PS5-08-04: A phase 1b, multi-centre, open-label, randomized study to evaluate the safety, tolerability, and clinical activity of combining paxalisib with olaparib or pembrolizumab/chemotherapy in patients with advanced breast cancer

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Background

PaxPlus-ABC (ACTRN12624001340527) is a Phase 1b, open-label, parallel-group study evaluating the dual PI3K–mTOR inhibitor, paxalisib combined with pembrolizumab or olaparib in women with advanced breast cancer. Preclinical studies in the aggressive 4T1 triple negative breast cancer (TNBC) model support combining paxalisib with olaparib or pembrolizumab plus chemotherapy (Melino, Tu et al. 2025; AACR 2024, SESS-2122). Here, we present liquid biopsy biomarker insights from both the preclinical models and the first enrolled patient in the ongoing clinical trial, including CTC cluster analysis and immune profiling.

Materials and Methods

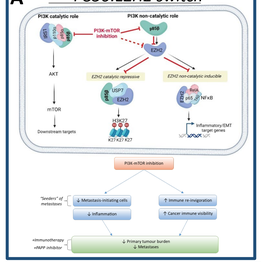
Preclinical: Liquid biopsy analyses assessed the efficacy of paxalisib combined with immunotherapy in the 4T1 mouse model. CTCs were profiled by giemsa staining and immunofluorescence. Spatial immune dynamics within the tumour microenvironment were examined using PhenoCycler proteomics.

Clinical: This Phase 1b open-label study includes two arms. Arm A (paxalisib + olaparib) enrols patients with germline BRCA-mutated, HER2-negative metastatic breast cancer; Arm B (paxalisib + pembrolizumab/chemotherapy) enrols PD-L1 CPS ≥10 TNBC. Primary objectives assess safety, tolerability, and Phase 2 dosing; secondary endpoints include liquid biopsy biomarkers, immune profiling, and clinical efficacy outcomes (PFS, ORR, CBR, TTR, TTP, OS).

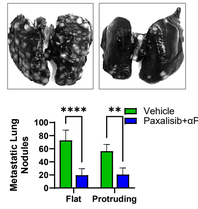
Results

1. Paxalisib Reduces Tumour Burden and Metastatic Spread While Reshaping the Immune Landscape in Pre-Clinical 4T1 Studies

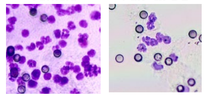
A *P85δ:EZH2 switch*



B *4T1 IV metastasis model*

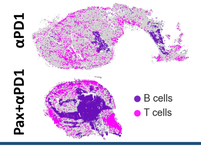


C *4T1 IV metastasis model*



Treatment Group	Animal No#	Circulating Tumour Cells (CTCs) Counts
Vehicle Control	1	>1500
	2	>1500
	3	>1500
Paxalisib + αPD1	1	3
	2	12
	3	295

D *4T1 Primary tumour model*

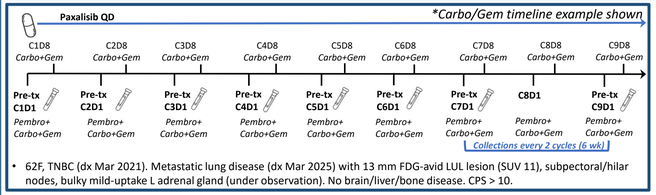


Cell population	Paxalisib+αPD1
T	Increase, periphery
B	Increase, central
CD4 T	Increase, periphery
CD8 T	Increase, periphery
Macrophage	Decrease, periphery
Neutrophil	Increase, central
DC	Increase, periphery

(A) Mechanism of Action. **(B)** Metastatic lung nodule counts in 4T1 mice treated with or without Paxalisib + αPD1. *, p<0.05; **, p<0.01; ****, p<0.001. **(C)** Giemsa-stained circulating tumour cell (CTC) counts. **(D)** Spatial profiling of immune subsets by PhenoCycler proteomics.

Results

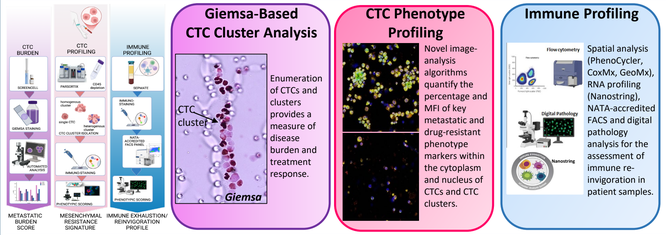
2. Clinical Trial Biomarker Collection Timeline – Paxalisib + Pembrolizumab + Carbo/Gem or Nab-Paclitaxel



- 62F, TNBC (dx Mar 2021). Metastatic lung disease (dx Mar 2025) with 13 mm FDG-avid LUL lesion (SUV 11), subpectoral/hilar nodes, bulky mild-uptake L adrenal gland (under observation). No brain/liver/bone disease. CPS > 10.

Example timeline of liquid biopsy collections from patient 101-001 Arm B. Blood is collected every 3 weeks to cycle 7, then every 6 weeks for biomarker analysis.

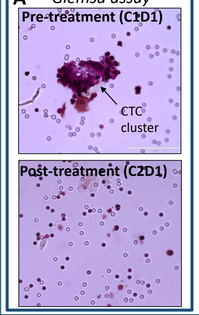
3. Liquid Insight: A Platform for Tracking Metastatic Spread in Real-Time



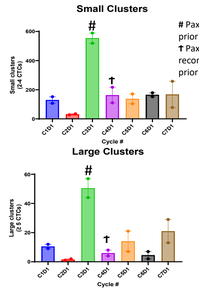
Liquid biopsy platform for longitudinal profiling of CTC clusters and immune cells as indicators of disease burden and immune re-invigoration.

4. Paxalisib Suppresses CTC Clusters, Supporting Stable Disease Control

A *Giemsa assay*



B *CTC cluster analysis*



C *Clinical Assessment*

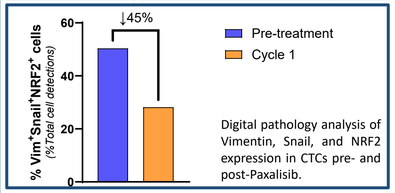
- Target lesion at baseline: 14mm longest diameter (x 11mm transverse)
- Restaging #1 at 3 cycles: 12mm longest diameter
- Restaging #2 at 6 cycles: 12mm in longest diameter (x 3mm transverse)
- **RECIST: stable disease**

- Pausing Paxalisib led to a marked surge in CTC clusters, indicating Pembrolizumab alone does not suppress CTC burden

Giemsa-based CTC Cluster assay images **(A)** and **(B)** analysis in longitudinal clinical trial patient bloods collected pre- and post-Paxalisib treatment. **(C)** Clinical readout from CT scan after 3 cycles of Paxalisib treatment.

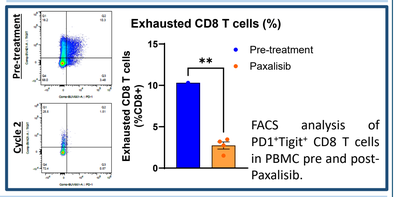
Results

5. Reduction in Aggressive Residual Disease Signature After One Cycle



Digital pathology analysis of Vimentin, Snail, and NRF2 expression in CTCs pre- and post-Paxalisib.

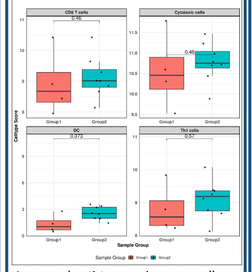
6. Paxalisib decreases T cell exhaustion



FACS analysis of PD1+Tigit+ CD8 T cells in PBMC pre and post-Paxalisib.

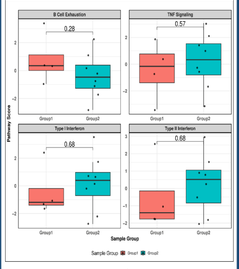
7. Paxalisib re-invigorates the immune landscape

A *Cell type score comparison*



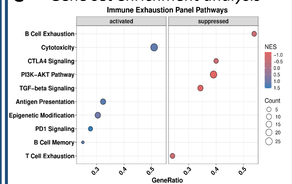
-Increased anti-tumour immune cells e.g. cytotoxic T cells, Th1 IFNg producing cells and antigen presenting DCs with Paxalisib treatment. Group 1: Pre, Group 2: Post-treatment.

B *Pathway score comparison*



-Activation of type I/ II Interferon and TNF signalling indicative of enhanced cytotoxicity, antigen presentation and MHC expression with Paxalisib treatment.

C *Gene set enrichment analysis*



-Global activation of adaptive immune responses and inhibition of immunosuppressive signalling (B and T cell exhaustion) with Paxalisib treatment.
-Confirmation of Paxalisib induced inhibition of its target, the PI3K-AKT pathway.

Nanostring RNA profiling of PBMCs isolated from longitudinal patient bloods pre- and post-Paxalisib treatment. **(A)** Cell type score comparison, **(B)** Pathway score comparison and **(C)** Gene set enrichment analysis.

Conclusions

Preclinical Studies: Paxalisib + pembrolizumab reduced primary tumour volume, metastatic spread and reshaped the tumour immune microenvironment in 4T1 preclinical models, prompting a Phase 1b trial enrolling up to 24 advanced breast cancer patients.

Clinical Trial Preliminary Data: Initial liquid biopsy analysis from the first treated patient shows:

- **Robust reduction in CTC clusters**
- **Epigenetic reprogramming of CTCs toward a less aggressive, less metastatic phenotype**
- **Significant depletion of exhausted T- and B-cell populations** and **immune re-invigoration**

Together, these early findings provide critical early evidence of Paxalisib's therapeutic activity in advanced TNBC.

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