A phase 1/2 study of EP0062 (vosilasarm), a first-in-class oral selective androgen receptor modulator (SARM), in combination with standard of care endocrine therapy +/- targeted therapies in patients with advanced or metastatic AR+/ER+/HER2− breast cancer

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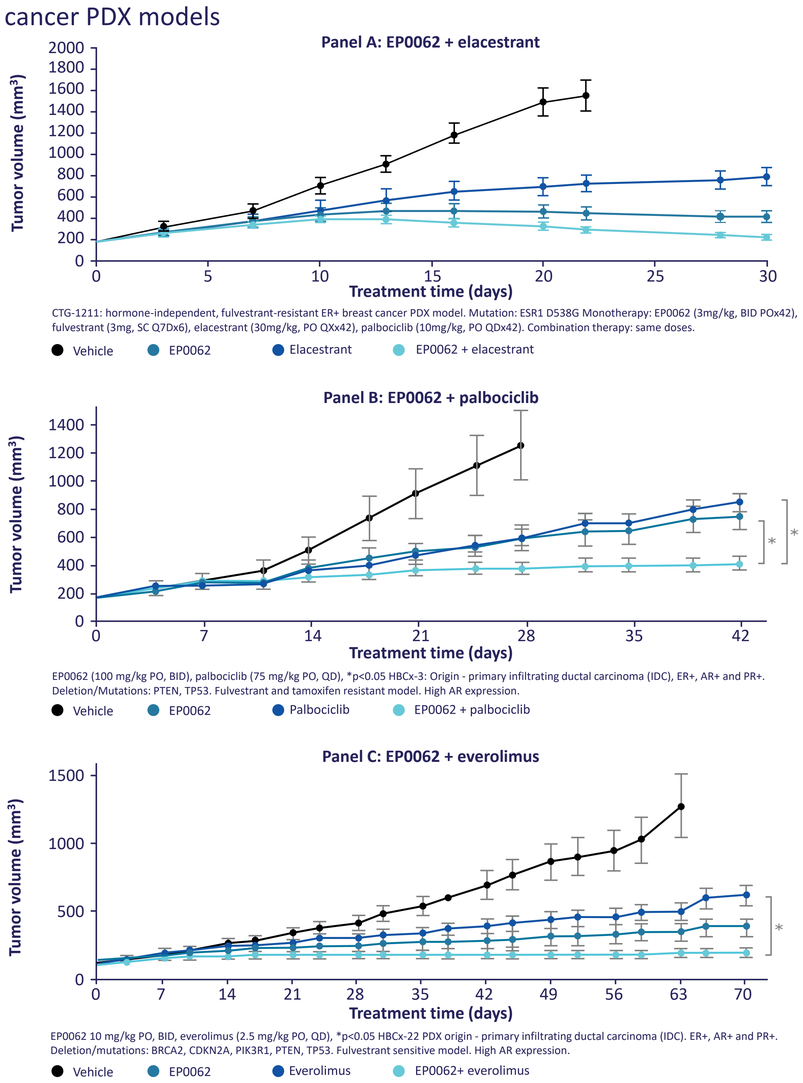
BACKGROUND

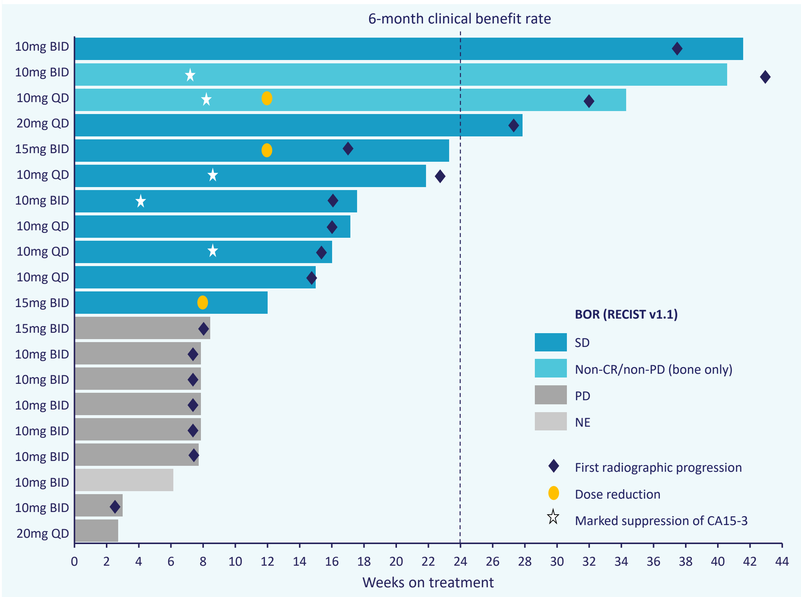
- EP0062 (vosilasarm), is a first-in-class, non-steroidal, oral selective androgen receptor modulator (SARM)
- Preclinically, EP0062 has been shown to:[1–3]
  - Be a potent tissue-selective androgen receptor (AR) agonist, suppressing the growth and proliferation of AR+/ER+/HER2− breast cancer cell lines and patient-derived xenograft (PDX) models
  - Activate the AR pathway, whilst genes within the estrogen receptor (ER) pathway (including ESR1) were suppressed
  - Have enhanced antitumor activity when combined with palbociclib, everolimus, or elacestrant (relative to the corresponding monotherapies), in endocrine-sensitive or resistant AR+/ER+/HER2− breast cancer PDX models (**Figure 1**)

Figure 1. Tumor growth inhibition of EP0062 combinations in breast cancer PDX models



BID, twice daily; ER, estrogen receptor; PDX, patient-derived xenograft; PO, orally; QD, once daily; SC, subcutaneous.

Figure 2. Duration of treatment



BID, twice daily; BOR, best overall response; CA, cancer antigen; CR, complete response; NE, not evaluable; PD, progressive disease; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

SUMMARY

- This is the first study to evaluate the safety and efficacy of a SARM in combination with standard of care therapies, following prior therapy with a CDK4/6 inhibitor
- Available preclinical and clinical data indicate that EP0062 (a first-in-class, non-steroidal, oral SARM) has promise in the treatment of breast cancer
- Monotherapy with EP0062 showed promising efficacy and safety in patients with AR+/ER+/HER2− locally advanced or metastatic breast cancer[4]
- Recruitment in the combination cohorts is ongoing in sites across Spain, the United Kingdom and the United States

- In the Phase 1 part of this study, promising evidence of clinical benefit with EP0062 monotherapy in advanced AR+/ER+/HER2− breast cancer was observed (**Figure 2**)
  - EP0062 was shown to have an acceptable and manageable tolerability and safety profile[4]

METHODS

Study design

- The ongoing Phase 2 cohorts described here (NCT05573126) are the first clinical evaluation of a SARM in combination with various standard of care therapies in patients who have previously received a CDK4/6 inhibitor
- This study is recruiting patients with AR+/ER+/HER2− advanced or metastatic breast cancer
- The study design for Module A (completed), which comprised dose optimization cohorts in a 3+3 design (n=20), has been previously published[4]
- In Module B (ongoing), EP0062 is being evaluated in combination with standard of care therapies to confirm safety and explore efficacy (**Figure 3**)

Figure 3. Combination cohorts

Module B: combination* cohorts

Arm 1: EP0062 + elacestrant — **Recruitment complete**
- ≤2 prior lines of endocrine therapy, including prior CDK4/6 inhibitor
- Confirmed ESR1 mutation required

Arm 2: EP0062 + everolimus + exemestane — **Ongoing**
- ≤2 prior lines of endocrine therapy in the advanced or metastatic setting, including prior CDK4/6 inhibitor

Arm 3: EP0062 + abemaciclib + fulvestrant — **Ongoing**
- 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

*Combinations as per approved regimen.

- The starting dose of EP0062, 10 mg twice daily, was selected from the completed Module A dose-finding/optimization cohorts[4]
- An initial 3–6 patients were enrolled in the safety run-in to assess the safety and tolerability of EP0062 + the combination agent, to establish the appropriate combination dose
- Further safety evaluation in up to 10 patients with optional expansion to 25 patients

Inclusion criteria

- Post-menopausal women
- Locally advanced or metastatic AR+/ER+/HER2− breast cancer
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–1
- AR+, defined as ≥10% AR nuclei staining by immunohistochemistry (IHC; either locally or centrally analyzed)
- 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: selective estrogen receptor degrader (SERD) +/− CDK4/6 inhibitor, or aromatase inhibitor +/− CDK4/6 inhibitor
- Measurable disease defined by RECIST version 1.1, or bone-only evaluable disease (with blastic and/or lytic component)

ASSESSMENTS & ENDPOINTS

Safety

- Incidence and severity of adverse events, serious adverse events, and toxicity grading
- Clinic follow-up every 8 weeks in the first 12 months, then every 12 weeks until disease progression

Efficacy

- Tumor 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
- Quality of life assessment

Pharmacokinetics

- PK sampling will be performed at the following times in Cycle 1:
  - Day 1: at pre-dose, and at 1, 2, 4, 8, and 24 hours post-dose
  - Days 8, 15, and 22: at pre-dose, and at 1–2 hours post-dose

Biomarkers

- Planned blood and tissue biomarkers in this study include:
  - Prostate-specific antigen
  - Cancer antigen 15-3
  - Circulating tumor DNA

Statistics

- No formal sample size calculations have been conducted

Acknowledgments

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. We would like to thank Dr Elisa Fontana from Sarah Cannon Research Institute, London, UK, for serving as Principal Investigator before handing over to Dr Rafael Grochot. Editorial support was provided by Emily Fang, MPharm, of Ashfield MedComms, an Inizio company, and was funded by Ellipses Pharma.

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