First-in-human Phase 1 study of BTX-9341, a first-in-class, CDK4/6 bifunctional degrader, as a monotherapy and in combination with fulvestrant in patients with advanced and/or metastatic HR+/HER2- breast cancer.

Amita Patnaik[1], Margaret Block[2], Danette Powell[3], Aparajita H. Chourasia[3], Massimo Cristofanilli[4], Ewelina Morawa[3], Jeremy Barton[3], *Rachel M. Layman[5], *Matthew Goetz[6]

[1]The START Center for Cancer Research, San Antonio, TX; [2]Nebraska Cancer Specialists, Omaha, NE; [3]Biotheryx Inc., San Diego, CA; [4]Weill Cornell Medicine, New York, NY;

[5]MD Anderson Cancer Center, Houston, TX; [6]Mayo Clinic, Rochester, MN; *Co-last authors

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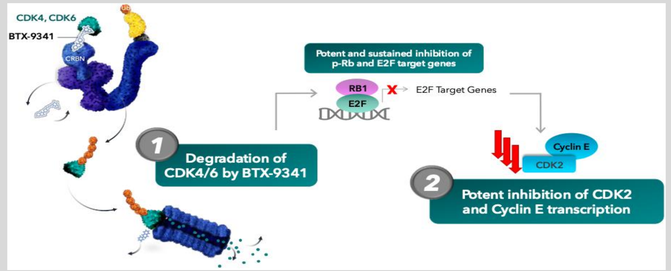
OBJECTIVE

The first-in-human (FIH), Phase 1 trial of BTX-9341 (BTX-9341-101) is a multicenter, nonrandomized, open-label trial to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of BTX-9341 as monotherapy and as combination therapy with fulvestrant in patients with advanced and/or metastatic hormone receptor (HR)-positive (+)/human epidermal growth factor receptor 2 (HER2)-negative (-) breast cancer who have received prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor therapy and have no mutations in retinoblastoma (RB).

BACKGROUND

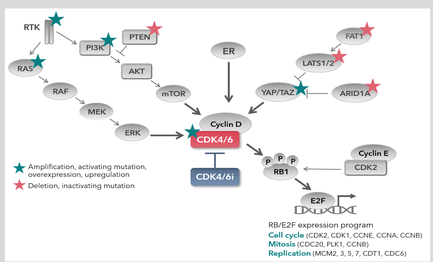
- BTX-9341 is a first-in-class, oral bifunctional degrader of CDK4 and CDK6, both clinically validated cell cycle targets in HR+/HER2- breast cancer.
- It consists of a CDK4/6 binding molecule conjugated to a cereblon (CRBN) binder via a linker resulting in CRBN-mediated proteasomal degradation of CDK4 and CDK6, which in turn leads to a robust inhibition of RB phosphorylation and cyclin-dependent kinase 2 (CDK2) and Cyclin E transcription (Figure 1).

Figure 1: Mechanism of action of BTX-9341



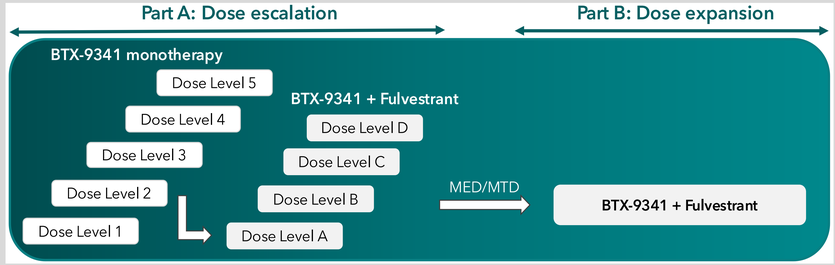
- Preclinical data highlight the superiority of BTX-9341 compared to CDK4/6 inhibitors in terms of inhibition of RB phosphorylation, inhibition of CDK2 and Cyclin E, cell cycle arrest, and *in vivo* efficacy in breast cancer xenograft models.
- Up to 70% HR+/HER2- breast cancer patients can develop resistance to the FDA approved CDK4/6 inhibitors (CDK4/6i) within 3 years and many of the resistance mechanisms converge on the CDK4/6 and CDK2 signaling node[1-5]. BTX-9341 also overcomes key resistance mechanisms that limit the impact of CDK4/6i in second-line (2L) HR+/HER2- breast cancer and exhibits synergy with the selective estrogen receptor degraders (SERDs) in naïve and CDK4/6i resistant models (Figure 2). **[See Poster Presentation ID: P4-11-02]**

Figure 2: CDK2/4/6 at a critical signaling node in resistance to CDK4/6 inhibitors



STUDY DESIGN

Figure 3: BTX-9341-101 Trial Design



Abbreviations: MED, maximum evaluable dose; MTD, maximum tolerated dose;

- BTX-9341-101 is a multicenter, nonrandomized, open-label trial to evaluate the safety, tolerability, PK, PD, and preliminary efficacy of BTX-9341 in patients with advanced and/or metastatic HR+/HER2- breast cancer who have received prior CDK4/6 inhibitor therapy and have no mutations in RB.
- The trial consists of initial dose escalation using accelerated titration and a Bayesian Optimal Interval (BOIN) design (Part A) of BTX-9341, both as monotherapy and in combination with fulvestrant (Figure 3). The dose expansion (Part B) of BTX-9341 in combination with fulvestrant will use a Bayesian Optimal Phase 2 (BOP2) design.
- The primary and secondary objectives and associated endpoints for Part A and Part B are listed in Figure 4.

Figure 4: BTX-9341-101 Trial Objectives and Associated Endpoints

Phase	Primary Objectives	Primary Endpoints	Secondary Objectives	Secondary Endpoints
Part A (Dose Escalation)	Evaluate the safety and tolerability of BTX-9341 monotherapy and/or combination therapy with fulvestrant and determine MTD/MED of BTX-9341	Assessment of DLT events and safety profile based on rate and severity of AEs over time after treatment with BTX-9341 monotherapy and/or combination therapy with fulvestrant	1. Characterize the plasma PK following single and multiple doses of BTX-9341 administered as a single agent and/or in combination with fulvestrant 2. Determine the efficacy of BTX-9341 administered as a single agent and/or in combination with fulvestrant	1. Assessment of plasma PK of BTX-9341 as a single agent and/or in combination with fulvestrant 2. Measurement of Investigator-assessed CBR, DOR, TTR and PFS of BTX-9341 as a single agent and/or in combination with fulvestrant
Part B (Dose Expansion)	Obtain preliminary evidence of BTX-9341 efficacy and establish the RP2D of BTX-9341 when administered in combination with fulvestrant	Measurement of Investigator-assessed ORR of BTX-9341 in combination with fulvestrant to confirm RP2D	1. All the secondary objectives from Part A 2. Determine the safety and tolerability of BTX-9341 administered in combination with fulvestrant	1. All the secondary endpoints from Part A 2. Assessment of rate and severity of AEs over time through EOT with BTX-9341 in combination with fulvestrant

Abbreviations: AE, adverse event; CBR, clinical benefit rate; DOR, duration of response; DLT, dose-limiting toxicity; EOT, end of treatment; MED, maximum evaluable dose; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetics; PFS, progression-free survival; RP2D, recommended phase 2 dose; TTR, time to response

- The exploratory objectives include assessment of PD biomarkers to study correlation between PK and BTX-9341 response. The PD biomarkers will include circulating tumor DNA (ctDNA), serum Thymidine Kinase (STK1), and CDK4 and CDK6 protein levels from peripheral blood mononuclear cells (PBMCs).
- Approximately 82 patients will be enrolled and assigned initially to Part A (dose escalation; ~36 participants) and later to Part B (dose expansion; ~46 participants). BTX-9341 is being evaluated as an oral therapeutic administered once a day (QD) in 28-day treatment cycles.
- BTX-9341-101 is enrolling eligible participants with current diagnosis of advanced and/or metastatic HR+/HER2- breast cancer per criteria listed in Figure 5.

Figure 5: BTX-9341-101 Trial Eligibility Criteria

Inclusion Criteria

- Age ≥ 18 years
- Metastatic and/or locally advanced HR+/HER2- breast cancer confirmed histologically by most recent tumor sample and must express ER with/without co-expression of PR or have received prior ET for at least 6 months
- Eastern Cooperative Oncology Group (ECOG) score of 0 or 1
- Acceptable hematalogical, liver and renal function

Part A (Dose Escalation)

- Measurable disease according to RECIST v1.1 and/or at least 1 lytic or mixed bone lesion assessed by CT or MRI or non-measurable bone disease
- Received no more than 1 chemotherapy, no limit to ET and received CDK4/6i therapy

Part B (Dose Expansion)

- Measurable disease according to RECIST v1.1
- Received no more than 1 chemotherapy, no more than 2 lines of ET and received CDK4/6i therapy

Exclusion Criteria

- Symptomatic visceral disease
- Known RB1 gene mutation
- Evidence or history of CNS metastasis or inflammatory breast cancer
- Any toxicity related to prior cancer therapy not resolved to Grade ≤ 1 or baseline

Abbreviations: RECIST, Response Evaluation Criteria In Solid Tumors Version 1.1; CT, computed tomography; ET, endocrine therapy; ER, estrogen receptor; PR, progesterone receptor; CNS, central nervous system

STUDY STATUS

- **BTX-9341-101 is currently active and recruiting participants**
- **For more information on the study and sites, please visit www.clinicaltrials.gov (NCT06515470)**

REFERENCES

1. Scheidemann, E.R., et al. *Int J Mol Sci* **22**, 12292 (2021); 2. Álvarez-Fernández, M., et al. *Cancer Cell* **37**, 514-529 (2020); 3. Li, Z., et al. *Cancer Cell* **34**, 893-904 (2018); 4. Li, Q., et al. *Cancer Discovery* **12**, 356-371 (2022); 5. Razavi, P., et al. *Cancer Cell* **34**, 427-438 (2018).

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