and best relative change from baseline in tumor size will be assessed at each tumor assessment post baseline for each arm of the study by investigators/local radiologists, and by ICR in part B only.

Change from baseline will be calculated as follows:

Change from baseline in tumor size(t) = Tumor Size(t) – Tumor Size(baseline)

where tumor size being defined as the sum of the longest diameters of the target lesions as per RECIST.

Relative change from baseline in tumor size will be calculated as follows:

Relative change from baseline in tumor size (t) = 100*(Tumor Size(t) – Tumor Size(baseline)) / Tumor Size(baseline)

Best relative change from baseline in tumor size will be the smallest relative change from baseline in tumor size.

#### *2.1.3.2.3 Clinical benefit rate*

The clinical benefit rate (CBR) will be estimated by dividing the number of participants defined as clinical benefit responders by the number of participants from the analysis population. Participants will be considered as clinical benefit responders if they achieve a (confirmed) CR or PR as BOR, or SD (or Non CR/Non PD if applicable) with an overall response recorded as SD (or Non CR/Non PD if applicable) or better at 24-1=23 weeks or later from first IMP intake, allowing for the ±7 days visit window for tumor assessment.

The clinical benefit rate (CBR) will be assessed for each arm of the study by investigators/local radiologists, and by ICR in part B only.

The clinical benefit rate in participants based on their ESR1 status (mutated or wild type) will also be assessed by investigators/local radiologists, and by ICR in part B only.

#### *2.1.3.2.4 Duration of response*

The duration of response (DOR) will be assessed by investigators/local radiologists for each arm of the study, it will also be assessed by ICR in part B.

The duration of response will be defined as the time interval from the date of the first occurrence of CR or PR that is subsequently confirmed (eg, in case of PR SD PR PR, the second PR date will be used for the calculation) to the date of the first documentation of disease progression or death due to disease progression, whichever occurs first.

If the participant receives a further anti-cancer therapy (ie, anti-cancer therapy or surgery related to cancer radiotherapy) before disease progression or death were observed, duration of response will be censored at the time of the last available response assessment performed before initiation of further anti-cancer therapy.

In the absence of disease progression, death or further anti-cancer therapy (i.e, anti-cancer therapy or surgery related to cancer radiotherapy) at the cut-off date, duration of response will be censored to the date of the last evaluable response assessment without evidence of progression.

#### *2.1.3.2.5 Progression free survival*

The progression free survival will be assessed by investigators/local radiologists for each arm.

The progression free survival will be defined as time from the date of the first treatment intake to the date of the first documentation of objective PD according to RECIST 1.1 definitions, clinical PD or death due to any cause, whichever occurs first.

#### *2.1.3.2.6 Time to first response*

The time to first response will be assessed by investigators/local radiologists in each arm of the study, it will also be assessed by ICR in part B. The time to first response will be defined as the time interval from the date of first administration of the study treatment to the date of the first occurrence of CR or PR that is subsequently confirmed assessed by investigators/local radiologists for each arm, and also assessed by ICR in Part B.

### 2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, weight, electrocardiogram (ECG) and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

***Observation period***

The observation period starts from the time when the participant gives informed consent and is divided into 3 periods:

- The **pre-treatment** period is defined as the time from the signed informed consent date up to the first dose of study treatments irrespective of treatment.
- The **treatment** period is defined as the time from the first dose of study treatment (irrespective of treatment) administration to the last dose of study treatments + 30 days.
- The **post-treatment** period is defined as the period of time starting the day after the end of the treatment period up to the end of the study (as defined in the protocol).

#### *2.1.4.1 Dose limiting toxicities (DLTs)*

For the dose-escalation parts (A, C, H and J) and safety run-in part (F), dose limiting toxicities will be summarized as follows:

- DLTs during Cycle 1
- Adverse events corresponding to DLT definition but occurring after Cycle 1

#### *2.1.4.2 Adverse events variables*

AEs（including serious adverse events [SAEs] and AEs of special interest [AESI]) will be collected from the time of signed informed consent until the end of study.

***Adverse event observation period***

- Pre-treatment adverse events are defined as any adverse event reported during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are adverse events that developed or worsened or became serious during the treatment period.
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

All AEs (including SAEs and AESI) will be graded according to National cancer institute common terminology for adverse events (NCI-CTCAE) v4.03 and coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT) and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

***Adverse events of special interest***

Specific analyses will be performed for the following AEs (see Section 2.4.6.2):

- Pregnancy of female participant entered in a study as well as pregnancy occurring in a female partner of a participant entered in a study with IMP.
- Symptomatic overdose (serious or non-serious) with study treatment.

#### *2.1.4.3 Deaths*

The deaths will be summarized as follows:

- Deaths on-study: includes all deaths occurring from the first IMP up to the participants' last protocol planned visit:
  - Deaths in TEAE period: includes all deaths occurring from the first IMP up to the end of treatment + 30 days,
  - Deaths in post-treatment period: includes all deaths occurring after the end of TEAE period up to study closure.
- Deaths post-study: includes all deaths occurring after the participants' last protocol planned visit until database lock.

#### *2.1.4.4 Laboratory safety variables*

Clinical laboratory data consists of blood analysis including hematology, biochemistry and urinalysis. Clinical laboratory values will be converted into standard international units that will be used in all listings and tables.

For laboratory safety variables, parameters measured on the day of the first study treatment intake will be considered as part of the baseline measurements.

For laboratory safety variables, the treatment period will start at first study treatment intake + 1 day.

Blood samples for clinical laboratories will be taken as defined in the study flowchart and as clinically indicated. Urinalysis tests on dipstick will be assessed at baseline and on Day 1 and 15 of each cycle, at EOT and if clinically relevant. Participants with 3+ or greater urine protein dipstick reading should undergo further assessment with a 24-hour urine collection for determination of proteinuria.

The laboratory parameters (excluding those used for disease assessment) will be classified as follows:

- Hematology
  - **Hemoglobin and coagulation**: hemoglobin, prothrombin time and international normalized ratio (INR).
  - **Platelet count**
  - **White blood cells**: white blood cells (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.

- Biochemistry
  - **Electrolytes**: sodium, potassium, chloride, calcium, albumin, magnesium, phosphate, bicarbonate/carbon dioxide,
  - **Renal function**: serum creatinine (sCr), estimated creatinine clearance by MDRD formula, blood urea nitrogen (BUN),
  - **Liver parameters**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total and direct bilirubin, gamma glutamyl transferase (GGT).
- Urinalysis
  - **Qualitative urinalysis**: protein, glucose, leukocytes, erythrocytes, ketone, pH.

#### *2.1.4.5 Vital signs variables*

Vital signs include: heart rate, respiratory rate, systolic and diastolic blood pressure, weight, temperature and ECOG PS (0, 1, 2, 3, 4).

For vital signs, parameters measured on the day of the first study treatment intake will be considered as part of the baseline measurements.

For vital signs, the treatment period will start at first study treatment intake + 1 day.

For a given parameter, a participant (respectively a cycle) will be considered as evaluable if at least one measure of this parameter is available during the on-treatment period.

#### *2.1.4.6 Electrocardiogram variable*

Electrocardiogram assessments will be described as normal or abnormal.

### 2.1.5 Pharmacokinetic variables

Pharmacokinetic parameters will be analyzed at the Sponsor by the Pharmacokinetics, Dynamics and Metabolism (PKDM) department. Main pharmacokinetic parameter will be determined for SAR439859, palbociclib, alpelisib, everolimus, abemaciclib and abemaciclib metabolites (M2, M18 and M20) by non-compartmental analysis (NCA) using PKDMS (running Phoenix software) for participants with full PK sampling. Other derived parameters will be calculated by B&P department.

The PK parameters will include, but may not be limited to the following:

| Parameters | Drug | Matrix | Definition/calculation |
|---|---|---|---|
| $C_{max}$ | amcenestrant, palbociclib, alpelisib, everolimus, abemaciclib, M2, M18 and M20 | Plasma, blood[a] | Maximum concentration observed |
| $C_{trough}$ | amcenestrant | Plasma | Plasma concentration observed just before treatment administration during repeated dosing |
| $AUC_{0-12}$ | amcenestrant, abemaciclib, M2, M18 and M20 | Plasma | Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (12 hours) |
| $AUC_{0-24}$ | amcenestrant, palbociclib, alpelisib, everolimus | Plasma, blood[a] | Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (24 hours) |
| AUC | amcenestrant, (Part A, Day 1 only) | Plasma | Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_Z}$ Values with percentage of extrapolation >30% will not be reported |
| $AUC_{last}$ | amcenestrant | | Area Under the Concentration versus time curve calculated using the trapezoidal method from time 0 to the real time tlast |
| CL/F (Part A, Day 1 only) | Amcenestrant | Plasma | Apparent total body clearance of a drug from the plasma calculated using the following equation: $CL/F = \frac{Dose_{EV}}{AUC}$ |
| $CL_{ss}/F$ | Amcenestrant, palbociclib, alpelisib, everolimus | Plasma, blood[a] | Apparent total body clearance after repeated extra-vascular (EV) doses of a drug at steady state from the matrix (plasma) calculated using the following equation: $CL_{ss}/F = \frac{Dose_{EV}}{AUC_{0-\tau EV}}$ |
| $t_{lag}$ | Amcenestrant | Plasma | Lag time, interval between administration time and the sampling time preceding the first concentration above the lower limit of quantification |
| $t_{max}$ | Amcenestrant, palbociclib, alpelisib, everolimus, abemaciclib, M2, M18 and M20 | Plasma, blood[a] | First time to reach $C_{max}$ |
| $t_{1/2z}$ | Amcenestrant (Part A, Day 1 only) | Plasma | Terminal half-life associated with the terminal slope (λz) determined according to the following equation: $t_{1/2Z} = \frac{0.693}{\lambda_z}$ where λz is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semi logarithmic scale. Half-life is calculated by taking the regression of at least 3 points. |

| Parameters | Drug | Matrix | Definition/calculation |
|---|---|---|---|
| $Ae_{0-24}$ (Arm #1 Part B, Day 22 only) | Amcenestrant | Urine | Amount excreted in urine from time 0 to 24 hours after the drug administration on Day 22 |
| $fe_{0-24}$ (Arm #1 Part B, Day 22 only) | Amcenestrant | Urine | Fraction of dose excreted in urine from time 0 to 24 hours after the drug administration on Day 22 |
| $CL_{R\ 0-24}$ (Arm #1 Part B, Day 22 only) | Amcenestrant | Urine | Renal clearance of the drug determined in the 0-24 hour interval, according to the following equation: $CL_{R0-t} = \frac{Ae_{0-t}}{AUC_{0-t}}$ |

*a* a blood matrix is for everolimus assay only

In addition, population PK approach may be used for SAR439859 and if possible, for combination drugs plasma concentrations. Individual PK estimates may be used to conduct exploratory exposure-response analyses for safety and efficacy. The population PK analysis will be reported in a stand-alone report.

### 2.1.6 Pharmacodynamic variables

#### *2.1.6.1 Estrogen receptor inhibition*

Participants in Part A will have an $^{18}$FES-PET/CT scan imaging performed at baseline and on treatment. For participants on a QD regimen, the second scan will be performed after at least 8 continuous days of treatment (ie, between Day 11 and Day 15) and between 16 to 24 hours after the previous administration of the study drug, with a time window of 2 hours around 24-hour theoretical time. For participants on a BID regimen, the second scan will be performed after at least 8 continuous days of treatment (ie, between Day 11 and Day 15) and between 7 to 12 hours after the previous administration of the study drug. The signal extinction between baseline and on study treatment $^{18}$FES-PET scans (ΔSUV) will constitute the pharmacodynamic readout of the ER target engagement.

Estrogen receptor inhibition will be described, per participant, by a percent reduction in 18FES avidity average over all selected lesions (see Appendix D). A successful suppression of estrogen receptors is defined as ≥90% of the target inhibition determined by $^{18}$FES-PET scans within the time window of 16 to 24h post-dose for QD regimen, and 7 to 12h post-dose for BID regimen.

#### *2.1.6.2 Estrogen receptor 1 gene mutation status in circulating free DNA*

All participants will be tested for ESR1 mutation. Twelve independent mutation status of ESR1 gene, including hotspot mutations described in the ligand domain, will be determined in all ESR1 mutated participants at baseline and at the end of Cycle 2 Day 28. The ESR1 gene mutation status (wild type, mutant) will be determined by multiplex droplet digital PCR (ddPCR) technology. For each ESR1 mutations, the type of mutation will be specified (missense, frameshift, inframe…) and the mutant frequency (%) and the mutant concentration (mL) will be given.

#### *2.1.6.3 Mutational profiling in circulating free DNA*

Cancer gene mutation present in the tumor observed at baseline might influence the response to SAR439859. Circulating free DNA will be extracted in all participants at baseline and EOT.

The relationship between the mutation status of a limited number of cancer genes and intrinsic or acquired resistance to SAR439859 treatment will be explored. The mutational status of panel of 77 cancer driver genes (Roche AVENIO panel) will be determined by next generation sequencing (NGS) technology. For both single nucleotide variants and indels, the type of mutation (missense, frameshift, inframe…), the mutant frequency (%) and the mutant concentration (mL) will be provided. In addition, other genomic aberrations (copy number variant, fusion gene) will be highlighted.

#### *2.1.6.4 Estrogen receptor degradation and tumor biopsy biomarkers*

The presence of estrogen receptor will be determined by central immunohistochemistry (IHC) and the ER results at baseline and on treatment will be compared to assess the level of ER degradation.

In addition, expression levels of Ki67, Bcl-2, PgR will also be evaluated by IHC. From tumor biopsies, tumor gene expression profiles related to ER degradation (and other gene signature and pathways) will be obtained. These analyses will be performed on transcriptome (mRNA).

### 2.1.7 Pharmacogenetic variables

A blood sample will be collected before treatment administration for pharmacogenetics analysis to investigate allelic variants of drug metabolism enzymes and drug transporters (DMET). The DMETplus panel will be considered for this study. In addition to the allelic variants, the gene-level haplotype will be provided. From gene-level haplotypes, a predicted phenotype will be derived for some genes (CYP2D6, CYP2C9, CYP2C19, NAT2 and UGT1A1).

### 2.1.8 Further therapy after discontinuation of investigational medicinal product administration during the study

Further therapies after discontinuation of IMP include further anti-cancer therapy, surgery and radiotherapy.

## 2.2 DISPOSITION OF PARTICIPANTS

Participant disposition will be summarized for each part of the study separately.

Screened participants are defined as any participants who signed the study informed consent.

Registered participants are screened participants who are planned to receive the study treatment, ie, for whom the investigator ticked “Yes” to the question “Will the participant continue into the study?” at the end of the screening period.

For participant study status, the total number of participants for each one of the following categories will be presented in the clinical study report (CSR) using a flow-chart diagram or a summary table:

- Screened participants
- Registered participants
- All-treated participants
- Ongoing participants
- Participants who discontinue the study treatment period and reasons for permanent discontinuation
- For Parts C and D: Participants who discontinue prematurely palbociclib and reasons for premature discontinuation
- For Part F and G: Participants who discontinue prematurely alpelisib and reasons for premature discontinuation
- For Part H and I: Participants who discontinue prematurely everolimus and reasons for premature discontinuation
- For Part J and K: Participants who discontinue prematurely abemaciclib and reasons for premature discontinuation

For all categories of participants (except for the screened and registered categories) percentages will be calculated using the number of participants in the all-treated population as the denominator.

For the two dose escalation phases, ie, Part A, C, H and J, and for the safety run-in phase, ie, Part F, disposition of participants will be depicted by actual dose level.

For all other parts, disposition of participants will be depicted for the recommended dose level.

All critical or major deviations potentially impacting DLT assessment (escalation phases and safety run-in phases) or efficacy analyses (expansion phases) and other deviations will be summarized for each part separately.

Additionally, the following analysis populations will be summarized in a table by number of participants on the all-treated population:

- All-treated/safety population
- DLT-evaluable population (Parts A, C, F, H and J)
- PK population
- Food effect population
- PDy population
- PK/PDy population
- Efficacy population

## 2.3 ANALYSIS POPULATIONS

### 2.3.1 Safety population (All-treated population)

The all-treated population is defined as all registered participants exposed to the investigational drug, regardless of the amount of treatment administered.

### 2.3.2 DLT-evaluable population

To be evaluable, participants should have received 1 cycle (28 days, oral administration), with intake of at least 75% of the intended doses, unless they discontinue study treatment before Cycle 1 completion due to a DLT (a participant who discontinues the study treatment before the end of Cycle 1 for another reason than DLT will be replaced), and in Part A have an evaluable $^{18}$FES-PET scan at baseline and between Days 11 and 15 of the first cycle. Any participant, who develops a DLT in Part A despite the absence of evaluable $^{18}$FES-PET scan, will be included in the DLT population.

Participants with incomplete safety evaluation during Cycle 1 and who experience a DLT at this cycle will be considered as evaluable for DLT.

Participants who are not evaluable for DLT assessment in the dose escalation parts will be replaced.

### 2.3.3 Pharmacokinetic population

The PK population is defined as all participants from the all-treated population with at least one evaluable drug concentration after study drug administration.

#### *2.3.3.1 Food-effect population (only for Part A)*

To be evaluable in the fed condition, drug has to be administered on Cycle 1/Day 3 in the time window 0 to 15 min after meal completion. To be evaluable in fasted condition, drug has to be administered on Cycle 1/Day 1 at least 10 h after the last meal and 3 h before the first following meal intake. Therefore, to be food effect evaluable, a participant has to be in fed condition at C1D3 and in fasted condition at C1D1.

### 2.3.4 Pharmacodynamic population

PDy analyses will be performed on all treated participants who had at least one pharmacodynamic parameter evaluable ($^{18}$FES-PET scan at baseline showing at least one target lesion and between Days 11 and 15 of Cycle 1 for Part A only, or ESR1 mutation status).

### 2.3.5 Pharmacokinetic/ Pharmacodynamic population

The PK/PDy population is defined as all participants from all-treated population with at least one drug concentration of study drug administration and at least one PDy parameter evaluable.

### 2.3.6 Efficacy population

The efficacy population (called response-evaluable population) is defined as all treated participants, with measurable disease at study entry, who provided a baseline and at least one postbaseline evaluable tumor assessment (meaning an evaluation different from non-evaluable, and a BOR different from non-evaluable according to investigator). Participants with an early progression as per RECIST v1.1, or who died from disease progression will also be included in this set.

## 2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation, median, minimum and maximum.

Categorical and ordinal data will be summarized using the number and percentage of participants.

All the tables will be presented by the actual dose level for dose escalation parts and safety run-in parts (Parts A, C, F, H and J). Separate tables will be provided for each part.

### 2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the safety population using descriptive statistics.

The medical and surgical history will be summarized according to the SOC and PT (SOC will be sorted according to the internationally agreed order (see Appendix F) and PT by overall decreasing frequency).

### 2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the safety population. The anti-cancer therapy will be presented separately.

Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and the participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore the participants may be counted several times for the same medication.

The tables for medications (prior and concomitant) will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across the dose levels and across the parts A and B on the one hand and C and D on the other hand. In case of equal frequency regarding ATCs, alphabetical order will be used.

Medications of specific interest such as antibiotics and hematopoietic growth factors (granulocyte-colony stimulating factor, granulocyte macrophage colony stimulating factor and erythropoietin or red blood cells transfusion) will be summarized and listed by dose level.

Prior endocrine resistance (primary, secondary or sensitive) will also be provided according to the definition in Section 2.1.1.

### 2.4.3 Anticancer therapies

In addition, the following specific medications will be summarized:

- A table for prior anti-cancer therapies will be provided using the ATC code (chemical class) and the standardized medication name. This table will be sorted by decreasing frequency of ATC followed by medication names based on the overall incidence across dose levels. In case of equal frequency regarding ATCs, the alphabetical order will be used.
- The same table will be provided for prior anti-cancer therapies in advanced setting.
- The same table will be provided for further anti-cancer therapies.

### 2.4.4 Extent of study treatment exposure and compliance

The extent of study treatment exposure will be assessed and summarized on the safety population (Section 2.3.1). For dose escalation parts and safety run-in part (A, C, F, H and J), it will be depicted by dose level.

The overall extent of exposure will be summarized with:

- Overall number of cycles started, defined by the number of cycles in which at least one dose of any study treatments is administered.
- Overall number of cycles started per participant
- Overall duration of exposure in weeks defined as [(Last day of last cycle – first day of first cycle+1)/7].
  - The first day of first cycle is defined as the first SAR439859 intake date.
  - The last day of last cycle is defined as the last SAR439859 intake date.
- Cycle duration: mean, median, min, max, and by class (<28 days, 28 days, >28 days and <32 days, ≥32 days and <36 days, ≥36 days)
- Number of days with palbociclib intake within cycle: mean, median, min, max, and by class (<21 days, 21 days, ≥21 days)

Following information by drug will also be summarized :

- Duration of treatment in weeks for SAR439859 defined as (date of last cycle last SAR439859 intake – date of first cycle first SAR439859 intake + 1)/7
- Duration of treatment in weeks for palbociclib defined as [min(date of death, date of last cycle last palbociclib intake + 7) – date of first cycle first palbociclib intake + 1]/7
- Duration of treatment in weeks for alpelisib defined as (date of last cycle last alpelisib intake – date of first cycle first alpelisib intake + 1)/7
- Duration of treatment in weeks for everolimus defined as (date of last cycle last everolimus intake – date of first cycle first everolimus intake + 1)/7
- Duration of treatment in weeks for abemaciclib defined as (date of last cycle last abemaciclib intake – date of first cycle first abemaciclib intake + 1)/7

- Cumulative dose for SAR439859, palbociclib (mg, for parts C and D), alpelisib (mg, for parts F and G), everolimus (mg, for parts H and I) and abemaciclib (mg, for parts J and K): the cumulative dose is the sum of all doses from cycle 1 day 1 up to treatment discontinuation
- Actual dose intensity (mg/day) for SAR439859 in Part A:

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{(\text{Duration of treatment in weeks} \times 7)\text{-}1}$$
- Actual dose intensity (mg/day) for SAR439859 in Part B, C, D, F, G, H, I and J:

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of treatment in weeks} \times 7}$$
- Actual dose intensity (mg/week/cycle) for palbociclib (for Parts C and D):

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of treatment in weeks}}$$
- Actual dose intensity (mg/day) for alpelisib (for Parts F and G):

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of treatment in weeks} \times 7}$$
- Actual dose intensity (mg/day) for everolimus (for Parts H and I):

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of treatment in weeks} \times 7}$$
- Actual dose intensity (mg/day) for abemaciclib (for Parts J and K):

  $$\text{ADI} = \frac{\text{Cumulative Dose (mg)}}{\text{Duration of treatment in weeks} \times 7}$$
- Planned dose intensity (mg/day) for SAR439859: PDI = planned dose C1D1
- Planned dose intensity (mg/week/cycle) for palbociclib (for Parts C and D):

  $$\text{PDI} = \frac{125 \times 7 \times 3}{4} = 656{,}25$$
- Planned dose intensity (mg/day) for alpelisib (for Parts F and G): PDI = planned dose C1D1
- Planned dose intensity (mg/day) for everolimus (for Parts H and I): PDI = planned dose C1D1
- Planned dose intensity (mg/day) for abemaciclib (for Parts J and K): PDI = planned dose C1D1
- Relative dose intensity (RDI, in %) for SAR439859, palbociclib (for parts C and D), alpelisib (for parts F and G), everolimus (for parts H and I), abemaciclib (for parts J and K) defined as

  $$\text{Relative Dose Intensity} = \frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}} \times 100$$

It is an indicator of the feasibility of the chosen schedule of administration.

Summary statistics will be provided for cumulative dose, actual dose intensity and relative dose intensity (according to the following categories: 0-80%, 80-100%, >100%).

In addition, a bar plot of duration of treatment (x-axis) per actual dose level / participant (y-axis) will be done. For each participant, the BOR will be displayed.

***Dose modifications or cycle information***

- Dose reduction: a dose is deemed to have been reduced if the daily dose taken by a participant is lower than the daily dose taken on the previous day or the day before dose(s) omitted.
- Dose omission: one omission of a SAR439859, palbociclib, alpelisib, everolimus or abemaciclib dose corresponds to a daily dose with a dose equal to 0 mg/day. Omission can occur within cycle n for part A, B, C, D, F, G, H, I and J. Several consecutive dose omissions will be counted as one episode of omission.

Dose information variables will be summarized descriptively (n, mean, standard deviation, median, minimum and maximum). Analyses will be performed based on the number of participants, and on the number of cycles. The number of participants with at least one SAR439859, palbociclib, alpelisib, everolimus or abemaciclib dose modification with the following details will be provided:

- Number (%) of participants with at least one dose modification (reduction or omission)
- Number (%) of participants with at least one dose reduction
- Number (%) of participants with at least one dose omission
- Number (%) of dose reductions by participant according to the following categories: 0, 1, >1
  - Among Palbociclib dose reductions: number of dose reductions to 100 mg or 75 mg
- Number (%) of episodes of dose omissions by participant according to the following categories: 0, 1, >1
- Number of participants with at least 7 consecutive days of dose omission
  - for SAR439859
  - for palbociclib (Parts C and D)
  - for alpelisib (Parts F and G)
  - for everolimus (Parts H and I)
  - for abemaciclib (Parts J and K)
- Number of SAR439859 administrations omitted
- Number of SAR439859 administrations reduced
- Number of episodes of dose omissions of SAR439859: 0, 1, >1
- Number of palbociclib administrations omitted (Parts C and D)
- Number of palbociclib administrations reduced (Parts C and D)
- Number of episodes of dose omissions of palbociclib: 0, 1, >1 (Parts C and D)
- Number of alpelisib administrations omitted (Parts F and G)
- Number of alpelisib administrations reduced (Parts F and G)
- Number of everolimus administrations omitted (Parts H and I)
- Number of everolimus administrations reduced (Parts H and I)
- Number of abemaciclib administrations omitted (Parts J and K)
- Number of abemaciclib administrations reduced (Parts J and K)

- Time from first IMP intake to first dose reduction of palbociclib (Parts C and D)
- Time from first IMP intake to first omission of 7 consecutive days of palbociclib (Parts C and D)

### 2.4.5 Analyses of efficacy endpoints

For Part B, both analyses for ICR primarily and investigators/local radiologists will be provided when the two assessments are available. For each arm, all efficacy analysis will be performed on the efficacy population defined in Section 2.3.6 only.

#### *2.4.5.1 Objective response rate*

The ORR will be estimated and provided with its 90% confidence interval using the Clopper Pearson interval.

##### *2.4.5.1.1 Subgroup analyses*

The ORR and CBR (with its 90% confidence interval) will be estimated in several subgroups of participants defined in the table below. Descriptive statistics will be presented for each prognostic factor.

**Table 7 - Subgroup analyses for Arm #1**

| Prognostic factor | Description |
|---|---|
| Prior CDK4/6i in advanced | Yes, No |
| Prior mTORi in advanced | Yes, No |
| Prior Fulvestrant in advanced | Yes, No |
| Prior Chemotherapy in advanced | Yes, No |
| Prior targeted therapy | Yes, No |
| ≤3 prior lines in metastatic setting, without both prior chemo and CDK4/6i (none or one of them is allowed) and without mTORi | Yes |
| without prior mTORi, CDK4/6i, Fulvestrant | Yes |
| ESR1 mutational status | Wild type, mutated |
| PgR status | Negative, positive |

**Table 8 - Subgroup analyses for Arm #2**

| Prognostic factor | Description |
|---|---|
| Prior CDK4/6i in advanced | Yes, No |
| Prior mTORi in advanced | Yes, No |
| Prior Fulvestrant in advanced | Yes, No |
| Prior Chemotherapy in advanced | Yes, No |
| Prior endocrine therapy in (neo)adjuvant | Yes, No |
| without Prior CDK4/6i and without Prior mTORi | Yes |
| Most recent intent of prior anti-cancer therapy | (neo)adjuvant, advanced |
| Visceral metastasis | Yes, No |
| ESR1 mutational status | Wild type, mutated |
| PgR status | Negative, positive |

**Table 9 - Subgroup analyses for Arm #3**

| Prognostic factor | Description |
|---|---|
| Prior Fulvestrant in advanced | Yes, No |
| Prior Chemotherapy in advanced | Yes, No |
| Prior endocrine therapy in (neo)adjuvant | Yes, No |
| Visceral metastasis | Yes, No |
| ESR1 mutational status | Wild type, mutated |
| PgR status | Negative, positive |

**Table 10 - Subgroup analyses for Arm #4**

| Prognostic factor | Description |
|---|---|
| Number of prior lines | 1, >1 |
| Prior endocrine therapy in (neo)adjuvant | Yes, No |
| Prior Chemotherapy in advanced | Yes, No |
| Prior Fulvestrant in advanced | Yes, No |
| Visceral metastasis | Yes, No |
| ESR1 mutational status | Wild type, mutated |
| PgR status | Negative, positive |

**Table 11 - Subgroup analyses for Arm #5**

| Prognostic factor | Description |
|---|---|
| Most recent intent of prior anti-cancer therapy | (neo)adjuvant, advanced |
| Number of prior lines | 1, >1 |
| Prior endocrine therapy in (neo)adjuvant | Yes, No |
| Prior Chemotherapy in advanced | Yes, No |
| Prior Fulvestrant in advanced | Yes, No |
| Visceral metastasis | Yes, No |
| ESR1 mutational status | Wild type, mutated |
| PgR status | Negative, positive |

According to number of participants within each category of these subgroups, analyses may not be performed, or categories may be pooled.

Other exploratory analyses could be considered.

#### *2.4.5.2 Relative change from baseline in tumor size*

A graphical representation of the best relative change from baseline observed per participant will also be provided. It will be sorted by decreasing of best relative change from baseline (waterfall plot).

Relative change from baseline over time will also be displayed (spider plot) during the on-study period both for the response-evaluable population and the response-evaluable population with best overall response equal to 'Stable Disease'.

#### *2.4.5.3 Clinical Benefit Rate*

For each arm, the CBR will be summarized with 90% CI using the Clopper Pearson interval.

#### *2.4.5.4 Duration of response*

For each arm, duration of response will be calculated and summarized for responder participants using the Kaplan-Meier method. For this analysis, censoring rules are the same than for progression-free survival analysis presented in Section 2.4.5.5.

#### *2.4.5.5 Progression free survival*

Progression free survival will be summarized for the efficacy population for all parts using the Kaplan-Meier estimation based on Brookmeyer and Crowley method.

In addition, the following analyses will be presented:

- Number (%) of events, with reason of event
- Number (%) of participants censored, with reason of censoring
- Kaplan-Meier estimates of the 25th, 50th and 75th percentiles and their associated 90% confidence interval (CI) will be provided. The 90% CIs will be constructed using a log-log transformation of the survival function and the methods of Brookmeyer and Crowley.
- Number of participants at risk as well as the probabilities of being event-free at 24 weeks (other time points may be considered) with 90% CIs will be estimated for each treatment group using the Kaplan-Meier method and a log-log approach based on a normal approximation following the Greenwood's formula.
- Kaplan-Meier curves will be plotted. These plots will include the number of participants at risk at key time points by treatment group.
- Median follow-up time (months) will be estimated using the reverse Kaplan-Meier method, where censored data are treated as events and events are treated as censored data.

For this analysis, censoring rules are presented in the following table.

| Situation | Date of outcome | Outcome | Category |
|---|---|---|---|
| No baseline tumor assessmentsa | Date of first treatment intake | Censored | No baseline tumor assessments |
| No evaluable post-baseline tumor assessments[a] | Date of first treatment intake | Censored | No evaluable post-baseline tumor assessments |
| Alive and no documented progression | Date of the last evaluable tumor assessment documenting no progression | Censored | Alive without progression |
| Documented progression (or Death) at or between scheduled visits | Date of progression (or Date of death) | Event | Documented progression (or Death without documented progression) |
| Documented progression (or Death) occurring after exactly one non-evaluable tumor assessment | Date of progression (or Date of death) | Event | Documented progression (or Death without documented progression) |
| Documented progression (or Death) occurring after two or more non-evaluable tumor assessment[b] | Date of the last evaluable tumor assessment documenting no progression | Censored | Event occurred after two or more missed tumor assessment |
| Clinical/non-radiological progression | Date of clinical/non-radiological progression | Event | Non-documented progression |
| Initiation of further anti-cancer therapy | Date of the last evaluable tumor assessment before start date of further anti-cancer therapy (if any), date of first treatment intake otherwise | Censored | Initiation of further anticancer therapy |

*a* Except if the participant dies within 17 weeks after the date of first treatment intake in which case a death event outcome will be considered for the PFS with date of outcome corresponding to the date of death

*b* An event occurring at least 18 weeks (excluded) after the last evaluable tumor assessment, documenting no progression or first intake date, whichever is last. 18 weeks corresponds to twice the time between two disease assessments per protocol (every 2*8 weeks), plus the 7-day window before and after.

#### *2.4.5.6 Time to first response*

For each arm, time to first response (CR or PR) will be calculated and summarized for responder participants.

#### *2.4.5.7 Multiplicity issues*

Not applicable.

### 2.4.6 Analyses of safety data

All safety analyses will be performed on the safety population as defined in Section 2.3.1.

#### *2.4.6.1 Analyses of DLTs*

The following summaries of DLTs will be generated for the DLT-evaluable population (Parts A, C, H, and J):

- A listing of participants who experienced a DLT (during Cycle 1) will be provided by dose level and with following information: investigator term/PT, grade, outcome, relationship with the treatment, day of occurrence, duration of the DLT, action taken. In case of a participant with more than one DLT with the same PT, all DLT should be presented in the listing and not only the worst grade.
- A listing of participants who experienced AEs meeting DLT definition after Cycle 1 will be provided by dose level and with the following information: investigator term/PT, grade, outcome, relationship with the treatment, day of occurrence within the cycle, duration of the DLT, action taken. In case of a participant with more than one DLT with the same PT, all DLT should be presented in the listing and not only the worst grade.

#### *2.4.6.2 Analyses of adverse events*

***Generalities***

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

Regarding treatment discontinuation, following definitions will be used:

- **Premature** treatment discontinuation is defined only for Part C, D, F, G, H, I, J and K as the discontinuation of palbociclib (for parts C and D) or alpelisib (for parts F and G) or everolimus (for parts H and G) or abemaciclib (for parts J and K) but SAR439859 is continued.
- **Definitive** treatment discontinuation is defined as the discontinuation of SAR439859.

The severity grade will be taken into account in the summary. For participants with multiple occurrences of the same adverse event, the maximum (worst) grade by period of observation is used. Summaries will be provided for all grades and for grade ≥3 (including Grade 5). Missing grades, if any, will be included in the “all grades” category.

Sorting within tables ensures the same presentation for the set of all adverse events for each observation period (pre-treatment, treatment-emergent and post-treatment). For that purpose, sorting for each observation period will be based on the order of all AEs across dose levels (including all AEs of monotherapy Parts A and B, and combination Parts C and D separately) presented by SOC and PT sorted by the internationally agreed SOC order (see Appendix F) and decreasing frequency of PTs within SOCs. This order will define the presentation order for all other tables unless otherwise specified.

***Analysis of all treatment-emergent adverse events***

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of participants with any
  - TEAE
  - Grade ≥3 TEAE
  - Grade 3-4 TEAE
  - Grade 5 TEAE (occurring during the treatment period)
  - Treatment emergent SAE
  - TEAE related to SAR439859
  - TEAE related to palbociclib (only Part C and D)
  - TEAE related to alpelisib (only for Part F and G)
  - TEAE related to everolimus (only for Part H and I)
  - TEAE related to abemaciclib (only for Part J and K)
  - TEAE leading to definitive discontinuation
  - TEAE leading to premature discontinuation of palbociclib (only Part C and D)
  - TEAE leading to premature discontinuation of alpelisib (only for Part F and G)
  - TEAE leading to premature discontinuation of everolimus (only for Part H and I)
  - TEAE leading to premature discontinuation of abemaciclib (only for Part J and K)
- All TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of participants with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order,
- All TEAEs by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC based on the overall incidence across dose levels (escalation and expansion). This sorting order will be applied to all other tables, unless otherwise specified,
- Most frequent (≥5% of participants overall, on PT) TEAE by primary SOC and PT,
- All TEAEs related to SAR439859 by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All TEAEs related to palbociclib (only Part C and D) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All TEAEs related to alpelisib (only Part F and G) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All TEAEs related to everolimus (only Part H and I) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All TEAEs related to abemaciclib (only Part J and K) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.

***Analysis of all treatment emergent serious adverse event(s)***

- All serious TEAEs by primary SOC, HLGT, HLT and PT, showing number (%) of participants with at least 1 serious TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All serious TEAEs by primary SOC and PT, showing the number (%) of participants with at least 1 serious TEAE, sorted by the order defined above.
- All serious TEAEs related to SAR439859, by primary SOC and PT, showing the number (%) of participants with at least 1 serious TEAE, sorted by the order defined above.
- All serious TEAEs related to palbociclib (only Part C and D) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All serious TEAEs related to alpelisib (only Part F and G) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All serious TEAEs related to everolimus (only Part H and I) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.
- All serious TEAEs related to abemaciclib (only Part J and K) by primary SOC and PT, showing the number (%) of participants with at least 1 related TEAE, sorted by the sorting order defined above.

***Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation***

- All TEAE leading to definitive treatment discontinuation by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE, sorted by the internationally agreed SOC order and decreasing frequency of PT,
- All TEAEs leading to premature treatment discontinuation of palbociclib (only for Part C and D), by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.
- All TEAEs leading to premature treatment discontinuation of alpelisib (only for Part F and G), by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.
- All TEAEs leading to premature treatment discontinuation of everolimus (only for Part H and I), by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.
- All TEAEs leading to premature treatment discontinuation of abemaciclib (only for Part J and K), by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. Summary by primary SOC and PT will also be presented, sorted by the internationally agreed SOC order and decreasing incidence of PT.

A listing of participants with a TEAE leading to premature or permanent treatment discontinuation will be provided. This listing will include the TEAE, the cycle of occurrence and the type of discontinuation (premature or permanent).

***Analysis of all treatment-emergent adverse event(s) leading to dose modification***

- All TEAEs leading to dose modification of SAR439859 (reduction or omission) by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE leading to dose reduction and/or dose omission, sorted by the sorting order defined above.
- All TEAEs leading to dose modification of palbociclib (only for Part C and D) (reduction or omission) by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE leading to dose reduction and/or dose omission, sorted by the sorting order defined above.
- All TEAEs leading to dose modification of alpelisib (only for Part F and G) (reduction or omission) by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE leading to dose reduction and/or dose omission, sorted by the sorting order defined above.
- All TEAEs leading to dose modification of everolimus (only for Part H and I) (reduction or omission) by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE leading to dose reduction and/or dose omission, sorted by the sorting order defined above.
- All TEAEs leading to dose modification of abemaciclib (only for Part J and K) (reduction or omission) by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE leading to dose reduction and/or dose omission, sorted by the sorting order defined above.

***Analysis of adverse events of special interest***

A listing of participants with at least one AESI cited in Section 2.1.4.2 will be provided. This listing will include the category of AESI, the cycle of occurrence and the outcome.

***Analysis of pre-treatment and post-treatment adverse events***

- All pre-treatment AEs by primary SOC and PT, showing the number (%) of participants with at least 1 pre-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC,
- All post-treatment AEs by primary SOC and PT, showing the number (%) of participants with at least 1 post-treatment AE, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC.

#### *2.4.6.3 Deaths*

The following summaries of deaths will be generated for the safety population.

- Number (%) of participants who died by study period (on-study: on-treatment, post-treatment, post-study) and cause of death (disease progression, AE, other).
- Number (%) of participants with TEAEs leading to death by SOC and PT (regardless of the date of death/period).

- Summary of AEs leading to death including fatal TEAEs (Grade 5 during treatment or any grade AE leading to death post-treatment) and Grade 5 post-treatment AEs, presented by primary SOC and PT as well as primary SOC, HLGT, HLT, and PT. These tables will be provided for death occurring:
  - in the context of disease progression (death within 30 days from last study treatment administration and the cause of death is disease progression),
  - in the context other than disease progression (death within 30 days from last study treatment administration and for whom cause of death is not disease progression or the death occurred more than 30 days from last study treatment administration and the cause of death is adverse event).
- Listing of deaths
- An overview of Grade 5 AEs (excluding pre-treatment) will be provided with the following categories:
  - Grade 5 AE (TEAE and post-treatment).
  - Fatal TEAE (regardless date of death/period).
    - Grade 5 TEAE with a fatal outcome during the treatment period,
    - Any Grade TEAE with a fatal outcome during the post-treatment period.
  - Post-treatment Grade 5 AE (excluding a TEAE that worsened to Grade 5 during the post-treatment period).

#### *2.4.6.4 Analyses of laboratory variables*

***Hematology and biochemistry***

Hematological and clinical biochemistry toxicities will be assessed from laboratory test parameters defined in Section 2.1.4.4.

For hematological parameters and for some selected biochemistry parameters, Sanofi sponsor generic ranges (LLN, ULN) are defined and will be used for grading. For other biochemistry parameters (eg, for hepatic enzymes ALT, AST, Alkaline phosphatase, total bilirubin), grading will be derived using local laboratory normal ranges. The number of participants with abnormal laboratory tests at baseline will be presented by grade and all grades together. The frequency of participants in each grade and all grades of laboratory abnormalities during treatment will be summarized. For participants with multiple occurrences of the same laboratory variable during the treatment, the maximum grade (worst) per participant will be used. The denominator used for percentage calculation is the number of participants with at least 1 evaluation of the laboratory test during the considered observation period. When appropriate, the summary table will present the frequency of participants with any grade of abnormal laboratory tests and with Grade 3-4 abnormal laboratory tests.

In addition, for hematology and biochemistry toxicities, shift tables showing the number of participants in each grade at baseline by worst grade during the on-treatment period will be provided.

***Urinalysis***

For dipstick analyses, a frequency table of results for each parameter (RBC, WBC, proteins, glucose, ketone bodies) will be provided using the worst value observed on-treatment.

Proteinuria measured on 24-hour urine collection will be summarized by worst grade on-treatment.

A summary of baseline results will also be provided for dipstick analyses and proteinuria measured on 24-hour urine collection, if relevant.

For laboratory tests for which NCI-CTCAE V4.03 scale is not applicable, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review.

PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by dose level for escalation parts, and overall for expansion parts.

#### *2.4.6.5 Analyses of vital sign variables*

Vital signs parameters are described in Section 2.1.4.5:

- A summary of baseline results will be provided for all parameters.
- For ECOG performance status, a shift table will be provided for the last and worst evaluations respectively relative to baseline.
- For blood pressure (SBP, DBP), heart rate, respiratory rate and temperature, a table will be provided with the last and worst evaluations (minimum and maximum value). In addition, for blood pressure and heart rate a graph describing mean changes from baseline and associated +/- SEM will also be done throughout the on-treatment period.

For vital sign variables, potentially clinically significant abnormalities (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review. PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The incidence of PCSA any time during the on-treatment period will be summarized by dose level for escalation parts, and overall for expansion parts.

Laboratory tests for which NCI-CTCAE V4.03 scale nor PCSA are not applicable will be analyzed using normal ranges, classified as <LLN or >ULN.

#### *2.4.6.6 Analyses of electrocardiogram variables*

The incidence of participants with at least 1 abnormal ECG at any time during the TEAE period will be summarized irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal

### 2.4.7 Analyses of pharmacokinetic and pharmacodynamic variables

#### *2.4.7.1 Pharmacokinetics variables*

Prior to all statistical analyses (except descriptive ones), $C_{max}$, $AUC_{0-24}$ (QD regimen only), $AUC_{0-12}$ (BID regimen only), $t_{1/2z}$ and $CL_{SS}/F$ values will be log transformed.

##### *2.4.7.1.1 Descriptive statistics*

Descriptive statistics (arithmetic mean, standard deviation, geometric mean, coefficient of variation (%), median, minimum and maximum) for concentration and corresponding NCA PK parameters as well as associated graphs will be performed for each parent drug and metabolite when relevant by the PK department. Other descriptive statistics will be provided by the B&P Department.

##### *2.4.7.1.2 Dose proportionality – Part A*

For $C_{max}$ and $AUC_{0-24}$, SAR439859 dose proportionality will be assessed on data from Part A of the QD dose regimen, separately for Day 1 and Day 22 using the empirical power model (PK parameter = $\alpha \times dose^{\beta}$), along with an "estimation" interpretation, according to the recommendations in Gough et al. (1995) [1]).

> *"The empirical power model provides a readily and interpretable measure of the degree of non-proportionality, which can be used both to confirm proportionality and to assess the pharmacokinetic and clinical significance of any departures."*
>
> *"The analysis of dose proportionality studies, however, requires estimation rather than significance testing in order that the pharmacokinetic and clinical significance of any non-proportionality can be assessed."*

The power model will be fit on the log-transformed scale:

$$\log(\text{PK parameter}) = \log(\alpha) + \beta \times \log(\text{dose}) + \text{Error}$$

Model lack-of-fit will be assessed by residual plots, and by an F-test of the residual mean square versus the pure error residual mean square (excepted for part 4, since only 2 dose levels). If the model fit is adequate, estimates with 90% confidence intervals for β will be obtained, and further used to obtain estimates and 90% confidence intervals for the PK parameter increase associated with an r-fold (r = 2 and r = high dose / low dose) increase in dose, by exponentiating r to the powers of the β estimate ("b") and confidence limits:

$$r^{b \pm t \times SE(b)}$$

If there is evidence of model lack-of-fit, then attempts could be made to fit the model over a reduced dose range (eg, exclude one extreme dose level). Otherwise, a fixed effect model will be used, with fixed term for dose, using logarithms of the relevant PK parameters. Estimates with 90% CIs for the parameter increases associated with pairwise dose increases will be obtained by first computing estimates with CIs for differences between pairwise dose levels in the fixed effects model framework, and then converting to ratios using the antilog transformation.

#### *2.4.7.1.3 Accumulation ratio – Part A, B, C & D, H & I, J & K*

Accumulation will be assessed on SAR439859, palbociclib, everolimus or abemaciclib for each treatment arm (monotherapy or combination therapy).

The dataset used will be fasted condition for Part A, fed or fasted for Part B and fed condition for all other parts. For $C_{max}$, $AUC_{0\text{-}24}$ (replaced by $AUC_{0\text{-}12}$ for BID) and $C_{trough}$, the accumulation will be assessed with a linear fixed effects model:

$$\text{Log}(R_{ac} \text{ Cycle 1 Day 21 or 22 versus Cycle 1 Day 1}) = \text{Dose} + \text{Error}$$

with Dose or treatment as fixed effects using SAS® PROC MIXED.

Accumulation ratio of Cycle 1 Day 21 or 22 versus Cycle 1 Day 1 will be assessed for each dose level and dosing regimen separately as well as pooled across dose levels for QD regimen within the fixed effect model framework. Accumulation ratio will be assessed by estimating the ratio of Cycle 1 Day 21 or 22 versus Cycle 1 Day 1 in the logarithms with corresponding 90% confidence intervals, further converted to Cycle 1 Day 21 or 22 / Cycle 1 Day 1 accumulation ratios with their corresponding 90% confidence intervals using the antilog transformation.

In addition, listings of individual accumulation ratios will be provided, along with their descriptive statistics (arithmetic mean, standard deviation, geometric mean, coefficient of variation (%), median, minimum and maximum). Individual accumulation ratio will be calculated as follows by Biostatistics & Programming department provided in appendices for all participants with available data:

- $R_{ac}\ C_{max} = \frac{\text{Cmax Cycle 1 Day 21 or 22}}{\text{Cmax Cycle 1 Day 1}}$
- $R_{ac}\ AUC_{0\text{-}24} = \frac{AUC_{0-24} \text{ Cycle 1 Day 21 or 22}}{AUC_{0-24} \text{ Cycle 1 Day 1}}$
- $R_{ac}\ AUC_{0\text{-}12} = \frac{AUC_{0-12} \text{ Cycle 1 Day 21 or 22}}{AUC_{0-12} \text{ Cycle 1 Day 1}}$
- $R_{ac}\ C_{trough} = \frac{C_{trough} \text{ C24h post-dose Cycle 1 Day 21 or 22}}{C_{trough} \text{ C24h post-dose Cycle 1 Day 1}}$

#### *2.4.7.1.4 Dose effect – Part A*

Dose effect will be assessed on data from Part A for QD regimen.

For $t_{1/2z}$ and $CL_{ss}/F$ of SAR439859, dose effect will be assessed with a linear fixed effects model,

$$\text{Log(parameter)} = \text{Dose} + \text{Error}$$

with Dose as fixed effects using SAS® PROC MIXED.

The p-value for the dose effect will be computed using that linear fixed effect model.

#### *2.4.7.1.5 Treatment effect – Parts C, F, H, J*

Treatment effect will be assessed with a linear fixed effects model on C1D22/21 $C_{max}$ and $AUC_{0-24}$ of each drug in Parts C (combination with palbociclib), Part F (combination with alpelisib), Part H (combination with everolimus), and Part J (combination with abemaciclib) when at least 2 dosing regimens are evaluated.

$$\text{Log(parameter)} = \text{Treatment} + \text{Error}$$

with Treatment as fixed effects using SAS® PROC MIXED.

The p-value for treatment effect will be computed using that linear fixed effect model, estimates and 90% confidence intervals will also be provided by treatment group and overall (whatever the treatment effect significance).

#### *2.4.7.1.6 Food effect – Part A*

Only participant evaluable for food effect will be included in the analysis. Food effect will be assessed comparing $C_{max}$ and $AUC_{0-24}$ between Cycle1/Day1 and Cycle1/Day3 in Part A (QD regimen only). Data from subject with significant carry-over effect on Day 3 will be excluded from the analysis ie, when $C_{trough}$ is >5% from $C_{max}$. A secondary analysis may be considered on adjusted concentrations or parameters.

For $C_{max}$, and $AUC_{0-24}$, the difference between food conditions will be assessed on log-transformed parameters with a linear model,

$$\text{Log(Parameter)} = \text{Food} + \text{Error}$$

with fixed terms for food, and with an unstructured matrix of formulation-specific variances and covariances for subjects, using SAS Proc Mixed®.

For $C_{max}$, and $AUC_{0-24}$, estimate and 90% confidence interval for the ratio of food condition geometric means (fed/fasted) will be obtained by computing estimate and 90% confidence interval for the difference between food condition arithmetic means within the model framework, and then converting to ratio of geometric means by the antilog transformation.

Furthermore, the distribution of $t_{max}$ and $t_{lag}$ values will be represented by histogram plots for each food condition, and a histogram of differences in $t_{max}$ and $t_{lag}$ between food conditions (fed versus fasted) will be provided. The food effect p-value on $t_{max}$ and $t_{lag}$ will be provided, using the exact marginal homogeneity test for ordered categorical data.

#### *2.4.7.1.7 Interaction ratio – Part F, G*

Alpelisib treatment ratios [alpelisib co-administered with SAR439859 (C1D22) vs alpelisib alone (C1D3)] for $C_{max}$ and $AUC_{0-24}$ will be listed by participant and summarized by treatment using descriptive statistics within Arm#3.

These parameters will be analyzed using the following linear model:

$$\text{Log(Parameter)} = \text{Treatment} + \text{Error}$$

with fixed term for treatment, and with an unstructured 2-by-2 matrix of treatment-specific variances and covariance for participant, using SAS Proc Mixed®. In case of convergence problems, other variance-covariance structures will be explored.

In case several dose level for alpelisib are assessed, the following model will be used:

$$\text{Log(parameter)} = \text{Treatment} + \text{Dose} + \text{Treatment x Dose} + \text{error}$$

For $C_{max}$ and $AUC_{0\text{-}24}$, point estimates and 90% confidence intervals (CIs) for the geometric means ratio of treatments (alpelisib co-administered with SAR439859 versus alpelisib alone) will be obtained for the differences between treatment means within the linear model framework, and then converting to ratios by the antilog transformation.

#### *2.4.7.1.8 Steady state – All Parts*

$C_{trough}$ analysis over time will be performed on SAR439859, palbociclib, alpelisib, everolimus and abemaciclib for each treatment arm (monotherapy or combination therapy).

This analysis will be provided on the PK population.

For each drug, each treatment arm, dose level and dosing regimen, individual $C_{trough}$, and descriptive statistics will be tabulated by nominal time (day) and cycle. Only $C_{trough}$ collected within 2 hours before next drug administration will be taken into account for descriptive statistics and LLOQ values will be replaced by zero.

For each drug and each treatment arm, mean (±SEM) $C_{trough}$ will also be presented graphically as a function of nominal sampling time (Day) over cycles. The effective (n) used for each timepoint will be presented on the x-axis.

For each drug, each treatment arm, dose level and dosing regimen, individual $C_{trough}$ will be presented graphically as a function of actual sampling time (Day) over cycles. A $C_{trough}$ value below the lower limit of quantification, will be replaced by LLOQ/2, using:

- SAR439859 LLOQ = 5 ng/mL
- palbociclib LLOQ = 1 ng/mL
- alpelisib LLOQ = 5 ng/mL
- everolimus LLOQ = 0.5 ng/mL
- abemaciclib LLOQ = 1 ng/mL

For Part A, $C_{trough}$ values on Day 3 and the day of $^{18}$FES-PET (between Day 11 and Day 15) will not be used for steady state graphical analysis.

#### *2.4.7.1.9 Variance components – Part A, B*

Variance components will be assessed on SAR439859 data from Part A (QD regimen only), Part B.

Within-subject and total standard deviations for log($C_{max}$) and log($AUC_{0-24}$) will be estimated using Day 1 and Day 22 parameters by equating observed and expected means squares within the following linear mixed effects model framework:

$$\text{Log(parameter)} = \text{Dose} + \text{Subject (Dose)} + \text{Day} + \text{Day*Dose}$$

with Dose, Day and Day*Dose interaction as the fixed effects and Subject (Dose) as the random effect. 90% confidence intervals will be computed using the simple $\chi^2$ method for the within-subject SD, and the Graybill-Wang (2) procedure for the total SD.

#### *2.4.7.1.10 4β-hydroxycholesterol – Parts A, B, J and K*

4β-hydroxycholesterol and total cholesterol concentrations will be assayed in Part A and Part B pre-dose samples at the following days: C1D1, C1D22 and C2D1 and in Part J and Part K pre-dose samples at the following days: C1D1, C2D1 and C3D1. The concentrations for Part A participants, QD regimen, will be available for the ones who gave their consent for future use of samples for additional research, as the test was not initially scheduled in this protocol Part.

Ratios of 4β-hydroxycholesterol concentrations will be calculated from samples collected before (C1D1) and after (C1D22, C2D1, C3D1) drug administration for each subject, according to the equation below:

$$R = \frac{4\beta\text{OH} - \text{chol}_{\text{post}}}{4\beta\text{OH} - \text{chol}_{\text{pre}}}$$

$$\text{Rnorm} = \frac{[4\beta\text{OH} - \text{chol/total chol}]_{\text{post}}}{[4\beta\text{OH} - \text{chol/total chol}]_{\text{pre}}}$$

Geometric mean and 90% CI of the above ratios will be provided for each arm by treatment group.

In addition, listing of individual 4β-hydroxycholesterol and total cholesterol concentrations with related individual ratios will be provided. Corresponding descriptive statistics will be calculated.

### *2.4.7.2 Pharmacodynamic variables*

All pharmacodynamic variables will be summarized by dose level using descriptive statistics and waterfall plots on PDy population.

#### *2.4.7.2.1 Estrogen receptor inhibition*

For Part A, a representation of the $^{18}$FES-PET % reduction observed per participant will be provided, with the clinical response and dose level information.

The following summaries will be generated for participants in Part A:

- Number (%) of participants with a percentage reduction ≥90% per dose level
- Number (%) of participants with a percentage reduction ≥70% per dose level
- Listing of % change by lesion type by dose level
- Number of sites with signal observed on the scan
- Type of organ with signal observed on the scan
- Time from first IMP to on treatment $^{18}$FES-PET (days)
- Time from last IMP before $^{18}$FES-PET to on treatment $^{18}$FES-PET (days)
- Time from last PK sample just before on treatment $^{18}$FES-PET to on treatment $^{18}$FES-PET (days)

Additionally, other thresholds could be investigated such as: number (%) of participants with a percentage reduction ≥50% or number (%) of participants with a percentage reduction ≥30%.

Additionally, the relationship between:

- Delta SUV and SAR439859 concomitant concentration (PK/PDy analysis) with graph
- Delta SUV and the clinical variables (ORR and the CBR (CR, PR and SD ≥24 weeks))
- Baseline SUV and the clinical variables (ORR and the CBR (CR, PR and SD ≥24 weeks))

will be investigated for pooled doses and by dose levels for Part A.

#### *2.4.7.2.2 Estrogen receptor 1 gene mutation status*

***Baseline population (participants with ddPCR data available at baseline):***

Descriptive statistics of the ESR1 mutational status (wild type, mutated) and for each of the twelve ESR1 mutations will be provided at baseline. The association between the ESR1 mutational status and some efficacy endpoints (PFS, clinical benefit status) will be given in the response-evaluable population (part A (>20 mg) and Part B).

***Pharmacodynamic population (participants with ddPCR data available both at baseline and at Cycle 2 Day 28):***

Descriptive statistics of the ESR1 mutational status (wild type or mutated) and for each of the twelve ESR1 mutations will be provided at baseline and at Cycle 2 Day 28. The evolution of the mutant frequency (%) and the mutant concentration (mL) of ESR1 gene over time will be also explored. The evolution of ESR1 will be also explored in a subset of participant depending on their prior treatments (CDK4/6i, mTORi,…). The evolution of the mutant frequency (%) and the mutant concentration (mL) will be also performed for each of the twelve ESR1 mutations according the clinical benefit status.

#### *2.4.7.2.3 Mutational profiling in circulating free DNA*

***Baseline population (participants with NGS data available at baseline):***

Descriptive statistics of the type of genomic aberrations at baseline will be provided. Genomic profile of participants (with clinical benefit or not) will be given at baseline through graphical visualization.

***Pharmacodynamic population (participants with NGS data available at baseline and EOT):***

Descriptive statistics of the number of genomic aberrations of some genes of interest at baseline and at EOT will be provided. The evolution of their mutant frequency (%) and their mutant concentration (mL) will be also described according to the clinical benefit status. The evolution will be also explored in a subset of participant depending on their prior treatments (CDK4/6i, mTORi…).

#### *2.4.7.2.4 Estrogen receptor degradation and tumor biopsy biomarkers*

Descriptive statistics of the tumor biomarkers such as ER expression, KI67, Bcl-2 and PgR will be provided at baseline and over time by comparing baseline and Cycle 2 Day 28. The relationship between the change of each protein expression and clinical response may be explored. Some tumor gene signatures (such as the ER activation signature and other gene signature of interest) may be also derived and described through descriptive statistics and graphical visualization.

#### *2.4.7.2.5 Estradiol*

Descriptive statistics of estradiol concentrations will be provided by visit for each arm and overall.

### *2.4.7.3 Analyses of pharmacokinetic / pharmacodynamics*

Correlation between SAR439859 PK parameters and efficacy or safety variables of interest may be assessed on PK/PDy population as defined in Section 2.3.5 for each study part and/or on pooled study parts. Individual PK estimates may be used to conduct exploratory exposure-response analyses for safety, pharmacodynamic, and/or efficacy. Only a subset of significant PK parameters will be considered.

Descriptive statistics and graphical presentation of SAR439859 PK parameters of interest will be done for monotherapy and combination therapy in regards of safety/efficacy endpoints. In case of need, a dedicated PK/PDy SAP will be prepared for more detailed analysis.

## 2.4.8 Pharmacogenetic variables

The number of participants will available DMET data will be provided for each dose level and overall. The UGT1A1 gene-level haplotypes and the associated predicted phenotype (eg, poor metabolizers, intermediate metabolizers, extensive metabolizers) will be also described for each dose level and overall.

### 2.4.9 Further therapy after discontinuation of investigational medicinal product administration during the study

A summary table will be provided for further therapies based on WHO-DD coding.

## 2.5 DATA HANDLING CONVENTIONS

### 2.5.1 General conventions

The following abbreviated modified formula will be used for computation of the diet in renal disease:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{sCr}) - 1.154 \times (\text{Age}) - 0.203 \times (0.742 \text{ if Female}) \times (1.212 \text{ if African-American})$$

### 2.5.2 Data handling conventions for secondary efficacy variables

Not applicable.

### 2.5.3 Missing data

The analyses and summaries of continuous and categorical variables will be based on observed data only. Percentages will be calculated using as denominator the number of participants with non-missing observation in the considered population. When relevant, the number of participants with missing data is presented.

***Handling of disease characteristics missing/partial dates***

- If the day is missing, it will be imputed by 1.
- If the month is missing, it will be imputed by 1 (only for medical history variables).
- If the year is missing, no imputation will be performed.

***Handling of medication missing/partial dates***

No imputation of medication (other than anti-cancer therapies) start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For prior anti-cancer therapies, following rules will be applied:

- Incomplete start date of prior anti-cancer therapy: if the day of the start date of the prior regimen is missing, the date will be imputed to the first day of the month; if the month is missing, the date will be imputed to the first month of the year.
- Incomplete end date of prior anti-cancer therapy: if the day of the end date of last prior regimen is missing, the date will be imputed to the last day of the month; if the month is missing, the date will be imputed to the last month of the year.

***Imputation of incomplete date for post anti-cancer treatment start date***

For post anti-cancer treatments, if the medication start date is missing, it will be imputed as follows:

- If the medication start day and month are missing and the medication start year is the same as treatment end year, the medication start date will be set equal to treatment end date + 1.
- If the medication start day and month are missing and the medication start year is after the treatment end year, the medication start day and month will each be set to 01.
- If the medication start day is missing and medication start year and month is the same as the treatment end year and month, the medication start date will be set to the treatment end date + 1.
- If the medication start day is missing and medication start month is before the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is after the treatment end month and the medication start year is the same as treatment end year, the medication start day will be set to 01.
- If the medication start day is missing and the medication start month is not missing and the medication start year is after the treatment end year, the medication start day will be set to 01.
- If the medication start day, start month and start year is missing, the medication start date will be set equal to the treatment end date + 1.

***Missing grade***

If the grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, no imputation will be done and missing grades will be summarized in the "all grades" category.

***Handling of missing assessment of relationship of adverse events to investigational medicinal product***

If the assessment of the relationship to the regimen is missing, then the relationship to the regimen has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

***Handling of other missing dates***

Incomplete date of cancer diagnosis:

- If the day of the cancer diagnosis is missing, the date will be imputed to the first day of the month.
- If day and month of the cancer diagnosis are missing, no imputation will be done.

Incomplete date of progression for the last prior regimen:

- If the day of the progression for the last prior regimen is missing, the date will be imputed to the end day of the month.
- If day and month of the progression for the last prior regimen are missing, no imputation will be done.

Incomplete date of prior surgery:

- If the day of the last prior surgery is missing, the date will be imputed to the end day of the month.
- If day and month of the last prior surgery are missing, no imputation will be done.

Incomplete date of prior radiotherapy:

- If the end day of the last prior radiotherapy is missing, the date will be imputed to the end day of the month.
- If the start day of last prior radiotherapy or day and month of the last prior radiotherapy are missing, no imputation will be done.

### 2.5.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be used for computation of baseline and worst values and/or grades.

### 2.5.5 Pooling of centers for statistical analyses

Data from all sites will be pooled together for analyses.

### 2.5.6 Statistical technical issues

Not applicable.

# 3 INTERIM ANALYSIS

In Arm #1 Part B, an interim analysis is planned when 45 participants are treated in order to decide, based on preset criteria, if the recruitment of planned additional participants is justified. If 4 or less responses (CR + PR) are observed on the first 45 participants evaluable for response, the study will be stopped for futility.

In order to support project strategic planning and design of future studies, interim analyses may be conducted during the study in addition to the futility interim analyses described above. They will have no impact on the trial itself. Within the framework of these analyses, calculations of posterior probabilities for response rate will be performed.

# 4 DATABASE LOCK

The final database lock is planned 4 weeks after last cut-off date in the study.

For each arm, a database lock of participants of this arm is planned 4 weeks after the cut-off date of the concerned arm defined in Section 2.

# 5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher. PK analysis will be done using PKDMS V3.0 or higher running with Phoenix 1.4 software.

# 6 REFERENCES

1. Gough K, Hutchison M, Keene O, Byrom B, Ellis S, Lacey L, McKellar J. Assessment of Dose Proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK Joint Working Party. Drug Inf J. 1995;29:1039-48.

2. Burdick RK, Graybill FA. Confidence intervals on variance components. In: Statistics, textbooks and monographs; New York (NY): Marcel Dekker. 1992;127:28-57.

# 7 LIST OF APPENDICES

# Appendix A Eastern Cooperative Oncology Group Performance Status Scale

| Performance Status | Description |
|---|---|
| 0 | Normal, fully functional |
| 1 | Fatigue without significant decrease in daily activity |
| 2 | Fatigue with significant impairment of daily activities or bed rest <50% of waking hours |
| 3 | Bed rest/sitting >50% of waking hours |
| 4 | Bedridden or unable to care for self |

# Appendix B National Cancer Institute Common Terminology Criteria for Adverse Events

Refer to NCI-CTCAE v.4.03 (28) in the Study Reference Manual, or online at the following NCI website: http://ctep.cancer.gov/reporting/ctc.html

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.

When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used.

The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.

An accurate baseline prior to therapy is essential.

# Appendix C Modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

***Definitions***

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows:

**Measurable**

- *Tumor lesions*: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
  - 20 mm by chest X-ray.
- *Malignant lymph nodes*: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See notes below on "Baseline documentation of target and nontarget lesions" for information on lymph node measurement.

**Non-measurable**

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

**Special considerations regarding lesion measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

*Bone lesions:*

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

*Cystic lesions:*

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

*Lesions with prior local treatment:*

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

***Methods of measurement***

- Measurement of lesions

  All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- Method of assessment

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- *Chest X-ray*: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

- *CT, MRI*: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

- *Ultrasound*: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

- *Endoscopy, laparoscopy*: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- *Tumor markers*: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- *Cytology, histology*: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

***Tumor response evaluation***

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either TTP or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having nonmeasurable disease only are also eligible.

## Response Criteria

**Table 1**

| Evaluation of target lesions | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.s |
| Partial Response (PR): | At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. |
| Progressive Disease (PD): | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). |
| Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study |

**Table 2**

| Evaluation of nontarget lesions | |
|---|---|
| Complete Response (CR): | Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis). |
| Incomplete Response/Stable Disease (SD): | Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits. |
| Progressive Disease (PD): | Unequivocal progression (see comments below)[a] of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression). |

*a* Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

## Evaluation of best overall response

It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

**Table 3**

| Target lesions | Non-target lesions | New lesions | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | No | SD |
| Not all evaluated | Non PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

**Table 4**

| Overall response First time point | Overall response Subsequent time point | BEST overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[a] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

*a* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 4.

## Appendix D 18FES-PET scan

$$Baseline_{suv} = \sum_{i=1}^{number\ of\ lesions} (suv_{baseline-max-Lesion\ i} - suv_{background\ (the\ highest)})$$

$$Th_{suv} = \sum_{i=1}^{number\ of\ lesions} (suv_{on\ treatment-max-Lesion\ i} - suv_{background\ (the\ highest)})$$

$$\%\ of\ reduction\ (inhibition) = \frac{Baseline_{suv} - Th_{suv}}{Baseline_{suv}} \times 100$$

## Appendix E Moderate fat breakfast example

| Food | Amount |
|---|---|
| Slices of bread | 40 g |
| Jam | 30 g |
| Butter | 10 g |
| Semi skimmed milk | 150 mL |
| Or powdered milk | 15 g |
| Or natural yogurt | 1 |

This type of diet generally contains approximately 9% protein, 27% lipids, and 64% carbohydrate, which provides about 400 to 500 kcal.

No fruit juice.

## Appendix F Internationally agreed SOC order

The internationally agreed order (Guideline on summary of product characteristics, December 1999, European commission) for SOC:

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and the lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic and mediastinal disorders
14. Gastrointestinal disorders
15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury and poisoning
25. Surgical and medical procedures
26. Social circumstances
27. Product issues

The other terms are sorted by dictionary code order.

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