PS5-09-27: A phase I/II single-arm trial of Azenosertib (ZN-c3) combined with carboplatin and pembrolizumab in patients with metastatic triple-negative breast cancer (ZAP-IT)

Abstract number 2416

Filipa Lynce[1,2], Nabihah Tayob[1,2,3], Nan Chen[4], Albert Grinshpun[5], Raechel Davis[1,2], Michelle DeMeo[1,2], Adrienne Waks[1,2], Jennifer Guerriero[2,6], Rita Nanda[4], Geoffrey Shapiro[1,2], Sara M. Tolaney[1,2]

AFFILIATIONS: [1]Breast Oncology Program, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Harvard Medical School, Boston, MA, USA; [3]Department of Data Science, Dana-Farber Cancer Institute, Boston, MA, USA; [4]Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA; [5]Oncology Breast Program, Shaare Zedek Medical Center, Jerusalem, Israel; [6]Brigham and Women's Hospital, Boston, MA, USA

BACKGROUND

- Despite recent advances in breast cancer treatment, metastatic triple negative breast cancer (mTNBC) remains incurable. WEE1 is a tyrosine kinase that inhibits cyclin dependent kinase 1, thus arresting the cell cycle at the G2 checkpoint and providing an opportunity for DNA damage repair. WEE1 is highly expressed in several cancer types, including breast cancer.
- A phase II study of the WEE1 inhibitor adavosertib with cisplatin in 34 patients with mTNBC showed an ORR of 26% (Keenan. CCR 2021). Although the regimen did not meet the pre-specified >30% ORR threshold, tumors from patients with clinical benefit displayed enriched immune gene expression and increased T-cell infiltration.
- Azenosertib is a selective, orally bioavailable WEE1 tyrosine kinase inhibitor with demonstrated in vitro and in vivo activity across solid tumors. In combination with carboplatin AUC5, the most common ≥G3 adverse events were of thrombocytopenia (36%), anemia (29%), neutropenia (7%) and fatigue (7%) (Liu et al. ASCO 2023).

In this study, **we will utilize a multi-target approach using a combination therapy** that will exploit the synergistic nature of these three agents:

1) **Platinum agents** lead to DNA breaks and increase amount of neoantigens, therefore potentiate immune response which in turn will be augmented by **pembrolizumab**

2) **Azenosertib** overcomes cell cycle inhibition by WEE1 and facilitates cancer cells to continue into cell cycle, leading to cell death (due to DNA breaks induced by carboplatin)

3) Increased cell death due to cell cycle progression in tumor cells increases immune activation within the tumor, and intensify the efficacy of combination therapy

TRIAL DESIGN AND ELIGIBLITY CRITERIA

ZAP-IT is an ongoing single-arm, open-label, phase Ib/II study designed to evaluate the safety and efficacy of azenosertib with carboplatin and pembrolizumab in patients with mTNBC.

Key eligibility criteria:

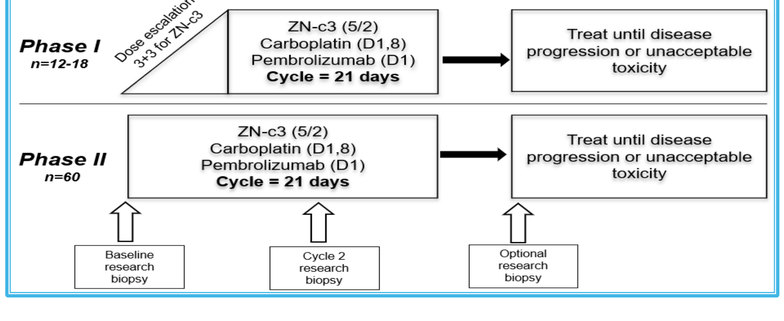
- Locally advanced/metastatic TNBC defined as ER ≤10%, PR ≤10%, HER2 negative; any PDL1 status
- ECOG PS 0-2
- 1-3 prior lines of therapy for advanced disease
- Prior therapy with an Antibody Drug Conjugate

TREATMENT PLAN

- Azenosertib taken orally once a day: 5 days on followed by 2 days off each week in a 3 week (21-day cycle)
- Carboplatin AUC 2 D1, D8 q3 weeks
- Pembrolizumab intravenously 200 mg, D1 every 21 days

Paired research biopsies will be required at baseline and at Cycle 2 of therapy in phase 2 patients. End of treatment biopsy will be optional.

TRIAL SCHEMA



ENDPOINTS

- **Primary endpoint, phase I:** to determine maximum tolerated dose (MTD) of azenosertib in combination with carboplatin and pembrolizumab
- **Primary endpoint, phase II:** to assess the efficacy, as defined by objective response rate (ORR) per RECIST 1.1 criteria, of the combination of azenosertib, carboplatin, and pembrolizumab in patients with mTNBC.
- **Secondary endpoints include** efficacy of the combination of azenosertib, carboplatin, and pembrolizumab in patients with mTNBC, as defined by progression-free survival (PFS), overall survival (OS), and duration of response per RECIST 1.1 criteria; and safety and tolerability of the combination of azenosertib, carboplatin, and pembrolizumab in mTNBC.

SUMMARY

- The ZAP-IT trial is evaluating azenosertib, carboplatin and pembrolizumab in metastatic TNBC. Accrual started in December 2024 and is ongoing (NCT06351332).

- To our knowledge, this is the first and only ongoing study testing the combination of a WEE1 inhibitor with carboplatin and a checkpoint inhibitor for the treatment of breast cancer.

Acknowledgments: Support from Zentalis Pharmaceuticals and Merck (IST).

CORRESPONDING AUTHOR: Filipa Lynce, MD, FASCO

EMAIL: filipa_lynce@dfci.harvard.edu **TWITTER:** @FilipaLynce

This presentation is the intellectual property of the author/presenter. Contact them for permission to reprint and/or distribute.