A study to evaluate the safety and efficacy of vosilasarm (EP0062), an oral Selective Androgen Receptor Modulator (SARM), as monotherapy and in combination with standard-of-care regimens in patients with relapsed locally advanced or metastatic AR+/HER2-/ER+ breast cancer

P2-10-18

San Antonio Breast Cancer Symposium
December 10-13, 2024

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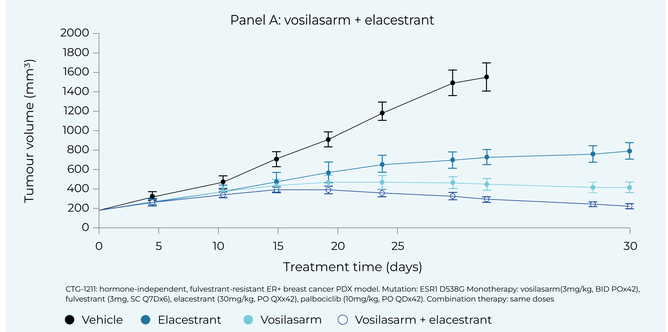
INTRODUCTION

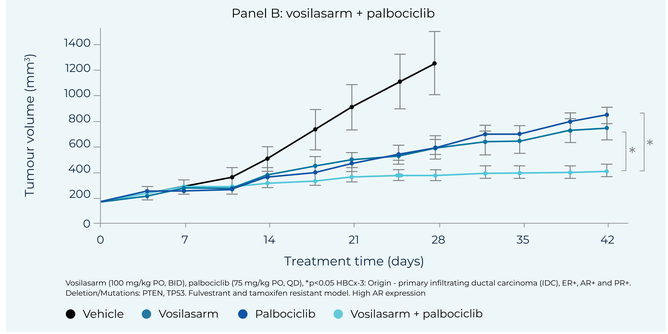
- AR activation exerts potent antitumour activity across a number of ER+ /AR+ breast tumours, including those resistant to standard-of-care endocrine therapy and CDK4/6 inhibitors[1]
- Mechanistically, agonist activation of AR alters the genomic distribution of ER and essential co-activators resulting in repression of ER-regulated cell cycle genes and upregulation of AR target genes, including known tumour suppressors
- Vosilasarm (EP0062) is an oral, non-steroidal, Selective Androgen Receptor Modulator (SARM) in development for the treatment of AR+/HER2-/ER+ locally advanced or metastatic breast cancer
- Preclinically, vosilasarm was shown to act as a potent tissue-selective AR agonist, suppressing growth and proliferation of multiple ER+/AR+ breast cancer cell lines and patient-derived xenograft models (PDX)[2]. Vosilasarm activated the AR pathway whilst genes within the ER pathway, including ESR1, were suppressed
- Vosilasarm was found to enhance antitumour activity when combined with palbociclib, everolimus or elacestrant in PDX models[2,3] (see **Figure 1**)
- The clinical promise of SARMs in breast cancer has been confirmed in several studies including an initial evaluation of vosilasarm in a small Phase 1 trial that demonstrated acceptable tolerability with evidence of clinical activity[4,5].
- Vosilasarm is the only SARM in active clinical development
- This ongoing study (NCT05573126) is evaluating the safety and initial efficacy of vosilasarm in patients with AR+/HER2-/ER+ locally advanced or metastatic breast cancer as monotherapy and in combination with established standard of care therapies

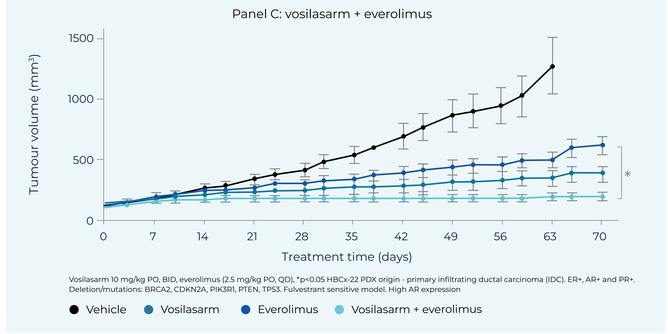
ACKNOWLEDGEMENTS

We are grateful to the patients and their loved ones for their key contribution to this work, and the participating sites for all their hard work.

Figure 1. Tumour growth inhibition of vosilasarm combinations in breast cancer PDX models

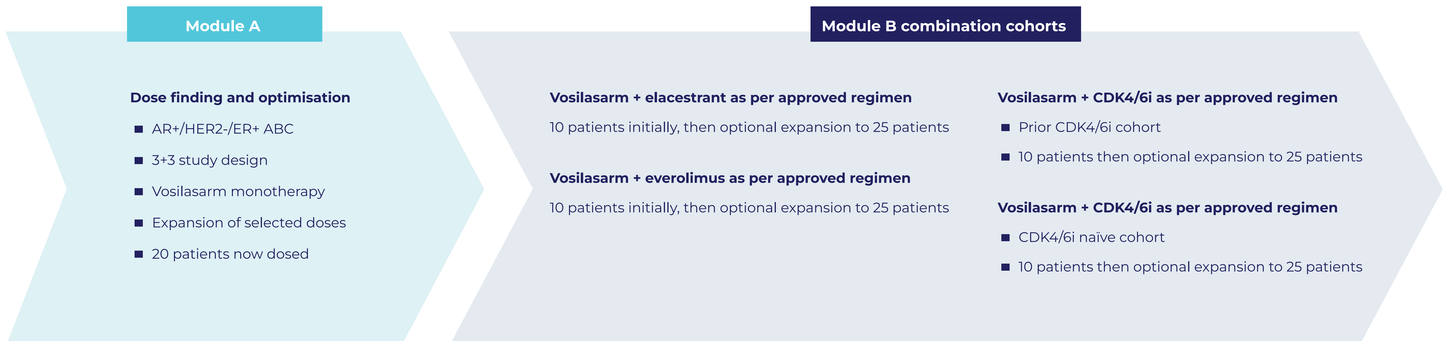






METHODS

Figure 2. Study design



Study design

- This study is recruiting patients with AR+/HER2-/ER+ advanced/metastatic breast cancer **(Figure 2)**
- Module A, which is ongoing, is comprised of dose optimisation cohorts in a 3+3 design, to investigate safety, tolerability, PK and PD and to define the optimum dose for planned combination expansions. 20 patients have been included to-date across 4 dose cohorts
- In Module B, vosilasarm is being evaluated in combination with standard-of-care (SOC) therapies in patients with relapsed AR+/HER2-/ER+ locally advanced or metastatic breast cancer to confirm safety and explore efficacy:
  - Cohort 1: vosilasarm + elacestrant in patients that have progressed on one or two prior lines of endocrine therapy, including prior CDK4/6 inhibitor (ESR1 mutation positive)
  - Cohort 2: vosilasarm + everolimus as per approved regimen in patients that have progressed on a prior endocrine therapy + CDK4/6 inhibitor
  - Cohort 3a (CDK4/6i Naïve): vosilasarm + CDK4/6i as per approved regimen in patients that have progressed on approved endocrine therapy during or within 6 months of completion of adjuvant endocrine therapy, or following 1 prior line of endocrine therapy in the advanced/metastatic setting
  - Cohort 3b (Prior CDK4/6i): vosilasarm + CDK4/6i as per approved regimen in patients that have progressed on treatment with a prior CDK4/6 inhibitor plus an aromatase inhibitor as initial therapy or recurrence on/ after treatment with a CDK4/6 inhibitor plus endocrine therapy in the adjuvant setting
- The vosilasarm dose has been selected from the dose finding/optimisation cohorts in Module A. Combination agents will be initiated at approved doses. An initial 3-6 patients will be enrolled in order to assess safety and tolerability of vosilasarm + the combination agent and to establish the appropriate combination dose for vosilasarm, with subsequent expansion to 10 patients per cohort. Cohorts may be further expanded to 25 patients dependent on safety and efficacy findings

Key inclusion criteria

- Post-menopausal women, ≥18 years
- ECOG performance status of 0 to 1
- Locally advanced or metastatic breast cancer
- ER+, HER2- as per ASCO College of American Pathologists (CAP) guidelines
- AR+, as defined as ≥ 10% AR nuclei staining by IHC
- Endocrine sensitive disease, defined as:
  - ≥ 2 years of adjuvant endocrine therapy prior to the development of advanced or metastatic disease

  OR
  - Previous response (without disease progression for ≥ 6 months) to one of the following treatments in the metastatic setting: SERD +/- CDK4/6 inhibitor, aromatase Inhibitor +/- CDK4/6 inhibitor
- Measurable disease defined by RECIST version 1.1, or bone-only disease

Pharmacokinetics

- PK assessments will be performed in Module A and B:
  - The first patient in each dose level has PK sampling up to 48 hours after the first dose on Cycle 1 Day 1
  - All other patients in Cycle 1 will undergo PK sampling for up to 24 hours
  - PK sampling will also be performed pre- and post-dose on days 8, 15 and 22

Statistics

No formal sample size calculations for Module A or B

Biomarkers

- Planned blood and tissue biomarkers in this study include:
  - prostate-specific antigen
  - cancer antigen 15-3
  - circulating tumour DNA

Assessments and endpoints

Safety

- Incidence of DLTs during Cycle 1 of vosilasarm treatment (28 days) – Module A only
- Adverse events, Serious adverse events and toxicity grading
- Physical examination, vital signs, cardiac assessments (ECG, echocardiogram, as required), weight, ECOG performance status, haematology, chemistry and urinalysis
- Clinic follow-up every 8 weeks in first 12 months, then every 12 weeks until disease progression

Efficacy

- Tumour response: objective response rate, complete response, partial response, stable disease, or progressive disease
- Clinical Benefit Rate (complete response, partial response, or stable disease) at week 24
- Duration of response
- Progression-free survival
- Overall survival
- Relationship between efficacy and AR levels
- Quality-of-life assessments

SUMMARY

- The available preclinical and clinical data indicate that SARMs have promise for the treatment of breast cancer
- This ongoing study (NCT05573126) is evaluating the safety and initial efficacy of vosilasarm (EP0062), an oral, non-steroidal, SARM for the treatment of AR+/HER2-/ER+ locally advanced or metastatic breast cancer
- Dose optimisation cohorts have been completed and recruitment of the combination cohorts will initiate shortly

References

1. Hickey *et al.*, Nature Medicine 2021 27: 310-320 **2.** Yu *et al.* Clin Cancer Res 2017 23(24) 7608 **3.** He *et al* SABCS 2019 **4.** LoRusso *et al.* Clinical Breast Cancer 2022 22;1 67-77 **5.** Palmieri *et al.* Lancet Oncol 2024 25: 317-325