Abstract TPS1121: IND.241 A CANADIAN CANCER TRIALS GROUP LIQUID-BIOPSY INFORMED PLATFORM TRIAL TO EVALUATE TREATMENT IN CDK4/6-INHIBITOR RESISTANT ER+/HER2- METASTATIC BREAST CANCER

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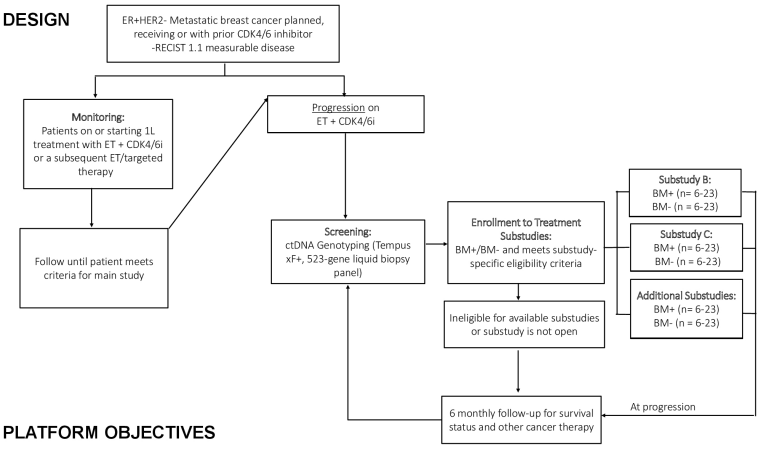
Background

- The combination of CDK4/6 inhibitor (CDKi) and endocrine therapy (ET) is standard first-line systemic treatment for patients with metastatic ER+/HER2-negative breast cancer (MBC).[1]
- Beyond this initial therapy, numerous agents are in development, but the lack of universal standards creates uncertainty regarding the optimal incorporation of predictive biomarkers.[2,3]
- Circulating tumor DNA (ctDNA) "liquid biopsy" presents a promising, non-invasive approach for blood-based tumor genotyping and response assessment with the potential to enhance biomarker-driven strategies and aid in development of new therapeutics.[4,5]

Methods

IND.241 is a master protocol platform with multiple substudies enrolling patients with ER+/HER2- MBC either prior to progression (PD) on CDKi + ET (Substudy A) or after PD and to investigate novel agents or drug combinations in 2nd/3rd lines (L) after progression on CDKi. NCT05601440.

DESIGN



PLATFORM OBJECTIVES

- **Primary:** central ctDNA genotyping (Tempus xF+, a 523-gene liquid biopsy panel) and evaluation of whether biomarker selection improves ORR or CBR as assessed by RECIST 1.1.
- **Secondary:** safety and toxicity for each drug/combination, PFS, OS.
- **Tertiary**: creating and maintaining a tissue and data bank including clinical data, genomics, and radiomics from all substudies to evaluate surrogates of treatment outcomes and potential biomarkers of response, resistance and disease progression.
- Monitoring substudy component (Substudy A) enrolls patients prior to CDKi+ET treatment failure and aims to characterize molecular profile, clinical features, ctDNA dynamics of resistance.

Substudy A Primary: create and maintain a tissue and data bank including tumour and liquid biopsies and clinical data for patients receiving first line CDK4/6i + ET treatment.

Substudy B,C, D, E Primary: ORR.

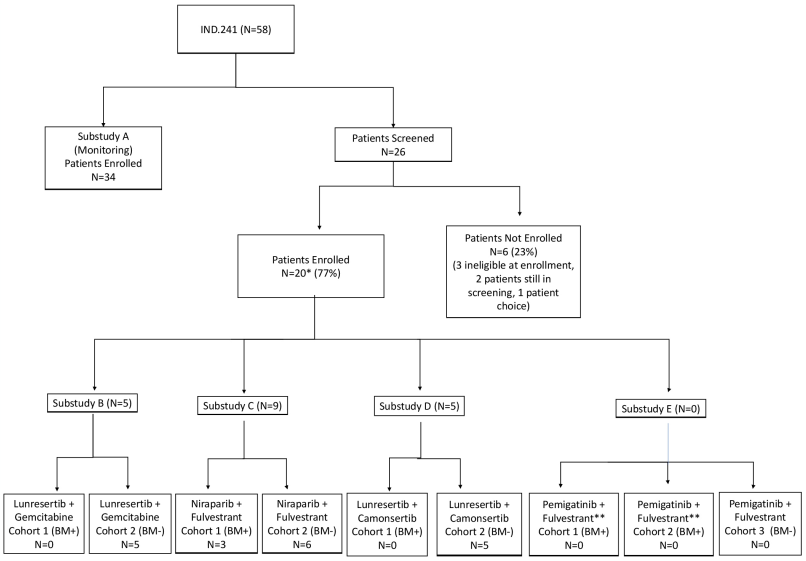
ELIGIBILITY FOR SPECIFIC SUBSTUDIES

- **Substudy A:** on or about to initiate 1L CDK4/6 + AI
- **Substudy B:** not eligible for further standard of care (SOC) ET; no prior Wee1, or PKMYT1 inhibitors or gemcitabine
- **Substudy C:** eligible for 2L fulvestrant SOC
- **Substudy D:** not eligible for further SOC ET; no prior Wee1, DNA-PK, PKMYT1 or ATR inhibitors
- **Substudy E:** eligible for SOC fulvestrant; no prior FGFR inhibitor

SUBSTUDIES

- Patients that are ctDNA positive for substudy-specific biomarkers (BM) are enrolled into corresponding BM+ cohorts of substudies.
- Patients with no substudy-specific biomarkers are randomized to BM negative cohorts.
- *Substudy B evaluates lunresertib (PKMYT1 inhibitor) + gemcitabine (BM+ CCNE1 overexpression/amplification)*
- *Substudy C evaluates niraparib (PARP inhibitor) + fulvestrant (BM+ alterations in BRCA1/2 (germline/somatic) or PALB2)*
- *Substudy D evaluates lunresertib (PKMYT1 inhibitor) + camonsertib (ATR inhibitor) (BM+ CCNE1 overexpression/amplification, FBXW7 or PPP2R1A alterations)*
- *Substudy E evaluates pemigatinib (FGFR inhibitor) + fulvestrant (BM+ amplifications in FGFR 1-3; BM+ FGFR fusion mutations)*

Enrollment



* One patient cancelled following enrollment to Substudy C, prior to starting treatment due to progression of brain metastases
** Substudy E includes 2 biomarker positive cohorts (see methods)

Summary

- CCTG's Investigational New Drug Program (CCTG Network: Early Therapeutics (CNET)) designed and is conducting this master protocol. CNET is a pan Canadian group of world class basic and clinical investigators at experienced early clinical trials sites.
- IND.241 employs a biomarker-driven platform study design approach to the evaluation of CDKi resistant ER+/HER2- MBC, using non-invasive ctDNA tumor genotyping to select patients for biomarker-driven substudies and define the ctDNA landscape across 1st, 2nd and 3L treatments.
- To date 19 patients have been enrolled into 4 treatment cohorts. Safety, efficacy and correlative evaluation is ongoing.
- Additional substudies are being developed and are added by protocol amendment.
- Opportunities to incorporate ctDNA dynamics and interventions based on molecular progression (Arm A) are being explored.

References & Acknowledgements

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