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

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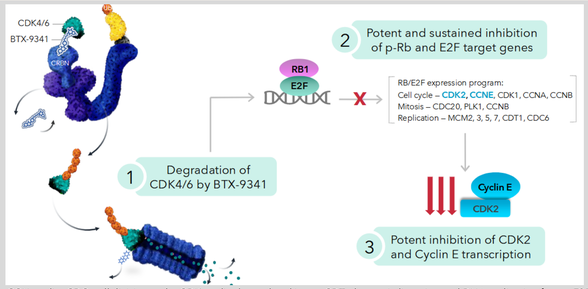
BACKGROUND

- BTX-9341 is a first-in-class, oral bifunctional degrader of cyclin-dependent kinase (CDK)4 and CDK6, both clinically validated cell cycle targets in hormone receptor (HR)-positive (+)/human epidermal growth factor receptor 2 (HER2)-negative (-) breast cancer (BC).
- 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).
- Preclinical data highlight its superiority compared with approved CDK4/6 inhibitors (CDK4/6i) in inhibition of phosphorylation of retinoblastoma (p-RB), cell cycle arrest, and in vivo efficacy in BC xenografts.
- BTX-9341 is active in CDK4/6i resistant models with p-RB half-maximal inhibitory concentrations (IC_{50}) of 1-15 nM and can overcome key mechanisms that drive CDK4/6i resistance.

Figure 1: Mechanism of action of BTX-9341

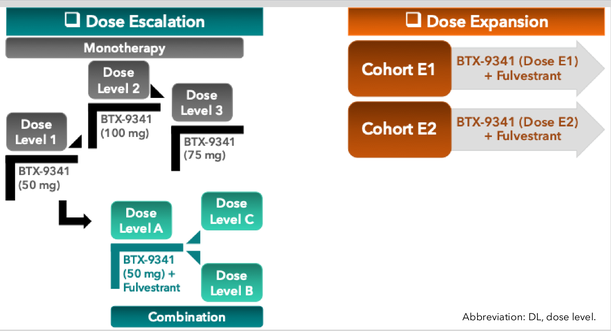


Abbreviations: CCN, cyclin; CDC, cell division cycle; CDK, cyclin dependent kinase; CDT, chromatin licensing and DNA replication factor; E2F, early 2-factor; MCM, minichromosome maintenance protein; PLK, polo-like kinase; p-Rb, phosphorylation of retinoblastoma; RB1, retinoblastoma 1 gene

STUDY DESIGN AND OBJECTIVES

- 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 HR+/HER2- BC who have received prior CDK4/6 inhibitor therapy and have no mutations in retinoblastoma (RB).
- BTX-9341 is administered orally (per os [PO]) once daily (QD) in 28-day treatment cycles.
- 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 2). The dose expansion (Part B) of BTX-9341 in combination with fulvestrant will use a Bayesian Optimal Phase 2 (BOP2) design.
- The primary objective of dose escalation is to determine the maximum tolerated dose (MTD) or maximum evaluable dose (MED) of BTX-9341 monotherapy and in combination with fulvestrant. Secondary objectives include the characterization of BTX-9341 on PK and efficacy; exploratory objectives include the assessment of BTX-9341 on PD and PK/PD relationships.
- BTX-9341-101 is currently active and recruiting patients. Early monotherapy data are available from the first-in-human Phase 1a study of BTX-9341.

Figure 2: BTX-9341-101 Trial Design



Abbreviation: DL, dose level.

RESULTS

Demographics and Baseline Characteristics

- As of the data cutoff, 16 patients were evaluated at the following BTX-9341 QD dose levels: 50 mg (dose level [DL]1), 100 mg (DL2), and 75 mg (DL3) monotherapy, and 50 mg in combination with fulvestrant (DLA).
- All patients were female, with a median age of 61 (38-83) years (Table 1).
- Patients received up to 5 lines of therapy in the metastatic setting prior to enrollment.
- Patients were pretreated with a median of 2 (1-6) prior lines of treatment. All patients had prior CDK4/6i treatment; 11 patients had prior chemotherapy, and all had prior endocrine therapy.

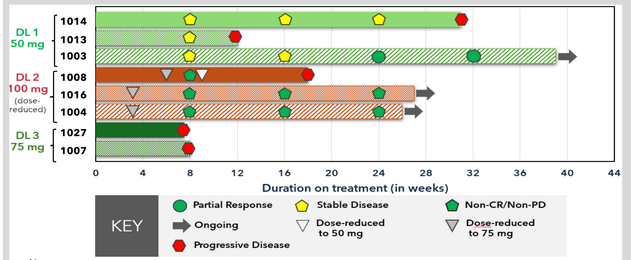
Table 1	N=16
Age (years), median (range)	61 (38 – 83)
Female, n (%)	16 (100)
White, n (%)	15 (93.8)
Visceral Disease, n (%)	12 (75)
Bone-only Disease, n (%)	4 (25)
All Prior Lines of Treatment, median (range)	2 (1-6)
≥3 All Prior Lines of Treatment, n (%)	5 (31)
Prior Lines of Treatment in Advanced/Metastatic Setting, median (range)	1 (1-5)
≥3 lines in Advanced/Metastatic Setting, n (%)	4 (25)
Prior Chemotherapy, n (%)	11 (68.8)
Neoadjuvant or adjuvant	9 (56.3)
Metastatic setting	4 (25)
Prior CDK4/6i, n (%)	16 (100)
Ribociclib	4 (25),
Months, median (range)	6.98 (2.76, 19.84)
Palbociclib	6 (37.5),
Months, median (range)	36.45 (2.56, 91.10)
Abemaciclib	8 (50),
Months, median (range)	8.74 (1 day, 21.78)
Prior Lines of ET, median (range)	2 (1-5)
Adjuvant Setting, n (%)	9 (56.3)
Advanced/Metastatic Setting, n (%)	
First line with CDK4/6i	14 (87.5)
Second line with CDK4/6i	1 (6.3)
Third line with CDK4/6i	1 (6.3)
Monotherapy	2 (12.5)
With other agents	5 (31.3)
PI3K/AKT/mTOR-based therapy, n (%)	6 (37.5)

Abbreviations: AKT, protein kinase B; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; ET, endocrine therapy; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3 kinase

Efficacy and Tumor Assessment

- Of the 8 evaluable monotherapy patients, the best overall responses in patients with measurable disease included 1 patient with a confirmed partial response (PR) and 3 patients with stable disease (SD) (first assessed at 8 weeks; i.e., the first time point for assessment in the protocol), and in patients with non-measurable disease, 2 patients had non-complete response/non-progressive disease (non-CR/non-PD) (Figure 3).
- Of the 5 evaluable combination patients in DLA, the best overall response included 1 patient with non-CR/non-PD (Figure 4).
- For all patients, the longest duration on treatment as of the data cutoff was 10 cycles.
- A clinical benefit rate (CBR) (defined as a best overall response CR, PR, or SD for patients with measurable disease or non-CR/non-PD for patients with non measurable disease, per RECIST v1.1 at Week 24) of 66.7% was observed in the completed cohorts (DL1 and DL2).

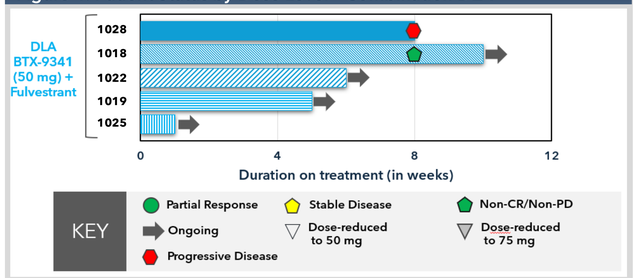
Figure 3: Patient Status by Dose Level - Monotherapy



Note:
- *Response criteria per RECIST v1.1: a) for target disease – CR, PR, SD and PD, b) for non-target disease only – CR, non-CR/non-PD (qualitative assessment from reduced non-target lesions to stable non-target lesions) and PD*
- *Data for participants on treatment by 06/13/25*

Abbreviations: DL, dose level; Non-CR/Non-PD, non-complete response/non-progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Figure 4: Patient Status by Dose Level – Combination DLA



Abbreviations: DLA, dose level A; Non-CR/Non-PD, non-complete response/non-progressive disease

Safety

- Treatment-related adverse events (TRAEs) in ≥10% of patients by preferred term for all grades are presented in Table 2.
- The most common TRAEs during the period were decreased neutrophil and white blood cell counts.
- As of the data cutoff, no dose limiting toxicities (DLTs) were observed at any dose levels during the 28-day DLT period.
- There were no Grade 5 TRAEs as of the data cutoff date.
- No TRAEs leading to discontinuation of treatment were reported.
- There were no dose reductions in DL1. The starting dose was reduced in all patients in DL2.
- No serious adverse events (SAEs) were reported.

Table 2	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Any TRAE, n (%)	2 (12.5)	2 (12.5)	6 (37.5)	2 (12.5)	12 (75.0)
TRAEs in ≥10% of Patients by Preferred Term for All Grades					
Neutrophil count decreased	0	2 (12.5)	6 (37.5)	2 (12.5)	10 (62.5)
Leukocyte count decreased	0	2 (12.5)	5 (31.3)	0	7 (43.8)
Lymphocyte count decreased	1 (6.3)	0	1 (6.3)	0	2 (12.5)
Fatigue	1 (6.3)	1 (6.3)	0	0	2 (12.5)

Abbreviation: TRAE, treatment-related adverse event

For more information on the study and sites, please visit www.clinicaltrials.gov (NCT06515470).

Pharmacokinetics

- At least 2-fold accumulation was observed after QD dosing, and steady-state trough concentrations were in the range of in vitro IC_{50} values at DL1 and higher dose levels (Table 3).

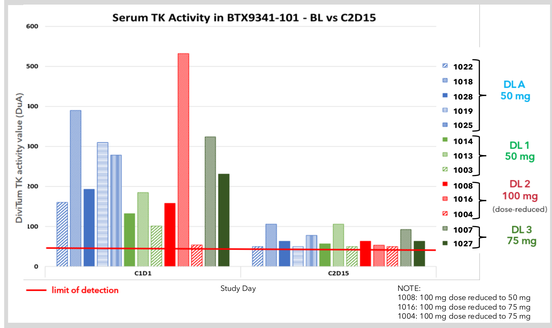
Table 3	DL1 (50 mg)	DL2 (100 mg)	DL3 (75 mg)
C1D1 (single dose PK)			
n	3	3	3
C_{max}, ng/mL	12.5 (60%)	23.2 (64%)	39.0 (66%)
T_{max}, h [A]	8 [8 – 24]	24 [8 – 24]	6 [2 – 24]
AUC_{last}, ng.h/mL	215 (64%)	383 (58%)	546 (58%)

[A] Median [range]
Abbreviations: AUC_{last}, area under the plasma concentration time curve from time 0 to the last time point; C, Cycle; C_{max}, maximum plasma concentration; D, day; PK, pharmacokinetics, T_{max}, time to maximum plasma concentration

Pharmacodynamics

- Serum thymidine kinase (TK) activity, a clinical biomarker for tumor response to CDK4/6 inhibition, showed excellent reduction (below limit of detection) in 9/13 patients (Figure 5).
- "On target" PD reductions in CDK4, CDK6, CDK2, and Cyclin E levels were observed in peripheral blood mononuclear cells.

Figure 5: Serum TK Reduction Across Dose Levels



Abbreviations: BL, baseline; C, Cycle; D, Day; DL, dose level; TK, thymidine kinase

CONCLUSIONS

- BTX-9341 monotherapy shows a favorable safety profile, with the most common TRAEs being decreased neutrophil and white blood cell counts.
- BTX-9341 demonstrated encouraging preliminary PK/PD as well as efficacy, including at doses that were tolerable, enabling further evaluation of monotherapy and in combination with fulvestrant.
- The trial will continue to enroll through completion of the dose expansion phase. (Clinical trial: NCT06515470).

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