# Phase II clinical trial of palbociclib and binimetinib in advanced triple-negative breast cancer (TNBC) with hyperactivation of ERK and/or CDK4/6.

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## Abstract

**Background:** We previously demonstrated that a kinase-based taxonomy of TNBC was most parsimonious than next-generation sequencing in defining TNBC subtypes associated with prognostic categories in early disease. The most aggressive TNBC variants were driven by a heterogeneous set of genetic aberrations that converged in the increased activity of 6 kinases: KIT, PNKP, PRKCE, P70S6K, ERK and CDK6 (Nat Commun; 9:3501-18). The combined inhibition of these kinases in pairs led to potent tumor regression in preclinical models, being the most powerful combination that one directed against CDK6 and ERK. This prompted us to design a phase II trial testing the combination of palbociclib (against CDK6) and binimetinib (against the ERK upstream kinase MEK, since no ERK inhibitor was available at that moment outside phase I trials) in advanced TNBC. Hyperactivation of CDK6 and/or ERK was selected as entry criterion.
**Trial design:** This was a single-arm, prospective, multicentric, open-label, phase II investigator-initiated trial. CDK6 and phosphor-ERK levels were measured in tumor samples by immunohistochemistry and normalized with a reference sample collection to a Z-score. Patients with scores for either kinase above the median were candidates for the trial. Key inclusion criteria included metastatic >18year-old TNBC, adequate organ function, measurable disease, and progression to 1-2 prior treatment lines (including immunotherapy, and a PARP inhibitor in case of germline BRCA1/2 mutation). Patients started continuous oral binimetinib at 45 mg/BID and palbociclib 100 mg/day from days 1 to 21, in 28-day cycles. Patients experiencing ≤ grade 1 tolerable side effects as the greatest toxicity were escalated to palbociclib to 125 in cycle 2. RECIST 1.1 and NCI CTC AE V 5.0 were used for assessing disease control (q8 weeks) and toxicity. The primary aims were to assess the efficacy and toxicity of this combination, and the secondary one to detect biomarkers of activity. At the time of trial design, in absence of available Sacituzumab for prescription, the reference PFS to beat in advanced lines for physician's choice in TNBC was 1.7 month (NEJM; 384:1529-41, 2021). With alpha and beta errors of 0.05 and 0.2, the minimum number of patients to demonstrate a 30% improvement in PFS to 2.5 months was 25.
**Results:** From November 2020 to April 2023, 69 patients were screened and 24 entered the trial (5 positive for phosphor-ERK; 2 for CDK6; 17 for both). Toxicity was generally mild and included grade 1-2 diarrhea (33% of the patients), grade 1-2 asthenia (50%), grade 1-3 neutropenia (75%), grade 2 retinal toxicity (8.3%) and grade 3 rash (4.2%); no grade 4/5 toxicities were observed. Median PFS was 1.83 months (range 0.3 to 11.3+). Phospho-ERK and CDK6 levels were not correlated (Pearson's R= -0.089; P=0.68); CDK6 levels did not show association with PFS time (R = -0.120; P=0.58). Interestingly, however, phosphor-ERK levels in the baseline tumor sample showed correlation with PFS time (R = 0.428; P=0.037).
**Conclusion:** The combination of palbociclib and binimetinib was generally safe, and PFS time showed correlation with baseline phosphorylation levels of ERK. However, the trial did not meet its primary endpoint.

## Introduction

-Therapeutic options are limited in metastatic TNBC after first-line immuno-chemotherapy
-We demonstrated in the past that (1):
1) A kinase-based taxonomy of TNBC identified the main signaling axes involved in aggressive clinical course.
2) The top aberrant signaling nodes driving adverse clinical course were ERK and CDK6, followed by KIT, P70S6K, PRKCE and PNKP
3) Combined inhibition of either of those targets 2x2 in preclinical mouse models of TNBC yielded synergism in 98.6% of the cases

Because of those reasons, we tested the combination of Palbociclib (to block CDK6) and Binimetinib (to block the MEK-ERK axis) in advanced TNBC

## Methods and Materials

**Trial design:** Single-arm, prospective, multicentric, open-label phase II investigator-initiated clinical trial.

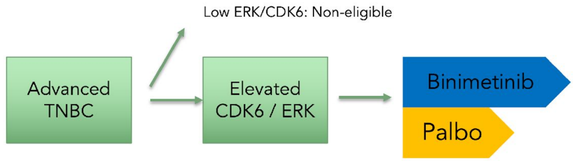


**Figure 1.** Clinical Trial Design. Patients were screened for ERK and/or CDK6 hyperactivation after progression to first-line treatment, with a turn-around time of 7 days

### Objectives

**Primary:**
-To assess the efficacy of the combination of binimetinib and palbociclib in patients with TNBC tumors with elevated CDK6 and/or ERK
-To study the safety and tolerance of the combination
**Secondary:**
-To detect biomarkers of activity
-Levels of baseline CDK6 and/or ERK
-Genomic aberrations predictive of benefit of the combination

### Treatment Schedule (28-day cycles)

**Palbociclib:**
-100 mg/day from days 1 to 21 of cycle 1
-In absence of significant toxicity, escalation to 125 mg/day (days 1-21) was allowed.
**Binimetinib:**
-45 mg BID days 1-28

## Methods and Materials

### Inclusion / Exclusion Criteria

**Inclusion:**
-Women >18 YO with advanced TNBC, progressing to a first-line treatment of PD-1/L1 inhibitor plus chemotherapy.
-Maximum of 2 treatment lines for advanced disease.
-BRCA1/2 mutants must have received a PARP inhibitor
-Elevated activity of CDK6 and/or ERK (evidenced by IHC H-score in Q1)
**Exclusion:**
-Inadequate organ function according to standard definitions, and/or life expectancy < 6 months, and/or ECOG 2-3-4
-Lack of recovery to tolerable grade 2 or less toxicity from previous therapy

## Results

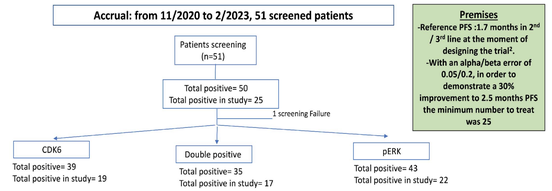


**Figure 2.** Accrual and screening positivity

### Enrollment

-Virtually all screened patients were positive for Q1 staining for at least one of the targets
-25 patients were enrolled, with one patient being screening failure.
-Accrual was stopped regardless not reaching 25 evaluable patients due to increasing number of competitive trials in the same clinical niche and slow accrual

## Results

**Table 1.** Toxicity description (numbrer of patients; N=24)

| | Grade 1/2 | Grade 3 |
|---|---|---|
| Diarrhea | 33% | 0% |
| Asthenia | 50% | 0% |
| Neutropenia | 50% | 25% |
| Retinal toxicity | 8.5% | 0% |
| Rash | 8.5% | 4.2% |

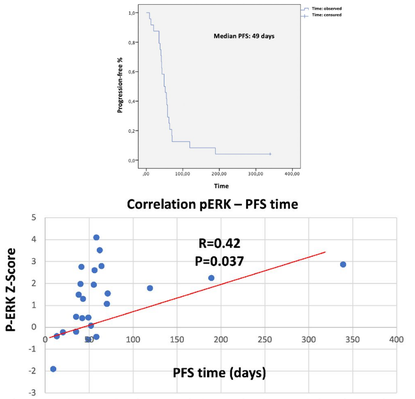


**Figure 3.** Kaplan meier PFS plot and Correlation with phospho-ERK levels

## Conclusions

1) The trial did not meet its primary endpoint
2) The combination showed acceptable tolerance
3) Metastatic TNBC population is enriched for CDK6 and ERK hyperactivation compared with primary tumors.
4) The efficacy of the combination seems to be correlated with baseline phospho-ERK levels

## Contact

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## References

1. Nat Commun; 9: 3501-18
2. NEJM; 384:1529-41

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