[PS1-10-07]

Progression free survival and exploratory endpoints from PALVEN: A Phase 1b study of Palbociclib, Letrozole and Venetoclax in ER and BCL2 Positive Metastatic Breast Cancer

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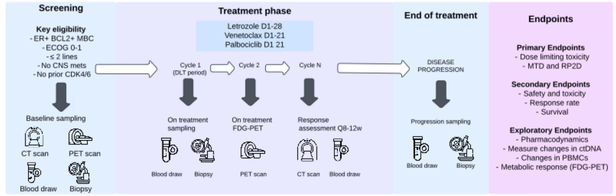
Background

- CDK4/6 inhibitors (CDK4/6i) induce growth arrest/senescence in breast cancer cells, which become refractory to apoptotic cell death.[1]
- In preclinical models, the BCL2 inhibitor venetoclax augmented tumor response to endocrine + CDK4/6i therapy by triggering apoptosis.[2]
- PALVEN (NCT03900884) is a phase 1b dose escalation study in pts with ER+ and BCL2+ MBC.[3]
- The maximum tolerated and recommended phase 2 dose has been defined as letrozole 2.5 mg (d1-28), palbociclib 75 mg (d1-21) and venetoclax 400 mg (d1-21).[4,*]

Methods

- Investigator-Initiated Phase 1b study, 3+3 dose escalation design.[3]
- Secondary endpoints, including PFS and OS, were analysed once the final pt had been on study for 48 wks.
- Pre-specified exploratory endpoints included CBR for defined subgroups, analysis of paired tumor biopsies, and ctDNA measurement.
- PROs of treatment-related symptoms, patient functioning and QoL were measured using EORTC QLQ-C30.

Figure 1. PALVEN study schema



Results (Secondary + Exploratory Endpoints)

At data cutoff 31 Jan 2025 (median follow-up 37.6 mo), 16 pts had received venetoclax, palbociclib and letrozole treatment; 15 were DLT-evaluable. 7 pts remained on study therapy including 4 pts who had completed ≥ 32 months of triplet therapy.

Table 1. Summary of efficacy (RECIST v1.1)

Response	All patients, n=15* (%)
Complete response	0 (0)
Partial response	9 (60)
Stable disease	5 (33)
Progressive disease	1 (7)
Overall response rate	9 (60)
Clinical benefit rate	14 (93)
Median PFS	29.2 months (95% CI: 18.4 not estimable)
Median OS	Not mature

*n=16 patients included in survival analysis

Figure 2. Kaplan-Meier curve (PFS)

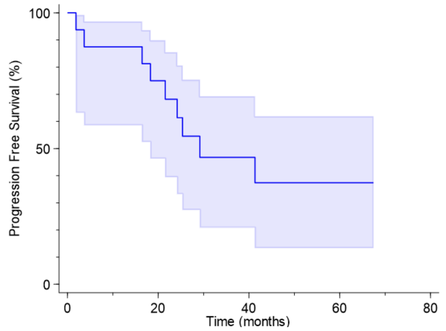


Table 2. Clinical Benefit Rate per RECIST v1.1 by subgroups

Subgroup	Clinical Benefit Rate, *n (%)*
1st line setting	12/12 (100)
≥2nd line setting	2/3 (67)
Visceral disease	5/5 (100)
Non-visceral disease	9/10 (90)
Primary endocrine resistance	3/3 (100)
Pts who relapsed >12m post adjuvant ET	3/3 (100)

Results (Secondary + Exploratory Endpoints)

- No additional treatment-related AEs observed from those previously reported at 24 wks.
- G≥3 haematological TRAEs were neutropenia (63%), reduced WCC (44%) and lymphopenia (19%).
- G3 neutropenia (without associated infections) was the main dose-limiting feature of combination therapy.
- Paired tumor samples available for 6 pts
  - Following 14 d of triplet therapy all tumors retained ER and BCL2 positivity.
  - A reduction/loss of PR staining was generally observed
  - Ki67 was reduced by ≥50% for all samples with a baseline Ki67 of ≥10%.

Figure 3. Paired tumor biopsies

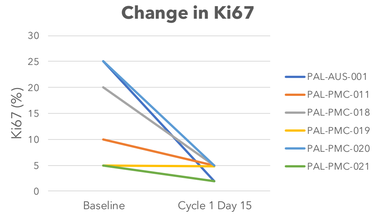
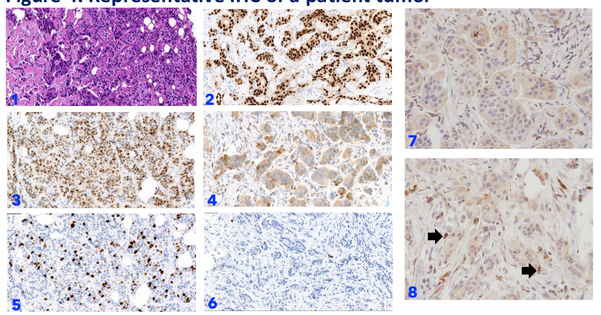


Figure 4. Representative IHC of a patient tumor



1. H&E 2. ER 3. PR 4. BCL2 5. Ki67 @ Baseline; 6. Ki67 @ C1D15; 7. CC3 @ Baseline; 8. CC3 @ C1D15

- Mean global health status score was 69 at baseline at remained stable throughout the study (67.6).
- Mean QoL scores over time for the most common reported symptoms (pain, nausea/vomiting, fatigue, constipation and diarrhoea) were low at baseline (<30) and remained stable throughout the study.

Figure 5. Global Health Status (mean)

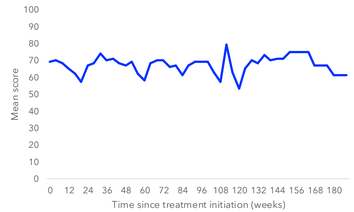
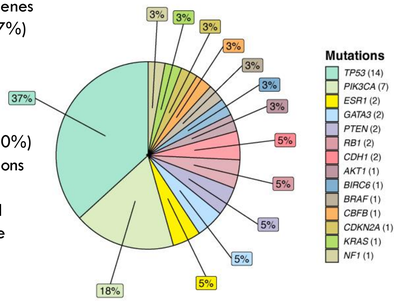


Figure 6. Baseline ctDNA molecular analysis

- Most commonly mutated genes at baseline were *TP53* (37%) and *PIK3CA* (18%).
- End of trial ctDNA was available for 10 patients.
- Acquired mutations were detected in 70%; *TP53* (50%) and *PIK3CA* (20%) mutations were the most common acquired alterations found
- No mutations in *BCL2* were detected



Conclusions

- Triplet therapy with palbociclib, letrozole and venetoclax is well tolerated. Uncomplicated neutropenia is a dose-limiting feature.
- Favorable CBR and PFS suggest that combining a BCL2 inhibitor with endocrine therapy and a CDK4 inhibitor (to mitigate neutropenia) warrants further investigation.

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San Antonio Breast Cancer Symposium
December 9-12, 2025

*Strong CYP3A inhibitors/inducers were avoided

SABCS 2024 ESMO 2024

IIS funded by NHMRC, NBCF, Cancer Australia, BCRF, with drug and funding support from AbbVie & Pfizer. We thank patients and their families for their participation in this trial and our collaborators from PMCC, RMH, WEHI, BaCT, VCB, the PCCTU Breast Team & RMH Trials Pharmacy.

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