San Antonio Breast Cancer Symposium – December 9-12, 2025 – Poster P5-08-27

Single arm phase II study with abemaciclib and bicalutamide in locoregionally advanced inoperable or metastatic androgen receptor-positive triple-negative breast cancer (ABBICAR)

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BACKGROUND

- **Triple negative breast cancer (TNBC)** accounts for 15% of breast cancers[1,2] with a 5-year survival of only 12% if metastatic[3].
- 20-40% of TNBC express the **Androgen Receptor (AR)**[4].
- Luminal Androgen Receptor (LAR) subtype is **less sensitive to conventional chemotherapy** and often occurs in older patients[5] which causes an unmet therapeutic need.
- Preclinical data and small phase I/II trials show that **anti-androgens** might be a treatment option. **Bicalutamide** is a non-steroidal anti-androgen and works by competitively binding to AR halting growth of AR expressing TNBC[6-8].
- **Abemaciclib** selectively blocks cyclin-dependent kinases 4 and 6 (CDK4/6) inhibiting cancer cell growth and division. Loss-of-function alterations in Retinoblastoma protein (RB1) are less frequent in LAR, making these tumors more prone to **CDK4/6-inhibition** as opposed to non-LAR TNBC[9].

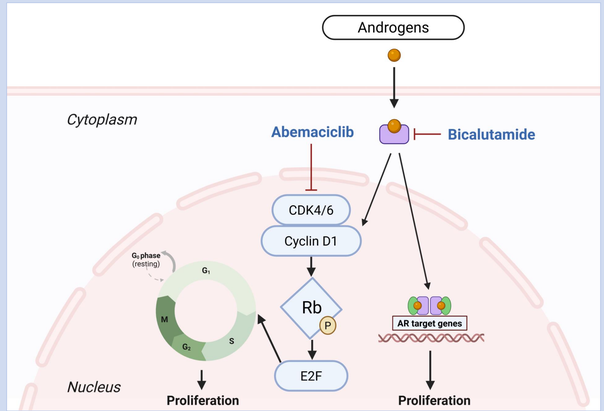


Figure 1: Anti-androgens can enhance the G1 cell cycle arrest induced by CDK4/6 inhibitors.

STUDY DESIGN & STATUS

ABBICAR is a **single arm phase 2 multicenter study** (NCT06365788, EU-CT 2022-502272-23-00) designed to evaluate the **efficacy and safety** of the combination of **abemaciclib** and **bicalutamide** in patients with **locally advanced or metastatic AR+ TNBC (or ER-low BC)**. Patients will receive continuous treatment as long as they are obtaining benefit and have not met the criteria for study withdrawal. **Inclusion started** 04/2024.

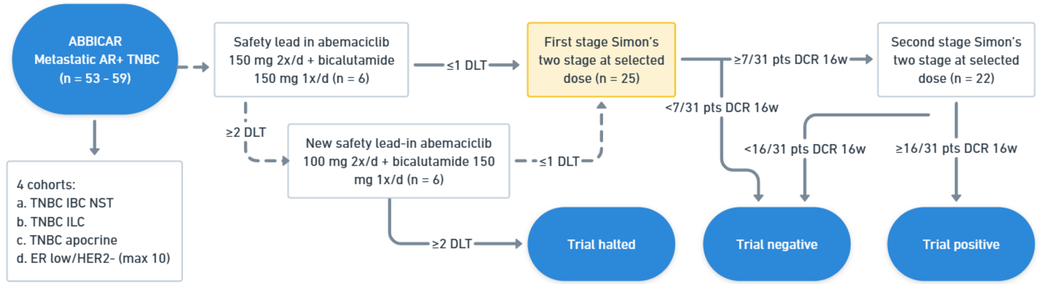


Figure 2: Trial design and current status of ABBICAR. The current stage is marked by a yellow frame.

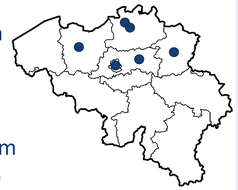
ASSESMENT

- **Tumor imaging:** baseline, every 8 weeks first 24 weeks, afterwards every 12 weeks
- Efficacy will be assessed according to **RECIST v1.1**.
- **AEs** will be graded according to NCI **CTCAE Version 5.0**.
- Patient reported outcomes: **QLQ-C30 questionnaire.**
- **Collection of ctDNA/PBMCs**: cycle 1, 2 and 5 or progression.

SITES

Belgium:

- University Hospitals Leuven, Leuven
- University Hospital Ghent, Ghent
- Brussels University Hospital, Jette
- Jessa Hospital, Hasselt
- Antwerp University Hospital, Edegem
- Ziekenhuis aan de Stroom, Antwerp



KEY INCLUSION CRITERIA

- **Women** aged at least 18 years with **ECOG 0-2**
- **Biopsy-confirmed** advanced or metastatic **AR+ (≥1% of cells) TNBC or AR+ ER-low/ HER2- breast cancer**
- **Measurable disease** per RECIST 1.1 or evaluable **bone-only disease**
- **Prior treatment**: ≥ 1 cytostatic regimen in advanced setting unless contraindicated; if ER low ≥ 1 line of endocrine therapy in advanced setting; if germline *BRCA1/2* mutation previous PARP inhibitor
- Prior treatment with **palbociclib or ribociclib allowed** if ≥ 6 months.

KEY EXCLUSION CRITERIA

- Prior invasive (metastatic) **HER2-positive** breast cancer
- Any **prior** exposure to **abemaciclib or anti-androgen** therapy
- **Brain metastases** (except asymptomatic, treated, stable, not requiring corticosteroids > 10 mg prednisolone)
- Serious / uncontrolled preexisting **medical condition**(s), for example interstitial lung disease, chronic active hepatitis, ulcerative colitis
- **Inadequate bone marrow reserve** or organ function
- Co-administration with **strong CYP3A4 inducers**

KEY STUDY ENDPOINTS

- **Primary endpoint:** disease control rate (DCR) at 16 weeks
- **Secondary endpoints** (all patients, cohorts, IHC AR ≥ 10%)**:** type/ incidence/ severity of adverse events (AEs); DCR at 16 weeks, overal response rate 16 and 24 weeks, progression free survival, overall survival

STATISTICS

- **Simon Minimax 2-stage design**
- **Null hypothesis (H_0)**: true disease control rate ≤ 20%
- **Type I error rate:** 5% (one-sided)
- **80% power** to reject H_0 if **true response rate 35%**

CONCLUSION

This trial explores a novel, chemotherapy-sparing treatment strategy for AR-positive TNBC. If successful, it could offer a more tolerable alternative to conventional chemotherapy. Results from the first stage are expected in Q2-Q3 2026.

REFERENCES & ABBREVIATIONS

References: 1. Giaquinto et al. CA Cancer J Clin 2022/ 2. Dietze et al. Nature Reviews Cancer 2015/ 3. Cancer Statistics Explorer Network. seer.cancer.gov/statistics-network/ 4. Ravaioli et al. Front Endocrinol 2022/ 5. Thompson et al. Nar Cancer 2022/ 6. Gucalp et al. Clin Cancer Res 2013/ 7. Proverbs-Singh, Endocr Relat Cancer 2015 /8. Traina et al. Journal of Clinical Oncology 2018/ 9. Asghar et al. Clinical Cancer Research 2017. **Abbreviations:** AR: Androgen Receptor, CDK: Cyclin-dependent kinases, DCR: Disease Control Rate, DLT: Dose Limiting Toxicity, ECOG: Eastern Cooperative Oncology Group, ER: Estrogen Receptor, HER2: human epidermal growth factor receptor 2, HR: Hormone Receptor, IHC: immunohistochemistry, ILC: Invasive Lobular Carcinoma; LAR: Luminal Androgen Receptor subtype; PBMC: peripheral blood mononuclear cell, PR: Progesterone Receptor, NST: No Special Type, TNBC: Triple Negative Breast Cancer.

ACKNOWLEDGEMENTS & COI

Acknowledgements: The authors would like to thank the patients for their participation. This study is funded by a grant of **Kom Op Tegen Kanker**. Drug support is provided by **Eli Lilly** and Company (abemaciclib) and **TEVA Belgium NV/SA** (bicalutamide). KB is funded by the Fund Nadine de Beauffort. Sketches were created with BioRender.com and the flowchart with Whimsical.com. **Conflicts of interest:** KB has none to report.

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