

# Recent progress in Cetuximab-based treatment for Triple-Negative Breast Cancer

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## Abstract

This study verifies the preclinical therapeutic effect of YM-1 silencing BAG3 combined with cetuximab targeted at epidermal growth factor receptor (EGFR) on Triple-Negative Breast Cancer (TNBC) cell lines both in vitro and in vivo. TNBC is defined as a unique subtype of breast cancer that leads to an increase in patients with interval cancers which can be detected annually. In actual research, targeted molecular therapies are involved in the field because of the immunological heterogeneity of TNBC. YM-1 has a potentially better inhibition target for EGFR instead of BAG3. By reviewing some existing preclinical research and targeted treatment for TNBC, this study is to propose a novel treatment target for TNBC based on cetuximab treatment.

**Keywords:** TNBC treatment, YM-1, BAG3

## I. Introduction

### A. Triple-Negative Breast Cancer

TNBC is defined as a special subtype of breast cancer that lacks expression of estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2) [1]. Threatening the health of women, TNBC has various classification which can cause different molecular mechanisms for malignant transformation. Better knowledge of TNBC types contributes to choose targeted treatment [2]. A review article reports that the metastatic pattern for TNBC is markedly different from other subtypes and is more likely to metastasize to the brain and lungs rather than bone. TNBC can also lead to an increase in patients with “interval cancers” which indicates high risk of recurrence [3]. Given that there are no effective treatment options, this study is to propose a novel therapeutic idea which involves critical targets for TNBC.

### B. Existed Treatment Options

It is worth noting that six subtypes of TNBC including basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR) can inform different therapy selection [4]. A variety of treatment regimens designed for different TNBC subtypes have been studied, which can be categorized into two main ways including TNBC chemotherapy and TNBC targeted therapy. In terms of TNBC chemotherapy, it was confirmed that after response to neoadjuvant chemotherapy, a better survival showed in TNBC patients [5]. One example of TNBC targeted therapy have revealed that the PARP (Poly

ADP-Ribose Polymerase) inhibitor shows synergistic antitumoral effects with chemotherapeutic drugs [6].

### C. Cetuximab Therapy

Through DNA microarray analysis, findings show that basal-like breast cancer (BLBC) and TNBC samples are more likely to have a high expression of EGFR which can be regarded as one of mechanisms causing TNBC among cell lines [7]. Cetuximab is a kind of recombinant monoclonal antibody and works as an EGFR inhibitor, based on which cetuximab can be developed into a kind of anticancer drugs for TNBC.

### D. YM-1 Therapy

One of the advances put forward a feasible solution that integrating targets for chaperones of EGFR, such as BAGfamily, in mammary carcinoma was possible to better inhibit the EGFR signaling pathway [8]. What's more, the protein interaction between EGFR and BAG3 was researched to find a potential better inhibition target for BAG3. Based on in silico approach, YM-1, a kind of small molecules, had the effect mentioned [9]. YM-1 is able to denature Hsp70 in cell lysates [10]. Further investigations on YM-1 also indicated that it was able to block binding interaction between Hsp70 and BAG3 which contributed to cancer cell invasion. And it is the reason why YM-1 is an excellent inhibitor targeted for BAG3[9].

### E. Purpose of the Research

In brief, although preclinical study data has proved EGFR can be a promising target for TNBC therapy, TNBC patients show less than 6% response rates with cetuximab treatment which targeted EGFR. Researchers

are dedicated to speculating and testing further growth factor inhibitors and bypass inactivation of EGFR [4]. This paper expects to take advantage of YM-1 to silence BAG3 which interacts with EGFR in signaling pathways of cancer progression.

## II. Research Model

### A. TNBC Potential Therapy

As a consequence of heterogeneity of TNBC, finding a broad spectrum therapy is necessarily difficult. Based on previous clinical trials, researchers have figured out typical targeted therapies which include chemotherapy, targeted therapy.

1) *chemotherapy*: In terms of BL1 and BL2 subtypes, cisplatin can inhibit growth of the cell lines particularly. It is found that M and MSL subtypes of TNBC can be positively respondent to NVP-BEZ235 and dasatinib which target for specific growth factors. Bicalutamide, an androgen receptor antagonist, is able to obstruct signaling existing in LAR cell lines [11-14].

2) *targeted therapy*: Given the findings that a number of pathways and mutations are reported in TNBC, targeted therapy is found to be of great value for treatment.

Dysregulated receptors are one of main solution. Directed at RTKs, tyrosine kinase inhibitors (TKIs) can be used as the antitumor drug which is often added into a kind of cocktail therapy [15]. Compared with traditional chemotherapy, TKI may cause skin and gastrointestinal toxicities instead of bone marrow toxicity [16]. Furthermore, the problem of drug tolerance in TKI is unavoidable at the moment due to ALX overexpressed in tumor cell lines [17]. Lapatinib, an anti-EGFR agent, has been studied to perform function in trastuzumab-resistant tumors which hopefully provides an opportunity to resolve chemical drugs resistance [18]. In spite of this, effectiveness of antibody targeted for EGFR still need further confirmation. Cetuximab which has acquired approval can excell significant function only combined with chemotherapy [19,20].

Modulating signal pathways can be also used to treat TNBC survival. For example, targeting signals in PI3K/PTEN/AKT pathway can be prosperous in treatment. MTOR can be upregulated through AKT pathway which may result in tuberous sclerosis complex [21]. Everolimus suppressing mTORC can be an effective treatment for hormone receptor (HR) +/HER2- advanced breast cancer based on clinical tests. The combination therapy, like everolimus-carboplatin, is even more satisfactory in treatment outcome of TNBC [22-24]. What's more, inhibition reactions of replication can be applied in TNBC treatment theoretically. In terms of BRCA positive TNBC,

a PI3K and mTOR inhibitor, combined with talazoparib (a PARP inhibitor) which can inhibit normal cell cycle have been conducted in the clinical trial.

Application of immunotherapy has promising anti-tumor effects. For instance, antibody-drug conjugates (ADC) are able to transport chemotherapy drugs to specific cancer cells. Ado-trastuzumab emtansine and fam-trastuzumab deruxtecan, targeted for HER2 are two main clinical drugs. Besides, sacituzumab govitecan (SG) which contains the antibody targeted for antigen trophoblast (Trop) can be applied in the treatment for metastatic TNBC. The findings have revealed that the expression of Trop is one of typical features in all breast cancers including TNBC [25]. Another advantage of SG treatment is the results after being treated is manageable. Additionally, ADCs can also target for other antigens including LIV-1, receptor tyrosine kinase-like orphan receptor 1 (ROR1) and so on, revealing prosperous application in the future.

### B. Abnormal Genetic and Signaling Pathways in TNBC

1) *Receptor tyrosine kinases (RTKs) family*: RTKs family has played an important role in signal translocation which is responsible for communication between inside and outside cell membrane. Except for various domains, RTKs family contains 58 different types of receptors which include EGFR, vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor receptor (IGFR), fibroblast growth factor receptor (FGFR) and AXL [12]. After RTKs family responds specifically to ligands, it often results in downstream activation, such as PI3K/AKT/mTOR pathway, RTK/Ras/MAPK pathway, janus kinase/signal transducer and so on [13]. Genetic mutations in RTKs family can cause malignant transformation so some TKIs can be applied in cancer treatment [14].

2) *PI3K/AKT/mTOR signaling pathways*: Contributing to cell proliferation and migration, PI3K is one of pathways which are responsible for TNBC progression. Through cascade phosphorylation, AKT is activated which can stimulate downstream mTOR. The process can participate in related metabolism including lipid synthesis [20]. Mutations presenting in AKT and mTOR activation can increase the possibility of patients diagnosed with TNBC. In brief, combination therapy based on PI3K/AKT/mTOR pathways still need further investigation. The relationship between negative regulatory factors and anti-tumor effects deserves future research.

3) *Antibody-drug conjugates(ADC)*: ADCs contain three main domains including cytotoxic payload, the recognition antibody and the linking domain [23]. Antibody is responsible for recognising and binding to

specific antigens present on the surface of tumor cells. ADCs can be degraded inside the cell to release antitumor drugs. Although ADCs have efficacy in therapy of solid tumors, they have difficulty in treating TNBC due to devoid targets [24].

### ***C. Combination Therapy of YM-1 and Cetuximab***

Given the fact that there is still need more efforts to establish effective treatment or therapy, this paper is to explore that when TNBC cells are treated with YM-1, with cetuximab inhibiting EGFR inhibition, the expression of BAG3 will be reduced as YM-1 can disrupt the interaction of BAG3 with HSP70. The combination of cetuximab and YM-1 treatment will reduce TNBC proliferation additively as well.

Single YM-1 and cetuximab targeted at EGFR show more or less function of inhibiting cell proliferation of TNBC but previous research showed that patients revealed low sensitivity to cetuximab [8]. This paper adopts the combination of YM-1 with cetuximab to test the therapeutic effect on TNBC. BAG3 has been implicated in cell signaling of TNBC cell proliferation except for EGFR. Previous studies have revealed that HSP70-BAG3 actively regulates cell signaling of cancer. Therefore, YM-1 acting as an inhibitor of HSP70-BAG3 interaction has the potential to suppress tumor growth of TNBC [9].

However, the mechanism of YM-1 transportation remains unclear which is supposed to be further investigated. The efficient transportation pathway of YM-1 needs to be clarified in order to act as one of drug treatments for TNBC. To get insight into improvement of the therapeutic method, better delivery ways, and more subtle mechanisms of YM-1 transportation should be more focused. Another potential problem is that function of YM-1 is negatively affected by other signaling pathways and thus the detection system or methods should be developed to locate interference of different targets in the signal regulation network in the future investigation. The deep interaction between BAG3 inhibition and EGFR targeted is still unclear which is vital to better design the drugs targeted at TNBC.

### **III. Conclusion**

The result of this study indicates that combination of YM-1 and cetuximab has lots of possibilities in therapeutic effect on TNBC. However, the distinct expression level of gene and protein may exist to influence the therapeutic effect, which can be further regulated to obtain better therapeutic effect. Besides, the effective transportation system and media of YM-1 can leads to increasingly treatment outcomes as the concentration of cetuximab

increases. Pharmaceutical YM-1 combined with cetuximab could be a promising drug design for TNBC therapy. What needs to mention is that the interactions of YM-1 targeted at BAG3 and any other signaling pathway are supposed to be investigated further in order to find the better treatment target for YM-1.

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