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Review Article

TARGETED THERAPY FOR TRIPLE-NEGATIVE BREAST CANCER: CURRENT TRENDS AND FUTURE DIRECTIONS: A REVIEW

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Abstract: Triple-negative breast cancer (TNBC) has a higher unmet medical need of developing better therapeutics. Since this class of breast tumors express neither Her2 nor express any of the hormone receptors, these cancers do not respond either to Her2 blocking antibodies or to hormonal therapies. Moreover, the TNBCs are genomically unstable with a wide range of mutations. Thus, TNBCs particularly show poor prognosis, wherein the treatment regimens are mainly dependent on conventional surgery and chemo and radiotherapy. Since the era of genomic sequencing and targeted therapy, many potential targetable proteins/ pathways in TNBC are being identified including BRCA1/2, PARP, PI3K-Akt, and immune modulators. Currently, several clinical trials are going on largely focusing on metastatic TNBCs. The development and clinical trials are largely hampered in the TNBC field due to their highly heterogeneous nature. New developments in the molecular sub-typing within TNBC allowed proper patient stratification and opened the doors towards personalized therapy. In this review, we will first discuss the new sub-classifications within TNBC. We will then discuss our current understanding of targeted therapy towards the TNBC. We will conclude with the future perspectives that we think the field should take forward, with a final goal to cure all types of TNBC.

Key words: Targeted therapy, Triple-negative breast cancer.

INTRODUCTION

Breast cancers where in the estrogen (ER) and progesterone (PR) hormone receptors are not expressed, as well as HER2 expression is low are broadly classified as Triple Negative Breast Cancers (TNBC). There is an average incidence of nearly 1.7 million cases of breast cancer cases every year

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globally, out of which nearly 15-20 % of cases fall under the TNBC category [1,2]. TNBCs represent a highly heterogeneous group, but with similar prognosis compared with other subtypes of breast cancer. Nearly 75% of TNBCs show basal-cell like characteristics and display an aggressive phenotype with a high proportion of metastasis [3,4]. TNBC has a high prevalence in younger women (below 40 years of age) and African women compared to other classified types of breast cancer and in general, has a very different relapse pattern.

Many therapeutic drugs targeting ER, PR and Her2 positive breast cancers are not generally effective for TNBC treatment, as they usually target either of the above three receptors. Hence, chemotherapy and surgery remain the mainstay for the TNBC treatment. Generally, among different breast cancer types, the survival period is shorter for TNBC patients, due to a very high rate of disease relapse. If the TNBC is localized, the primary treatment option is surgery, while under the conditions where it is already metastasized, chemotherapy is preferred, wherein the primary focus of the treatment is to improve life quality by enhancing the pCR (pathological clinical response), PFS (progression-free survival) and extending the patient's OS (overall survival) rate. Even though conventional chemotherapy shows some responsiveness in TNBC patients, who are in their early stage of their cancer, the clinical response is extremely poor, when the cancer becomes advanced. Taxanes, anthracyclines and anti-metabolites, either in an adjuvant or in neo-adjuvant settings are the only FDA-approved treatment regimens for TNBC [5].

Although novel drug targets and clinical trials are in pipeline, there is a huge need to develop new and improved combination therapies to treat TNBC [1, 6]. In order to develop new targeted therapies of high efficiency for treating TNBCs, it is essential to understand the characteristics, clinical behavior as well as the microenvironment pertaining to this subtype of breast cancer. In this review, we will initially discuss the sub-classes of cancer within TNBC that respond differently to various insulting agents, followed by various targeted therapies currently being developed for the TNBC treatment. We will conclude the review by discussing the future prospects and developments of targeted therapies for this class of cancers.

Sub-classification and characterization of TNBC: As mentioned in the introduction, according to the classical breast cancer cataloging, all breast cancers that are ER, PR and Her negative fall under the TNBC category. This type of classification majorly hampers the clinical development of targeted therapies, since many different types of breast cancers in default come under this umbrella. For example, it is accepted that TNBC shows a basal-cell phenotype. However, nearly 25% of TNBC's do not show basal-like phenotype [7]. This diversity within TNBC can be further emphasized by the high-level occurrence of occasional histopathological subtypes, like adenoid cystic (90-100%), medullary type (95%), metaplastic (90%) and apocrine (40 to 60%) carcinomas [8]. Thus, there is an unmet need to sub-classify the TNBC's, to understand the pathophysiology of the disease progression. Lehmann et al. based on the gene ontology and expression profiles of 587 TNBC samples identified six major sub-types within the TNBC, including BL1(Basal-Like 1), BL2 (Basal-Like 2), IM(Immune modulator), MES(Mesenchymal), MSL(Mesenchymal Stem-Like), and LAR(Luminal Androgen Receptor) [9]. Burstein et al. classified TNBC into four stable subtypes: LAR, MES, BLIS (basal-like immune-suppressed), and BLIA (basal-like immune-activated) [10]. BL1 tumors have higher expression of oncogenes for cell division and DNA damage genes, while BL2 tumors have high expression rates of tyrosine kinases, genes that accelerate cell proliferation and genes that modulate other metabolic signaling events. MSL subtype of TNBC is sensitive to SRC, PI3K and mTOR inhibitors, having moderate pCR rates [11]. MES and MSL subtypes show low expression of genes responsible for cell proliferation and show enhanced expression of genes favoring EMT (epithelial-mesenchymal transition) [12]. MES, BLIS, and BLIA are described by diverse clinical diagnoses, where in the BLIS and BLIA tumors represent worst and best outcomes, respectively [8]. Studies like these and others confirmed the heterogeneous nature of TNBC's and possible reasons behind the variations in sensitivity to standard-of-care chemotherapy. TNBC tumor subtype characterization in-depth, along with a proper understanding of the clinical and pathological features should help in patient risk-stratification and should be able to guide helpful treatment decisions. More importantly, these classifications will help in identifying biomarker selection, new (potential)

discovery of drug targets as well as robust clinical trial designing [13,14].

Therapeutic targets for TNBC: Even though the majority of TNBC treatment depends on conventional surgery, chemotherapy and radiotherapy, rigorous research in this field had identified several molecular targets that have a high potential for treating the TNBC. Below, we will explain the potential biological targets that can be explored for TNBC treatment.

Targeting "BRCAness": Both germline and somatic mutations in Breast cancer susceptibility 1 and 2 (BRCA1/2) genes predispose a given person for acquiring breast cancer [15]. BRCA1/2 proteins play an essential part in response to DNA damage, a crucial pathway that ensures both normal as well as malignant breast cell survival [16,17]. BRCA proteins participate in the homologous recombination repair process. Mutations in BRCA genes lead to their loss of function, due to which the cells switch to the alternative mechanisms of DNA repair. This take-over of error-prone DNA repair pathways from the more conserved error-free DNA repair leads to genomic instability and cancer [18]. The prevalence of BRCA1/2 mutations varies widely ranging from 1.8% of sporadic breast cancers in Spain to nearly 37% in TNBC's in the United States [19].

"BRCAness" is complex of trait causing BRCA gene dysfunction due to genetic mutations, methylation or deletions. Tumors with "BRCAness" are highly sensitive to chemotherapy in the first appearance [18,20], and even after recurrence [21]. Some of the common targets of "BRCAness" are PARP inhibitors [22,23], inhibitors of growth factor receptor [24] and angiogenesis inhibitors [25], Androgen Receptor (AR) inhibitors [26] and immune checkpoint inhibitors [27], etc. It is fixed that DNA damage is the major root cause of cancer development. It is also important to appreciate the fact that the "effective DNA damage" of cancer cells is the rationale behind chemo- and radiotherapy treatment regimes. In this scenario, it is well-established that targeting "BRCAness"of the cancer cells will increase the DNA strand breaks increasing mortality of cancer cells [28,29].

PARP inhibitors for TNBC treatment: PARP (Poly ADP ribose polymerase) inhibitors are shown to suppress BRCA pathway-dependent homologous recombination mechanisms in heritable TNBC [23,30]. Since PARP helps in the single-strand DNA break repair, targeting this protein can cause multiple DNA breaks in cells harboring mutations in BRCA1, BRCA2 or PALB2 genes. Since multiple double-stranded breaks cannot be repaired efficiently and simultaneously, it leads to the death of such mutated cells [31] (Fig. 1). Some of the FDA-approved drugs targeting PARP are Olaparib (approved in December 2014), Rucaparib (approved in December 2016) and Talazoparib (approved in 2018) used for targeting germline BRCA mutated cancers [32]. Niraparib is yet another interesting PARP1/2 inhibitor that was approved in March 2017 [33]. Pamiparib (BGB-290) is an ongoing phase III clinical trial (https://clinicaltrials.gov/ct2/show/NCT03427814). Veliparib (ABT-888) also a PARP inhibitor failed in phase III trials [34, 35]. Iniparib (BSI- 201) was considered to be a PARP inhibitor, but determined not to be a true inhibitor for PARP and failed in trails on TNBC [36,37]. Combination of radiation therapy with PARP inhibitors is shown to decrease the side effects and lead to more powerful therapy with lower radiation dose.

Growth factor inhibitors for TNBC treatment: Epidermal growth factor receptor (EGFR; also known as ErbB-1 or HER1 in humans) is a transmembrane protein receptor and the ligand binding transforms the EGFR receptor from an inactive monomer to an active homodimer, which in turn causes phosphorylation of Tyrosine (Y) residues in the C-terminal domain of the EGFR [38]. EGF (Epidermal growth factor), TGF"α"(Transforming Growth Factor "α"), AREG, epigen/EPGN, BTC/betacellulin, epiregulin/EREG and HBEGF/heparin-binding EGF are the known ligands that bind and activate the EGFR receptor [39]. Ligand binding and receptor activation evokes PI3 kinase-AKT, PLC gamma-PKC, RAS-RAF-MEK-ERK, as well as STATs modules, leading to synthesis of new DNA and proliferation of cells [40]. These downstream proteins modulate proliferation, adhesion and migration in advanced TNBC tumors. For mammary ductal development, EGFR signaling is necessary [41,42]. Mutations, deletions or methylation that disturb the normal EGFR functions lead to cancer progression.

The discovery of EGFR as an oncogene made it possible to grow several therapeutic strategies for targeting the EGFR cascade (Fig. 2). Some of the EGFR inhibitors include Cetuximab, Icotinib, Panitumumab, SCT200, and Trastuzumab. Cetuximab and Panitumumab are of IgG_1 and IgG_2 type of

monoclonal antibodies, respectively [43], are known to inhibit EGFR signaling. These two antibodies differ in their antibody-dependent cellular cytotoxicity mechanisms [44]. Other antibodies such as Nimotuzumab and Matuzumab are in clinical development that targets EGFR [45]. Gefitinib, Erlotinib, and Brigatinibare examples of small molecule kinase inhibitors that block the EGFR [46].

"Nanodiamond"(ND) is a carbon-based material that emits fluorescence, is biocompatible and also acts as a drug-delivering agent. Researchers had also developed ND-PTX-Cet, which is an ND, and carries Paclitaxel (PTX), a microtubule inhibitor, along with Cetuximab [47,48]. This compound inhibited growth and viability of MCF-7, MDA-MB-231, and in BT474 human breast cancer cell lines and proved its EGFR inhibiting capability. Having achieved all these milestones, majority of the clinical trials of EFGR inhibitors were not successful in TNBC due to low response rates. Thus, further studies are needed for potentially targeting EGFR positive TNBC patients with a higher prognosis.

Drugs targeting Angiogenesis pathway: Angiogenesis is the formation of new blood vessels. Vascular Endothelial Growth Factor (VEGF) is a signaling protein, which binds to and activates both VEGF Receptor 1 and 2 (VEGFR1 and VEGFR2), and stimulates angiogenesis, vascular permeability, cell migration, and gene expression [49]. By overexpressing VEGF, tumors get adequate blood supply and are then able to grow and metastasize. Targeting VEGF/VEGFR inhibits angiogenesis leading to control of tumor progression. Bevacizumab is an inhibitor of VEGF and is in phase II clinical trials [50], while Apatinib is an angiogenesis inhibitor targeting VEGFR2 receptor and is also in phase II trials [51]. Other VEGF/VEGFR inhibitors are Pembrolizumab, Aflibercept, Ipatasertib, and Lenvatinib are other drug targets in various phases of clinical trials (https://clinicaltrials.gov/).

Drugs targeting the PI3K- AKT - mTOR pathway: It is generally accepted that the TNBC patients show a higher incidence of PI3K and PTEN mutations, in comparison to other breast cancer subtypes [52]. The PI3K - AKT - mTOR pathway is involved in TNBC survival as well as chemoresistance. AKT is a signal transduction process that promotes cell survival and growth when stimulated by extracellular signals. The readers are referred to recent excellent reviews on targeting the PI3K-Akt pathway for blocking TNBC progression [53-55] (Fig. 2). Even though, the inhibitors of PI3K - Akt pathway has a great potential in treating the TNBC tumors, currently the progress is hampered by various reasons. Among them, the copy number changes or the mutations among genes like TP53, MYC and/ or RB is of great concern. PI3K / Akt inhibitors as single agents were not totally successful for treating TNBC [56]. However, Akt inhibitors in combination with the first-line chemotherapy are showing some promising results in TNBC patients [57,58]. It was suggested that the TNBC patients display resistance to PI3K inhibitors due to the cross-talk of the PI3K pathway with WNT/β-catenin signaling [59].

Nearly three-quarters of TNBC tumors show mTOR phosphorylation [60]. mTOR was found to have a direct correlation with overall survival and reoccurrence free rates with TNBC stages I and II. Rapamycin, a well-established mTOR targeting drug showed a 77-99% inhibition in cancer progression, more than that of classical chemo-drug, Doxorubicin. Targeting both mTORC1 and mTORC2 can block the feedback loop causing AKT activation by mTORC1, in response to inhibition of mTORC2. Clinical studies, using TNBC patient-derived xenograft models showed the mTOR inhibitor AZD2014 is more effective in decreasing the phospho-AKT levels, when compared to Everolimus [61].

Androgen-Receptor Inhibitors: It is estimated

Explanation of figures:

Fig. 1: Effects of PARP inhibitors in BRCA negative tumors. Schematic diagram showing the efficiency of PARP inhibitors in treating BRCA mutated cells. DNA breaks induced by the PARP inhibition in BRCA Wt cells will be repaired by the base-excision repair. Since BRCA mutant cells lack efficient base-excision repair, PARP inhibition leads to overwhelming double-stranded DNA breaks and replication fork collapse, leading to the death of such cells.

Fig. 2: Role of EGFR and PI3K - Akt - mTOR pathway in inhibiting Triple - negative breast cancer growth. Schematic diagram showing the EGFR along with its downstream molecules including PI3K - Akt - mTOR, JAK and Ras signalling pathways. Various inhibitors that are clinically validated to inhibit this pathway and are currently in various phases of the clinical trial for targeting TNBC are also shown.

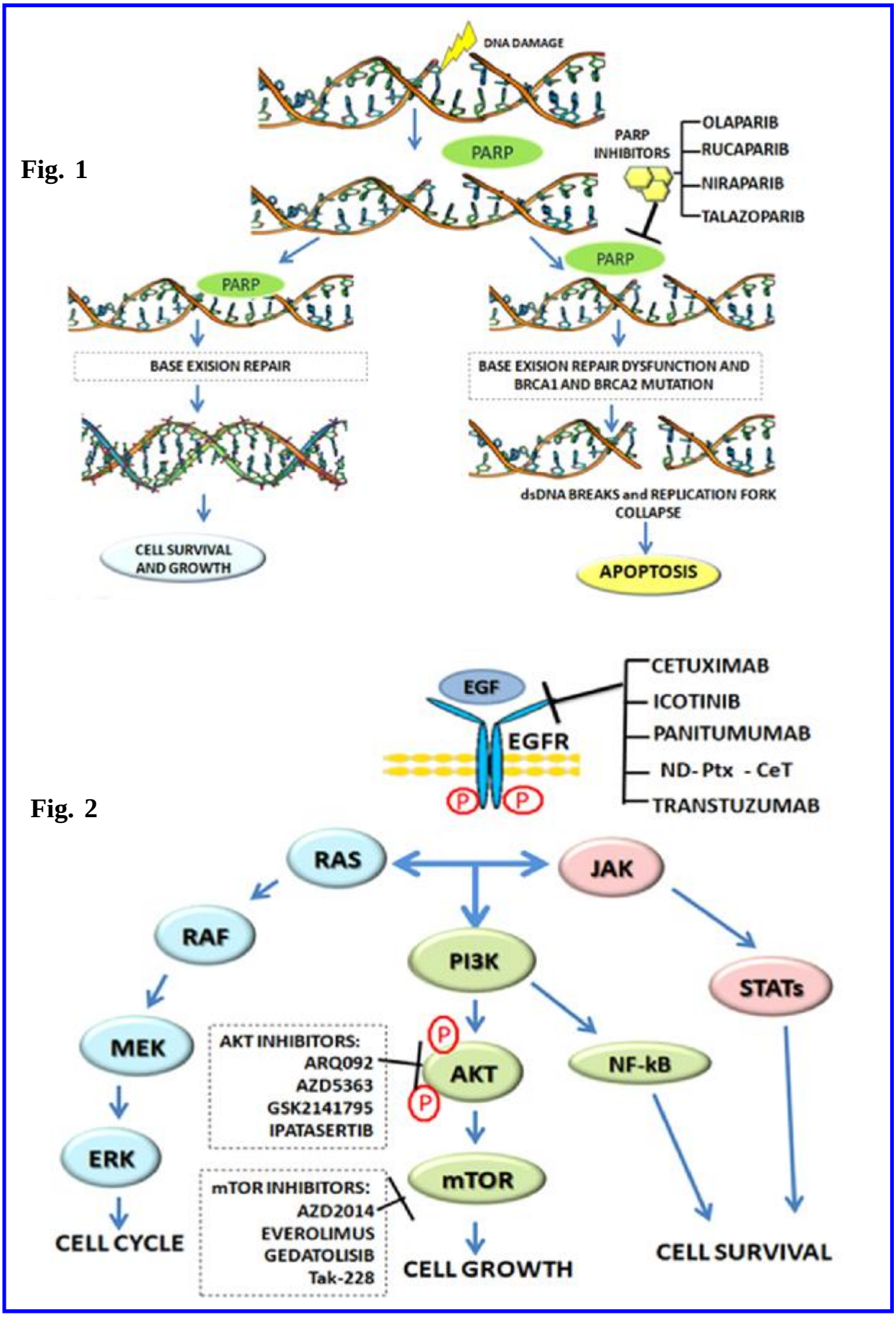
DNA DAMAGE
PARP
PARP INHIBITORS
OLAPARIB
RUCAPARIB
NIRAPARIB
TALAZOPARIB
PARP
PARP
BASE EXISION REPAIR
BASE EXISION REPAIR DYSFUNCTION AND BRCA1 AND BRCA2 MUTATION
dsDNA BREAKS and REPLICATION FORK COLLAPSE
CELL SURVIVAL AND GROWTH
APOPTOSIS
EGF
EGFR
CETUXIMAB
ICOTINIB
PANITUMUMAB
ND- Ptx - CeT
TRANSTUZUMAB
RAS
JAK
RAF
PI3K
STATs
MEK
AKT INHIBITORS:
ARQ092
AZD5363
GSK2141795
IPATASERTIB
AKT
NF-kB
ERK
mTOR
mTOR INHIBITORS:
AZD2014
EVEROLIMUS
GEDATOLISIB
Tak-228
CELL CYCLE
CELL GROWTH
CELL SURVIVAL

Fig. 1

Fig. 2

that nearly 36% of TNBC's show androgen receptor (AR) positivity [62]. AR is a type of nuclear receptor that gets activated by the binding of androgenic hormones including testosterone and di-hydro-testosterone. TNBC's that show higher AR and luminal cytokeratin expression fall under the category of "LAr TNBC". It has been shown that the expression of AR can accurately predict the TNBC chemo-resistance [63], thus potentially serving as a biomarker for this purpose. The main function of the AR, being a transcription factor, is to regulate gene expression. Anti-androgens are known to primarily target the protein's ligand-binding domain. Some of the AR inhibitors are bicalutamide [64,65], CR1447 [66], Darolutamide [62], Enzalutamide [67], GTx-024 [68]. Clinical trials with GTx-024 in TNBC were terminated due to a lack of efficiency (https://clinicaltrials.gov/ct2/show/NCT02368691). Drugs targeting alternative functional domains of the AR proteins are still under development.

Immunotherapy for TNBC: T-cells express programmed cell death protein -1 (PD-1) on the surface and acts as an immune checkpoint by inhibiting effector T-cell function within the self-tissues. PD-1 receptor is recognized by any of the two ligands, PD-L1 and PD-L2. Expression of PD-L1 by tumors can block the immune response on cancer cells, and thus help the tumor growth by evading immune cell-mediated apoptosis. PD-L1 presence in the tumor microenvironment can lead to therapeutic resistance and increases the risk of recurrence [69]. About 50% of breast cancers express PD-L1 associated with TNBC and tumors of high histological grade [70,71]. PDR001, pembrolizumab, nivolumab and SHR1210 are some of the PD-1 inhibitors that are in various phases of clinical trials for treating the TNBC. Pembrolizumab is a humanized, IgG_4 isotype monoclonal antibody that binds to PD-1 and abrogates PD-1 interaction with PD-L1 and PD-L2. Several phase III trials are currently underway to evaluate the role of Pembrolizumab monotherapy for the treatment of TNBC. Nivolumab is yet another fully humanized immunoglobulin (IgG_4) monoclonal antibody directed against PD-1. In the metastatic TNBC, Nivolumab is currently being studied in adaptive phase II trial. In this the monoclonal antibody is delivered as monotherapy, but after various induction treatments (NCT02499367).

Therapeutic inhibition of PD-L1 using blocking antibodies like atezolizumab [72], and Durvalumab [73,74] either alone or as neoadjuvant therapy for TNBC are in various clinical trial phases. Yet another anti-PD-1 blocking antibody, FAZ053 developed by the Novartis has just started the "first-in-human" phase I trial for checking the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and TNBC anti-tumor activity (clinical trial; NCT02936102). PD-L1 and PD-1 antibodies can restrict their binding causing effector T cells to eliminate tumors [75]. Research on immune cells that can be reprogrammed to target and kill cancerous cells is being developed and combinational immuno-therapy combining PD-1 and PD-L1 with other checkpoint inhibitors, kinase inhibitors and other targeting agents with metastatic and neoadjuvant setting seems to give more promising results with decreased sensitivity and tolerance.

Other important therapeutic targets for treating TNBC: Some of the other targeted molecules or pathways whose inhibition can be potentially applied for TNBC treatment include IGF/IGF-1R signaling [76], cell cycle checkpoint inhibitors [77], and Nicotine/nicotinic acetylcholine Receptor (nAChR) signaling pathways [12].

The normal stem-cell self-renewal, normal cell growth, maintenance of body size and the energy metabolism in normal physiology are all controlled by the IGF / IGF-1R signaling system. However, IGF/IGF-1R also plays a vital role in tumor formation, resistance and in survival [12]. In addition, IRS-1/2 activation was reported in TNBC, suggesting that the IGF system is linked to this type of cancer [76]. Further, breast cancer patients generally show high IGF-1 levels in their serum [78], and TNBC cell lines and xenografts show the gene signature that correlates with the IGF activation [79], suggesting that these tumors can be sensitized to anti-IGF-IR therapy.

Several cell cycle checkpoint inhibitors are also in various phases of clinical trials, with a possible hope to block the TNBC progression. The development of CDK4/6 inhibitors showed a substantial improvement in progression-free survival (PFS) of metastatic breast cancer therapy. Pre-clinical studies suggest that CDK4/6 inhibitors block the progression of non-luminal breast cancer cell lines [80]. Trilaciclib, an investigational CDK4/6 inhibitor in a randomized phase II study with metastatic TNBC patients showed an improved overall survival (OS) rate when combined

with Gemcitabine and Carboplatin (ClinicalTrials.gov Identifier: NCT02978716). However, this combination failed to meet a safety-related primary endpoint [81]. Ribociclib is another investigational CDK4/6 inhibitor, which just completed the phase I trial, wherein the results are encouraging. Phase I trial data suggest that the combination of Ribociclib along with Bicalutamide is tolerable in patients with centrally confirmed AR-positive TNBC [82]. There are several other drugs like SHR6390 (CDK4/6 inhibitor) [83] and PF-06873600 (both CDK4/6 and CDK2 inhibitor) (ClinicalTrials.gov Identifier: NCT03519178) that are in various phases of testing for TNBC treatment.

Nicotine is a carcinogen present in cigarettes and tobacco. Nicotine has been shown to upregulate the stemness related genes expression as well as promote the EMT behavior and metastasis of the cancer cells [84]. Because of these reasons, any therapy that potentially targets the stemness properties induced by Nicotine should block the proliferation of Cancer Stem Cells (CSCs). Bupropion is an FDA-approved drug targeting α9-nAChR (α9- Nicotine/nicotinic acetylcholine Receptor), which potentially functions to block the metastasis in nicotine-induced TNBC [12].

CONCLUSIONS AND FUTURE DIRECTIONS

The Breast cancers (BC), which show negative Her2 expression and also negative for both ER and PR expression are considered as TNBC's and in the real-life scenario nearly 10 to 20% of BC's fall into this category. TNBCs are generally more aggressive with poor prognosis compared to other types of breast cancers. They also tend to be elevated in their degree compared to other types of breast cancers. Since neither ER, or PR, or Her2 fuel the growth of these classes of cancers, most likely they don't respond to the hormonal therapy medicines. Thus conventionally, TNBCs are managed with a combination of surgery, chemotherapy, and radiation therapy."One size fits all" chemotherapy regime/treatment paradigm has to be changed based on the molecular sub-grouping. TNBC, at the molecular and immunological level, is highly heterogeneous and the treatment option must depend on targeting the particular driver of that sub-class of TNBC. In recent years we have entered the new era of targeted therapy, wherein the drugs work by targeting cancer's specific genes, proteins or the tissue micro-environment that drives the growth and survival of cancer cells.

PARP inhibitors such as talzenna (chemical name: talazoparib) and lynparza (chemical name: olaparib) are approved by the FDA for treating people with Her2-negative breast cancer, with a mutation in BRCA1/2. PARP inhibitors causes excessive DNA damage in BRCA mutant cells, compared to Wt cells. There is also great hope that the TNBC standard of care will be changed by the immune checkpoint blocking antibodies. Immuno-therapy medicines make the patient's immune system work smartly and hardly attack the cancer cells. Clinical trials have suggested that there is however a modest response rate with these immune checkpoint inhibitors as monotherapy. In the case of TNBC specifically, Atezolizumab as a single agent shows only a 10 to 26% response rate. However, the success rate of treating TNBC is much better when the immunotherapy drugs are combined with chemotherapy. Tecentriq (chemical name: Atezolizumab) is the first immunotherapy medicine approved by the FDA. For unresectable, locally advanced or metastatic triple-negative, PD-L1-positive breast cancer, Tecentriq, in combination with the chemotherapy medicine abraxane (albumin-bound paclitaxel) is approved as the first treatment. Tecentriq , by inhibiting PD-L1, effectively permits the patient's immune system cells to look at the cancer cells and kill them. The researchers have found a strong correlation between tumor-infiltrating lymphocytes and the overall survival of patients when treated with the immunotherapy agents.

Other agents that are targeted for TNBC treatment include the PI3K-Akt pathway. Deficient PTEN expression is common in TNBC and often associated with Akt activation in these tumors. The new generation Akt inhibitors are known to cause gastrointestinal (GI) toxicity and diarrhea but are more manageable and tolerable than the previous generation Akt inhibitors. Antibody-drug conjugates represent another new class of highly potent anticancer drugs for targeting TNBC. One best example of this class of targeted therapy is the sucituzumab-govitecan conjugate, a topoisomerase inhibitor that blocks DNA replication. A phase I/ II trial with refractory TNBC patients showed an overall response rate of 33.3% with this antibody-drug conjugate, which is really exciting.

The success of targeted therapy depends on the mastering in the refinement of the population in focus and the molecules that we intend to target. There

are numerous clinical trials going on with targeted therapy in TNBC, and we anticipate that these will pave the way for new options in TNBC treatment. However, patients are still waiting for the obtainable treatment options and we need some more time to see these promising progresses to be visible in our cancer clinics. Considering a wide mutation spectrum of the TNBC, genotype-specific clinical trials should allow maximum patient benefit. Similarly, since immunotherapy in combination with the conventional chemo is showing a great promise, there is a great need to determine the best combinations possible for effective TNBC therapy.

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