VERITAC-2: a global, randomized phase 3 study of ARV-471, a PROTAC erlotinib TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, vs fulvestrant in ER+/HER2-advanced breast cancer

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Objective
- The phase 3 VERITAC-2 study (NCT05656423) will compare the efficacy and safety of vepdegestrant (ARV-471) with the selective ER degrader (SERD) fulvestrant in patients with ER+/HER2-advanced breast cancer after prior combination cyclin-dependent kinase (CDK)4/6 inhibitor therapy and endocrine therapy

Background and Rationale
- Vepdegestrant (ARV-471) is an oral PROTAC ER degrader that binds to and degrades wild-type ER and clinically relevant mutants1
- Vepdegestrant directly binds the cerebro E3 ubiquitin ligase and ER to trigger ubiquitination of ER and its subsequent proteasomal degradation, whereas SERDs indirectly recruit the ubiquitin-proteasome system, secondary to conformational changes and/or immobilization of ER2
- The SERD fulvestrant must be administered intramuscularly3, and at its optimal dose, ER protein degradation is limited to only 40%–50%4,5
- In breast cancer xenograft models, vepdegestrant treatment provided substantially greater ER degradation and tumor growth inhibition compared with fulvestrant6
- In VERITAC, the phase 2 expansion cohort of a first-in-human phase 1/2 study (NCT04072952), vepdegestrant monotherapy showed clinical activity and was well tolerated in heavily pretreated patients with ER+/HER2-advanced breast cancer6
- The clinical benefit rate (CBR)4 was 37.1% (95% CI: 21.5–55.1) and 38.9% (95% CI: 23.1–56.5) in the 200-mg (n=35) and 500-mg (n=36) oral, once-daily (QD) cohorts, respectively
- Clinical activity was also observed in the mutant ESR1 subgroup: CBR was 47.4% (95% CI: 24.4–71.1) and 54.5% (95% CI: 32.2–75.6) in the 200-mg (n=19) and 500-mg (n=22) QD cohorts, respectively
- Most adverse events (AEs) were grade 1/2, with few AEs leading to dose reduction (500 mg, n=3) or discontinuation (200 mg, n=1; 500 mg, n=2)
- In a subset of patients who received 200 mg QD across the phase 1/2 study (n=9), up to 95% ER degradation was observed, with a median (range) of 69% (28%–95%)
- The phase 3 monotherapy dose (200 mg QD) for the current study was chosen based on comparable efficacy and favorable tolerability relative to 500 mg QD, and robust ER degradation

Study Design
- In this open-label, global, multicenter, phase 3 study (Figure 1), patients are randomized 1:1 to receive vepdegestrant or fulvestrant in 28-day cycles
- Eligible patients have ER+/HER2-advanced breast cancer and prior treatment with a CDK4/6 inhibitor therapy in combination with endocrine therapy (Table 1)
- Outcome measures are shown in Table 2

Study Status
- Enrollment is ongoing
- Countries with currently open and planned study sites are shown in Figure 2

Table 1: VERITAC-2 key eligibility criteria

Table 2: VERITAC-2 outcome measures

References

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