P4-10-16

INX-315, an Oral, Potent and Selective CDK2 Inhibitor in Patients with CDK4/6 Inhibitor Resistant ER+/HER2- Breast Cancer or CCNE1 Amplified Solid Tumors:

PHASE 1 MONOTHERAPY DOSE ESCALATION

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BACKGROUND

- Cyclin-dependent kinases (CDK) are a family of serine / threonine kinases that heterodimerize with regulatory subunits called cyclins to drive cell cycle progression, cell division, and associated biological processes
- CDK2 plays a prominent role in promoting G1/S transition and S phase progression
- Dysregulated CDK2 activity commonly occurs through (i) amplification of CCNE1 (gene that encodes cyclin E1 protein), a known resistance mechanism to oral CDK4/6 inhibitors[1] and/or (ii) overexpression of cyclin E1
- CCNE1 amplified or cyclin E overexpressing cancers have worse survival in several tumor types including ovarian[2,3] and breast cancer[4,5]
- INX-315 is an oral, potent, and selective small molecule inhibitor of CDK2 for the treatment of human cancers[6]

CONCLUSIONS

- INX-315 monotherapy was generally well tolerated with only 1 DLT observed to date
- The majority of TRAEs were grade 1 or 2 with only 16% of patients experiencing a grade 3 or greater TRAE
- INX-315 demonstrated monotherapy antitumor activity in heavily pretreated patients with metastatic ER+/HER2- breast cancer and CCNE1 amplified, metastatic, platinum-resistant ovarian cancer
- Monotherapy and combination dose expansion are ongoing

References:
(1) Jhaveri K, et al. Expert Rev Anticancer Ther. 2021; 21:1105-1124
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(3) Petersen S, et al. Gynecologic oncology. 2020; 157:405-10
(4) Luhtala S, et al. Tumor Biology. 2016; 37:9813-23
(5) Lundgren C, et al. Acta Oncologica. 2015; 54:543-9
(6) Dietrich et al. Cancer Discov. 2024; 14(3):446–467

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METHODS

STUDY DESIGN AND TREATMENT

- INX-315-01 (NCT05735080) is a first-in-human, Phase 1/2, open-label, dose escalation, combination, and dose-expansion study of orally administered INX-315 (Figure 1)

KEY INCLUSION CRITERIA (PART A)

- ER+/HER2- breast cancer that has progressed on/after a CDK4/6 inhibitor
- Platinum-resistant or platinum-refractory CCNE1 amplified (by NGS) epithelial ovarian cancer that has progressed after standard systemic therapy
- Solid tumor with known amplification of CCNE1 (by NGS) that has progressed after standard therapy, been intolerant to or is ineligible for standard therapy
- At least 1 measurable lesion per RECIST v1.1
- Age ≥18 years; Eastern Cooperative Oncology Group performance status 0 or 1; and adequate bone marrow, renal, and liver function
- No prior therapy with a CDK2 inhibitor, including CDK2/4/6 inhibitors

ASSESSMENTS (PART A)

- Primary Objectives: safety, tolerability, dose-limiting toxicities, and recommended doses for expansion (RDEs) as monotherapy and in combination with fulvestrant
- Secondary Objectives: characterize the single and multiple dose pharmacokinetics of INX-315 and assess preliminary antitumor activity

STUDY DESIGN

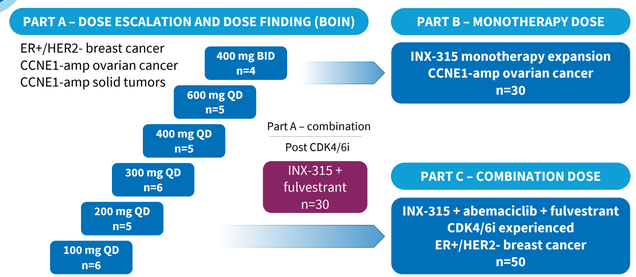

Figure 1. Study schema

PHARMACOKINETICS

- INX-315 plasma concentrations increased in a dose proportional manner
- Steady-state trough concentrations were ≥ the predicted effective concentration of 100 ng/mL
- Low Cmax to Cmin ratio likely to translate to best-in-class safety

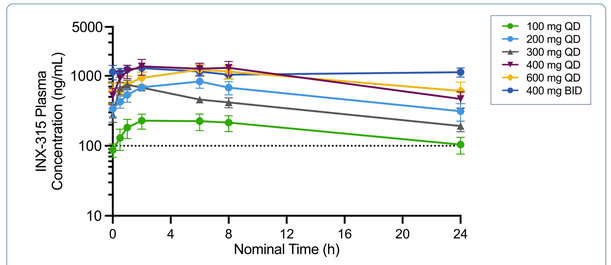

Figure 2. Day 15 mean INX-315 plasma concentrations by cohort

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PART A

CHARACTERISTIC	PATIENTS (N=31)
CHARACTERISTIC	
Age (years), median (range)	60 (29, 78)
Sex, N (%)	
Male	8 (26)
Female	23 (74)
Race, N (%)	
White	24 (77)
Asian	4 (13)
Black or African American	2 (7)
Other or not reported	1 (3)
Tumor type, N (%)	
ER+/HER2- breast cancer	10 (32)
HGSOC/fallopian (CCNE1 amplified)	10 (32)
Other solid tumors (CCNE1 amplified)	11(36)
Baseline ECOG, N (%)	
0	19 (61)
1	12 (39)
Prior lines, median (range)	4 (1, 9)
BREAST CANCER PATIENTS ONLY (N=10)	
Prior CDK4/6 inhibitor, n (%)	10 (100)
Prior fulvestrant, n (%)	9 (90)
Prior aromatase inhibitor, n (%)	9 (90)
Prior chemotherapy, n (%)	9 (90)
Prior antibody drug conjugate, n (%)	3 (30)

SAFETY

- Treatment-related adverse events (TRAEs) were observed in 26 patients (83.9%) (Table 2)
- The most frequent treatment-related AEs were thrombocytopenia (48.4%), nausea (38.7%), neutropenia (38.7%), and diarrhea (29.0%)
- Serious adverse events (SAEs) occurred in 10 (32.2%) patients, none were considered related to INX-315
- No fatal AEs were reported, and no AEs led to treatment discontinuation
- Dose limiting toxicity (DLT) was observed in 1 patient (grade 3 fatigue at 600 mg QD) resulting in a dose reduction
- Evaluation of the 400 mg BID dose level is ongoing
- 600 mg INX-315 QD has been selected by the safety monitoring committee for combination with fulvestrant and monotherapy expansion in Part B

TABLE 2. TRAEs OCCURRING IN ≥15% OF PATIENTS BY GRADE (PART A, SAFETY EVALUABLE PATIENTS, N=31)

TRAE BY PT, N(%)	GRADE 1	GRADE 2	GRADE 3	GRADE 4	TOTAL
With ≥1 TRAE	9 (29.0)	12 (38.7)	4 (12.9)	1 (3.2)	26 (83.9)
Thrombocytopenia	11 (35.5)	3 (9.7)	0	1 (3.2)	15 (48.4)
Nausea	9 (29.0)	3 (9.7)	0	0	12 (38.7)
Neutropenia	2 (6.5)	6 (19.4)	3 (9.7)	1 (3.2)	12 (38.7)
Diarrhea	6 (19.4)	2 (6.5)	1 (3.2)	0	9 (29.0)
Anemia	4 (12.9)	2 (6.5)	1 (3.2)	0	7 (22.6)
Vomiting	5 (16.1)	1 (3.2)	0	0	6 (19.4)
Fatigue	1 (3.2)	2 (6.5)	2 (6.5)	0	5 (16.1)
Leukopenia	1 (3.2)	2 (6.5)	2 (6.5)	0	5 (16.1)

EFFICACY

- Among all response-evaluable patients in Part A (n=30), 3 (10%) had a partial response and 19 (63%) had stable disease (Table 3; Figure 3)
- In patients with ER+/HER2- breast cancer, PR was observed in 1 (10%) and SD was observed in 5 (50%)
- In patients with CCNE1 amplified HGSOC/fallopian, PR was observed in 2 (20%) and SD was observed in 8 (80%)
- Pharmacodynamic studies (ctDNA, TK activity) are ongoing

TABLE 3. BEST OVERALL RESPONSE PER INVESTIGATOR ASSESSMENT

N (%)	ALL PATIENTS (N=30)	BREAST CANCER (N=10)
Complete response (CR)	0	0
Partial response (PR)	3 (10)	1 (10)
Stable disease (SD)	19 (63)	5 (50)
Progressive disease (PD)	8 (27)	4 (40)

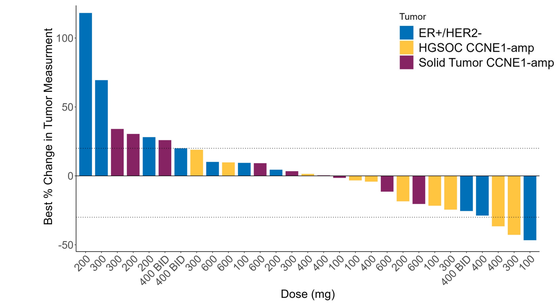

Figure 3. Waterfall plot of best percent change from baseline in sum of diameters for all patients (RECIST v1.1) (N=29)

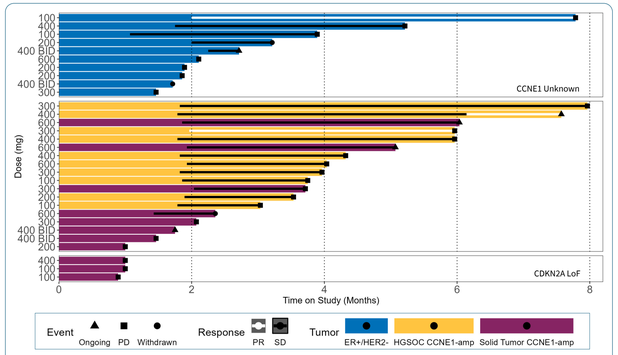

Figure 4. Swimmer plot (RECIST v1.1) (N=31)

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