Molecular alterations in triple-negative breast cancer – the road to new treatment strategies

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Abstract

Triple-negative breast cancer (TNBC) is a heterogeneous disease and specific therapies have not been available for a long time. Therefore, conventional chemotherapy is still considered the clinical state-of-the-art. Different subgroups of TNBC have been identified based on protein expression, mRNA signatures and genomic alterations. Important elements of TNBC biology include a high proliferative activity, an increased immunological infiltrate, a basal-like and a mesenchymal phenotype, and a deficiency in homologous recombination which is in part associated with loss of BRCA1/2 function. A minority show expression of luminal markers such as androgen receptors combined with a lower proliferative activity. These biological subgroups are overlapping and we are currently not able to combine them into a unified model of TNBC biology. Nevertheless, the molecular analysis of this disease has identified potential options for targeted therapeutic intervention. This has led to promising clinical strategies including modified chemotherapy approaches, DNA damage response targeting, angiogenesis inhibitors, immune checkpoint inhibitors, or even anti-androgens, that are currently evaluated in phase 1-3 clinical studies. The current review focusses on the most relevant clinical questions, summarizes the results of recent clinical trials and gives an overview on ongoing trials and current trial concepts that will lead to a more refined therapy of this tumor type.

Key messages:

1. Triple-negative breast cancer (TNBC) should be regarded as a working category that, although useful for current clinical decisions, may have only limited value as a defined biological category for future targeted therapy approaches due to its “triple negative” definition.

2. TNBCs are a highly heterogeneous group of tumors. Different approaches to classify these tumors have been established including classical pathology, mRNA expression profiling, DNA sequencing including analysis of copy number variations and structural rearrangements, and other molecular methods.

3. Important parameters of TNBC biology, include a high proliferative activity, an increased immune cell infiltrate, a basal-like and a mesenchymal phenotype, a deficiency in homologous recombination partly linked to a loss of BRCA1 function, and an expression of androgen receptors.

4. The different molecular phenotypes are observed in overlapping small subsets of TNBC, and there are non-TNBC tumors that may present with identical molecular characteristics.

5. The current biological classifications do not allow a unified model of TNBC that can be introduced as a molecular diagnostic tool.

6. Nevertheless, the increased knowledge on the molecular alterations in TNBC has led to several promising clinical approaches (including DNA damage response targeting, anti-androgens and immune checkpoint inhibitors) that are currently evaluated in phase 2-3 clinical studies and might lead to new treatment strategies.

Search strategy and selection criteria:

We searched the medline database for the search terms „(therapy) AND (((("triple negative breast neoplasms"[MeSH Terms] OR ("triple"[All Fields] AND "negative"[All Fields] AND "breast"[All Fields] AND "neoplasms"[All Fields]) OR "triple negative breast neoplasms"[All Fields] OR ("triple"[All Fields] AND "negative"[All Fields] AND "breast"[All Fields] AND "cancer"[All Fields]) OR "triple negative breast cancer"[All Fields])) AND ("2011/01/01"[Date - Publication] : "3000"[Date - Publication])))“. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

In addition, the abstracts of San Antonio Breast Cancer Symposium 2014 and 2015 and the ASCO Meeting 2015 and 2016 were reviewed for clinical trials with a focus on TNBC. Considering the fact that a large number of clinical trials in TNBC are currently ongoing, we focussed this clinical series on those trials with published results for most clinical strategies. Only for the new immune checkpoint inhibitor approaches, we have decided to include a table summarizing selected ongoing clinical trials. For other treatment strategies, we refer to published recent review articles that already provide an overview on ongoing clinical trials.

It should be noted that some of the most recent trial results have been reported only as meeting abstracts and presentations, and a more comprehensive description of the results is expected upon publication of the full-papers in the upcoming months. Due to the large number of clinical trials for the different TNBC subtypes it was not possible to include all clinical trials in this review article, and the presentations was focussed on those trials that were most intensely discussed in the medical community, based on the judgement of the authors. For additional trials, review articles are cited to provide readers with more details and more references than this Seminar has room for.

TNBC as a clinical problem

Triple-negative breast cancer (TNBC) represents 15% of breast carcinomas and is defined by the absence of the three main breast cancer biomarkers, i.e. lack of expression of estrogen receptor (ER) and progesterone receptor (PR) as well as lack of amplification/overexpression of HER2.[1] This negative definition together with biological and clinical heterogeneity has led authors to consider TNBC as “title of convenience” rather than a defined biological entity.[2] From a clinical perspective TNBC represents a highly relevant subgroup given that patients with TNBC do not benefit from endocrine or HER2-targeted agents and chemotherapy represents the only established therapeutic option.

Considering the unfavorable prognosis and aggressive biology of TNBC[3,4,5] many different experimental therapies are currently tested in phase 1 to 3 clinical studies. From these clinical studies, important response signals are emerging. Although the results of the new trials are of great interest, they should be interpreted with caution for patient-related clinical decisions because the current evidence is based mainly on small phase 1 or 2 trials or biomarker-driven analyses of subcohorts.

Established chemotherapy strategies for TNBC

Despite their unfavorable prognosis when regarded as a single group, many TNBCs are highly chemotherapy sensitive, and TNBCs have an increased neoadjuvant response rate compared to other breast cancer subtypes.[6,7,8] This phenomenon (i.e. an improved chance of pathological complete response (pCR) in contrast to an overall unfavorable prognosis) is commonly referred to as “triple negative paradox.”[9] It can be partly explained by the fact that highly-proliferating tumors have a poor prognosis and a high chance of response to chemotherapy at the same time. In addition, the poor prognosis of the group is driven by the very rapid onset of metastasis and poor prognosis of the TNBC subset that fail to respond to chemotherapy.

Relevant chemotherapy trials and metaanalyses are summarized in table 1. The ETCBCG overview has shown that the relative chemotherapy benefit resulting in approximately one-third reduction of breast cancer mortality is similar across breast cancer subtypes and independent of ER status.[10] In neoadjuvant studies, the difference between overall survival of responders and non-responders is particularly high in the TNBC subgroup, as shown in a comprehensive metaanalysis.[11] In this metaanalysis the pCR rate for TNBC was 33.6%, and the hazard ratio (HR) for improved overall survival of pCR patients vs. non-responders was 0.16 (95% CI 0.11–0.25) for the TNBC subgroup. Neoadjuvant approaches are therefore a central treatment strategy for TNBC.[4,12] Standardized systems for measurement of neoadjuvant response and residual cancer burden have been published.[13,14] In a metaanalysis of 3337 patients from 10 clinical studies, dose-dense therapy approaches were particularly effective in the HR-negative subgroup measured by immunohistochemistry.[15] However, this has not been observed in all clinical trials and it is also dependent on the selection and risk of the luminal tumors that are used for comparison as well as the method used for molecular classification.[16]

Modified chemotherapy concepts including platinum compounds - new biomarker strategies

Neoadjuvant approaches: The addition of platinum has been investigated as a promising approach for optimization of chemotherapy. In the GeparSixto trial, increased pCR rates[17] and improved survival rates[18] with neoadjuvant carboplatin compared to a non-standard liposomal anthracycline and taxane control arm have been observed in the TNBC, but not in the HER2-pos subgroup. The increase in pCR caused by carboplatin was greater in a) patients without a BRCA1/2 mutation[18] and b) patients with increased tumor-infiltrating lymphocytes.[19] The homologous recombination deficiency (HRD) assay that has the aim to measure so-called genomic scars as indicators of HRD showed that HRD-assay high scoring tumors had higher pCR rates compared to HR-non-deficient tumors, but this was observed independent of treatment and the effect of carboplatin could not be predicted.[20] In the CALGB 40603 trial, pCR rates in the overall TNBC trial population were improved with addition of neoadjuvant carboplatin (and bevacizumab),[21] but the increased pCR rate was not linked to an improved survival of the experimental treatment groups.[22] This is an example illustrating that pCR is an important prognostic parameter on a patient level, but not necessarily on a trial level. The Geicam 2006-03 trial has not shown any difference between pCR rates with neoadjuvant EC followed by docetaxel with or without carboplatin. This trial was restricted to an immunohistochemically defined basal-like subtype of TNBC and suggested no advantage to addition of platinum as an alkylating agent when patients had already received an alkylating agent regimen. In this trial the baseline treatment was weaker in the carboplatin containing arm compared to the control arm.[23]

Trials in the metastatic setting: In the CBCSG006 trial Hu et al. have reported in the metastatic setting in unselected advanced TNBC that the substitution of cisplatin for paclitaxel in the standard of care gemcitabine and paclitaxel regimen improved progression-free survival.[24] No *a priori* specified biological sub-group analyses were conducted.

The phase 3 TNT trial has directly compared carboplatin vs. docetaxel in TNBC and patients with germline *BRCA1/2* mutation and specified *a priori* biological subgroup analyses. In this trial, so far reported only as an abstract, the response to carboplatin therapy was not superior to that standard of care, docetaxel in the overall unselected TNBC group. The response to carboplatin was significantly greater than to docetaxel in patients with *BRCA1/2* mutated tumors, was similar to docetaxel in PAM50 basal-like cancers and was significantly inferior to docetaxel in the non-basal-like subtype, although the numbers in this non-basal-like group were very small.[25] The HRD-assay,[26] identified a high score group with higher response rates in both therapy arms; but the score appeared not to predict platinum-specific response. These data are supported by previous non-randomized data in a phase 2 trial of 20 patients with BRCA mutation and metastatic breast cancer that has reported an overall response rate of 80% with single-agent cisplatin therapy.[27] Similarly, in the non-randomized neo-adjuvant PreCOG 0105[28], and the non-randomized TBCRC009 trial[29] in the metastatic setting, increased responses to platinum therapy were observed in the group of patients with BRCA mutations. In these trials as well as an additional analysis,[30] response was also linked to higher HRD-assay scores. It should be noted that without a non-platinum control arm it is not possible to assess the specificity of the HRD-assay for platinum as opposed to standard of care therapy response, and additional investigations are required.

Post-neoadjuvant strategies: In the post-neoadjuvant setting, the CREATE-X trial[31] has reported that postneoadjuvant capecitabine leads to improved survival in poor-responders to neoadjuvant therapy. The TNBC subgroup (37% of patients) showed a hazard ratio (HR) of 0.58 in favor of postneoadjuvant capecitabine treatment. The IBSCG 22-00 trial[32] has investigated a metronomic maintenance therapy with cyclophosphamide and methotrexate after adjuvant or neoadjuvant chemotherapy. In the subgroup of nodal-positive TNBC a non-significant trend for improved DFS was observed, which was not seen in the complete study cohort.

Biomarker options for prediction of chemotherapy response: There are several reported predictive factors for increased response to neoadjuvant chemotherapy. Most of these factors reflect the more aggressive phenotype, such as high grade, negative hormone receptor status and high proliferation rate.[8] These factors are positive predictive factors for neoadjuvant response, but – at the same time – negative prognostic factors. Interestingly, immunological markers are often positively linked to both, increased neoadjuvant response as well as improved prognosis.[33,34] These factors build a biological hypothesis for new therapeutic strategies, as shown below, but they are currently not used to stratify patients for clinical therapy decisions.

Furthermore, there are no predictive markers that are significant across all different studies. For example, *BRCA1/2* mutations are predictive for increased response to cisplatinum or carboplatin therapy in the metastatic setting in the TNT and TBCRC009 trial. In contrast in the neoadjuvant GeparSixto trial, patients with *BRCA1/2* mutations had a higher response rate to the control therapy (but a lower increase in response rate with the addition of platinum therapy). In this trial a high response of treatment naïve patients with *BRCA1/2* mutations to control arm anthracycline/taxane based therapy appears to undermine any additional effect of platinum on response rates in a chemotherapy naïve primary treatment setting.

Biologic and genomic alterations as a basis for new therapeutic strategies

Definition of TNBC by current guidelines and subtypes identified by classical pathology

The histological presentation of classical TNBCs is characterized by high mutational rate, high nuclear grade as well as the presence of necrosis and inflammatory infiltrates. However, these characteristics are observed in other high-grade breast carcinomas, as well. Therefore, in clinical practice, TNBC is currently defined by what it is not. TNBCs have in common that they are negative for the standard breast cancer markers and cannot be treated by established therapies such as endocrine and anti-HER2 therapy. This designation is helpful in the clinical setting since it provides a convenient name for this group of tumors for clinical decisions. Nevertheless, we cannot understand the true biology of these tumors using this definition.

The updated guidelines on determination of hormone receptors and HER2 status in breast cancer have also influenced which tumors are designated triple-negative. The current guidelines[35] have changed the cutpoint for ER and PR from 10% to 1%. This was based on historical studies[36] that have shown a benefit from endocrine therapy even with very low levels of hormone receptors. Gene expression analysis has shown that 76% of tumors with very low (1-9%) hormone receptor expression were ESR1 negative on the mRNA level, 48% were classified as basal-like and only 8% classified as luminal, all of them as luminal B.[37] It is an open question if these tumors would also benefit from new therapeutic strategies that are currently developed for TNBC. The lower cutpoints for ER and PR therefore are useful to increase the number of patients eligible for endocrine therapy, but they might decrease the number of patients eligible for future TNBC-specific therapies, depending on the inclusion criteria in current clinical TNBC trials.

Some subtypes of TNBC can be reliably identified upon histopathological evaluation of H&E slides, in particular tumors such as adenoid-cystic carcinomas (ADCC). These tumors are histologically similar to salivary gland tumors and show a typical MYB–NFIB gene fusion that is also found in salivary gland ADCCs.[38,39] In contrast to classical TNBC, they have a low proliferation rate and a comparably good prognosis even with less aggressive treatment.[40,41] Several other rare subtypes of TNBC have been described, including low grade adenosquamous carcinoma[42], fibromatosis-like metaplastic carcinoma,[43] and secretory carcinoma[44], and the published small cases-series suggest that these subtypes might also have an improved prognosis. Therefore, the identification of these subtypes is important for selection of less aggressive individual patient treatment strategies and these low-proliferating tumors should not be included in TNBC clinical trials.

Gene expression profiling strategies for classification of TNBC

There have been several successful approaches to classify TNBC by gene expression profiling showing that basal markers, including keratin 5, EGFR and laminin, are typical for TNBC.[45,46] Basal-like tumors are enriched in TNBCs, but 21% of TNBC are not basal-like, and 31% of basal-like tumors are not triple-negative.[47]

In a gene expression study specifically focused on TNBC, additional subtypes have been identified,[48] including two basal-like (BL1 and BL2), an immunomodulatory (IM), a mesenchymal (M), a mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) type. Interestingly, important markers relevant for these additional subtypes derive from stromal cells, in particular fibroblasts and T-cells, which provides an additional molecular validation of the histopathological observation of increased tumor-infiltrating lymphocytes in TNBC.[47] Recently, these subtypes have been revised and limited to four distinct subtypes, i.e. BL1 and BL2, M, and LAR type TNBC.[49] In a similar approach, Burstein et al.[50] have described four subtypes: luminal/androgen receptor (LAR), mesenchymal (MES), basal-like/immune-suppressed (BLIS) and basal-like/immune-activated (BLIA). TNBC subtypes have different response rates to neoadjuvant chemotherapy with highest response rates for BL1 patients, and lower response rates in the BL2, LAR and M subtypes.[49,51] The luminal androgen receptor subtype (approximately 16% of TNBC)[49,52] might be an interesting candidate for an anti-androgen therapy, and a gene expression signature is under development to predict the response to AR inhibition.[53]

Taken together, the gene expression analysis has shown that immune-markers, androgen-receptor biology, mesenchymal phenotype, stem-cell markers and basal-markers are relevant for subclassification of TNBC. It should be noted that the transfer of TNBC subtyping to the daily clinical practice is not without challenges, due to the complex nature of the combined gene signatures. The original TNBC classifier developed by Lehmann et al.[48] is based on the measurement of a total of 2188 genes, but recently it has been suggested that the number of genes could be reduced to 101 genes,[54] which might be more manageable in the daily diagnostic practice. Currently, these molecular subtypes are not part of routine assessment of TNBC, but they provide a framework for the design of clinical studies that focus on the most relevant molecular alterations in the diverse TNBC subgroups.

Tumor-infiltrating lymphocytes (TILs) as indicators of immunogenicity

The tumor-associated immunological infiltrate is an important classical pathology parameter for TNBC. Traditionally, the subtype of medullary breast cancer shows a dominant lymphocytic infiltrate and a comparably good prognosis.[55,56] The most important parameter for the clinical behavior of this tumor type is the lymphocytic infiltrate, and conventional invasive-ductal carcinomas with an increased lymphocytic infiltrate have a similarly good prognosis as the medullary group.[57] Consequently, the current WHO classification has suggested that these tumors are not separate entities but represent the end of a spectrum of tumors that are characterized by an immunologically active tumor microenvironment.[58] Some candidate mechanisms for how an activated immunological microenvironment may be maintained by the tumor in subpopulations of TNBC have been proposed.[59]

This is in line with a large number of studies investigating TILs in breast cancer.[60] These studies have shown that TILs are linked to increased response to neoadjuvant chemotherapy in breast cancer.[33] Neoadjuvant response is a well-established prognostic factor in triple-negative breast cancer,[4,11] and increased TIL levels have also been shown to be linked to improved prognosis in this subtype.[34,61]

The focus on immune parameters is quite important for upcoming immunotherapy approaches including immune-checkpoint inhibitors, and the current data suggest that the modulation of the immune response might be able to increase therapy response in subgroups of TNBC.[62] Interestingly, the immunosuppressive parameters PD1 and PD-L1 show a positive correlation with the other immunological markers as well as with tumor-infiltrating lymphocytes.[63]

***BRCA1/2* mutation status and homologous recombination deficiency (HRD)**

The majority of hereditary (i.e. *BRCA1/2* mutated) breast cancers show a triple negative profile.[64] However, since BRCA-associated breast cancers are significantly less common compared to cases of TNBC, the majority of unselected TNBC are still wildtype for *BRCA1/2*.

Tumors with *BRCA1 or 2* mutations typically have a deficiency in homologous recombination (HRD) which means that damage to the DNA structure, in particular DNA double-strand breaks, and stalled or collapsed DNA replication forks, cannot be repaired properly. Over the life of the tumor, HDR leads to typical alterations in the DNA structure, which have been termed "genomic scars". Typical characteristics of *BRCA1/2* mutation associated genomic scars are large regions of loss-of-heterozygosity (LOH), increased numbers of telomeric allelic imbalances (NtAI) and large scale transitions (LST).[65]

Recently, typical rearrangement signatures with high numbers of tandem duplications have been linked to basal-like TNBC with high HRD index and BRCA mutations.[70] Interestingly, these alterations are typical for BRCA-mutant tumors but they have also been identified in tumors without a BRCA mutation.

The currently described genomic scars have high sensitivity for *BRCA1* or *2* mutation but appear to have poor specificity and positive predictive value for identifying tumor response that is specific to platinums rather than standard of care chemotherapy. Taken together this suggests that some BRCA wild-type tumors have a deficiency in homologous combination[66] but that biomarkers that have clinical utility must still be sought.

At present, even in the absence of a BRCA mutation a significant proportion of TNBCs show biologic similarities with BRCA-associated breast cancers. This phenomenon is commonly referred to as BRCAness.[67] It is a current major research focus to define molecular markers of HDR that can be used to select patients whose tumors will develop specific responses to PARP inhibitor or platinum therapy.[68] Similar to the immunological parameters, BRCA mutations and genomic scars are relevant molecular alterations for development and progression of TNBC, rather than specific markers for a defined subtype.

Genomic analysis of somatic mutations and copy number changes in triple-negative tumors

Comprehensive genomic investigations[69,70] have provided extensive data on the mutational landscape of breast cancer, but they have not identified any tumor mutations that are characteristic for TNBC. The total number of non-synonymous somatic mutations measured by whole-exome sequencing in the TCGA database is higher in TNBC (median 49 mutations) compared to Luminal BC (median 27 mutations).[71] Nevertheless, this mutational load in TNBC is still relatively low compared to malignant melanoma, NSCLC or MSI-colon cancer.[72] The main breast cancer mutations in PIK3CA and p53 are also the predominant mutations in TNBC, which higher mutations rated for p53 (50-80%) and slightly lower rates for PIK3CA (10-20%) compared to luminal tumors.[73,70] PIK3CA mutations have been found to be increased in androgen-receptor positive TNBC.[74]

It has been shown that copy number alterations (CNAs) and mutations are predominant in different subsets of tumors,[75] and breast cancer, including TNBC, is a typical example of the C-class of tumors that show predominantly copy number alterations,[76] but also a high rate of tp53 mutations.[75] Fusion genes including genes encoding microtubule-associated serine-threonine kinase (MAST) and members of the Notch family have been described in subsets of breast cancer.[77] Different types of Notch gene rearrangement, which might be targetable by agents such as gamma-secretase inhibitors, are found in subsets of TNBC.

New targeted therapeutic approaches in TNBC

Immune checkpoint inhibitors

There are several reasons why TNBC is regarded the optimal subtype of all breast cancers for immune checkpoint inhibition, with monoclonal antibodies including pembrolizumab (targeting PD1) and atezolizumab (targeting PDL-1). TNBC has the highest mutational frequency of breast cancer subtypes, which might increase the chance of immunogenic mutations generating neoantigens.[72,71] Furthermore, TNBC have increased levels of TILs and the prognostic role of TILs seems to be particularly strong among patients with TNBC.[62]

In a phase-1b KEYNOTE-012 trial[78] (table 2) patients with metastatic PD-L1-positive TNBC were treated with pembrolizumab. PDL-1 positivity (≥ 1% of tumor or stromal cells) by immunohistochemistry was observed in 58.6% of TNBC. Of the 32 patients that were registered onto the trial, 27 patients were evaluable for antitumor activity. An overall response rate of 18.5% was reported in association with a median time to response of 17.9 weeks. Most importantly, the noted median duration of response was not yet reached, and a subset of patients also showed long-lasting responses. In the NCT01375842 phase 1a multicenter trial, 27 patients with pretreated metastatic PD-L1 positive TNBC were treated with PD-L1 inhibitor atezolizumab (MPDL3280A), leading to an ORR of 24%.[79]

It is known that conventional chemotherapy can be immunogenic,[80] which suggests a synergy between chemotherapy and immune therapy. In a phase 1b expansion trial[81] patients with metastatic TNBC with ≤ 3 prior lines of therapy were treated with atezolizumab in combination with nab-paclitaxel, followed by maintenance therapy with atezolizumab until loss of clinical benefit. Primary endpoints were safety and tolerability; secondary endpoints included clinical activity. A PD-L1 expression in at least ≥5% of TILs was a prerequisite for participation in the trial. 32 patients were evaluable for safety analysis at a median follow-up of 5.21 months. The most common treatment-related adverse-event was a decrease in neutrophil counts (occurring at grade 3-4 in 41% of cases). Overall response rates were 67%, 25%, and 29% for patients in first, second and third line, respectively.

A corresponding phase trial III is currently recruiting patients world-wide. This trial (IMpassion130, NCT02425891) is a phase III, multicenter, randomized placebo-controlled study of atezolizumab in combination with nab-paclitaxel compared with placebo with nab-paclitaxel for patients with first-line metastatic TNBC. In this trial, PD-L1 positivity is not required, since it is increasingly recognized that PD-L1 positivity might not predict an increased chance of response against PD-L1 inhibitors.

These promising results have fostered initiation of a plethora of clinical trials including alternative PD1/PD-L1 inhibitors as well as combination regimens with tyrosine kinase inhibitors, MEK inhibitors, PI3K inhibitors, anti-angiogenic agents or combination with other checkpoint inhibitors[82] or co-stimulatory molecules. Table 3 lists selected clinical trials of PD1 or PD-L1 inhibition that are currently recruiting patients.

PARP-inhibitors and other genetics-based therapy strategies

Preclinical and clinical studies show that BRCA-mutated tumors have increased responses to PARP-inhibitor therapy, which can be elegantly explained by the concept of synthetic lethality.[83] This concept implies that simultaneous loss of function of two genes, such as those caused by BRCA-mutation and PARP-inhibition, results in cell death, while loss of only one does not change cellular viability. One mechanistic model for synthetic lethality suggests that PARP inhibitors induce single-strand DNA breaks or trap PARP-1 on DNA causing DNA replication forks to arrest and progress to double-strand breaks. BRCA-deficient tumors are not able to repair these double-strand breaks and are therefore more sensitive to the PARP inhibitor. It should be noted that additional alternative mechanistic explanations have been suggested (for details see[84]).

In the NCT00494234 non-randomized phase 2 trial patients with BRCA-mutated advanced breast cancer including those with TNBC were treated with olaparib 100mg or 400 mg twice daily (table 2). In particular in the group treated with 400mg, an objective response rate of 41% was observed.[85]

In the neoadjuvant I-SPY2 trial[86], an adaptive trial design was used to evaluate the combination of the PARP inhibitor veliparib with carboplatin in addition to a standard anthracycline taxane neoadjuvant therapy. The addition of veliparib-carboplatin increased pCR rate in the TNBC group from 26% to 51%. Due to the trial design it is not possible to attribute the increase in response to the PARP inhibitor or the platinum or a synergy in the combination.

Based on this phase 2 results, the Brightness phase 3[87] trial is currently evaluating the addition of Carboplatin or carboplatin-veliparib to standard neoadjuvant therapy. The OlympiA trial[88] is currently evaluating one year of olaparib as additional adjuvant therapy in patients with BRCA-mutations including those with high recurrence risk TNBC. An overview on the development of PARP inhibitors and additional clinical trials is given in a comprehensive review by Sonnenblick et al.[89]

In addition to agents focusing on PARP inhibition, clinical trials are ongoing that target other genomic alterations, including comprehensive trial programs such as SAFIR02 (NCT02299999) and the Aurora[90] initiative.

It has been shown that 4% of TNBC have an amplification of FGFR-2[91] and that FGFR signaling is involved in growth regulation of TNBC in preclinical models.[92] Based on these findings, clinical trials of FGFR inhibition have been conducted in TNBC and other types of breast cancer (Overview:[93]). A recent phase 2 study[94] included breast carcinomas with FGFR-1 amplification and gastric carcinomas with FGFR2 amplification. In this trial 1 of 8 breast cancer patients (12.5%) showed a response to the FGFR inhibitor AZD4547, while 3 of 9 gastric cancer patients (33%) had a response. The responding patients were characterized by high levels of gene amplification, which is relatively rare in breast cancer.

The NOTCH signaling pathway is involved in regulation of stem cell renewal.[95] Alterations of NOTCH receptors including rearrangements,[96] fusion genes[77] as well as mutations[97] have been observed in subsets of TNBCs and have been linked to increased response to gamma-secretase inhibitors. First results of phase 1 dose-finding studies of gamma-secretase inhibitors in TNBC have recently been published.[98]

Bevacizumab

Bevacizumab has been shown to increase pCR rates in triple-negative breast cancer in the GeparQuinto trial[99,100] (Bev: 36% vs. control: 21%; ypT0ypN0), the CALGB 40603 trial[21,22] (59% vs. 48%; pT0/is), the SWOG S0800[101] trial (59% vs. 29%; ypT0/isyN0) and the ARTemis trial[102] (45% vs. 31%, ypT0/isyN0). In contrast, in the NSABP-B40 trial, the increased pCR rate with bevacizumab was observed only in the hormone receptor positive subgroup (23% vs. 15%),[103] but not in the TN-subgroup (52% vs. 47%). Up to now, most neoadjuvant trials have not reported a survival advantage of the bevacizumab treatment. The exception is NSABP-B40, where a significant overall but not disease-free survival benefit that was observed.[104] In the adjuvant BEATRICE study, no difference in invasive-disease free survival and in overall survival was reported with the addition of bevacizumab to adjuvant chemotherapy.[105] It has been suggested that the current data does not allow the use of bevacizumab in early breast cancer, but that the combined evaluation of the neoadjuvant trials as well as biomarker-based stratifications might allow a better understanding of the clinical benefit of bevacizumab in defined subgroups.[106]

Androgen receptor inhibitors

There is a large and increasing body of evidence suggesting a potential role for androgen receptor (AR) targeting in a subset of breast cancer patients. In a recent meta-analysis of thirteen relevant studies including 2826 patients with TNBC an AR positivity rate of 24.4% was observed.[52] Most importantly, AR seems to represent a potential therapy target for endocrine therapy among patients with TNBC. Early study results suggest activity of AR inhibition in AR positive TNBC. Gucalp et al. examined clinical activity of the AR antagonist bicalutamide in patients with ER/PR-negative advanced breast cancer with >10% immunohistochemical nuclear staining for AR. Of 424 patients that were screened for AR positivity, 12% tested AR-positive. The authors reported a 6-month clinical benefit rate of 19% and a median PFS of 12 weeks.[107]

Bonnefoi and colleagues reported the results of a phase II clinical trial of Abiraterone acetate (AA) in 30 women with centrally reviewed AR-positive (≥10% by immunohistochemistry, IHC), but otherwise triple-negative heavily pretreated metastatic or inoperable locally advanced BC. An ORR of 6.7 and a median PFS of 2.8 months was observed. Side effects included fatigue, hypertension, hypokalaemia and nausea.[108] In the MDV3100-11 phase 2 trial[109] 118 patients with AR positive TNBC were treated with the AR inhibitor enzalutamide, and 57 patients were evaluable for clinical benefit. At 16 weeks, a clinical benefit rate of 35% was observed. The observed benefit appeared higher in patients with tumors that were positive for an AR-related gene signature.

Additional clinical trial concepts for androgen receptor inhibitors include combination with palbociclib (NCT02605486) [110] as well as PIK3CA inhibitors.[111] Several additional clinical trials[112] of androgen receptor inhibitors are currently ongoing that cannot be discussed here in more detail. [113]

Towards a unified model of TNBC biology?

In conclusion, the knowledge about triple-negative breast cancer has increased during the last years, and we are observing relevant response signals in clinical trials. It should be emphasized that none of the new therapies has been finally evaluated in phase 3 trials and that still chemotherapy is the only validated therapy option for treatment of TNBC in clinical practice. Nevertheless, the current results are promising because they are based on hypotheses that are derived from systematical evaluations of biological alterations in these tumors, including a deficiency in homologous recombination, an increased immunological infiltrate and an expression of androgen receptors. These alterations are typically only observed in all subgroups of TNBC and they are also not exclusive for TNBC. They should be seen as independent biological factors that form the basis for therapeutic interventions. The final biological model of TNBC will be determined by the results of the ongoing clinical trials and should focus on those markers that identify both biologically and clinically relevant subtypes.

Figure legend:

Figure 1: Overview on relevant molecular alterations in triple-negative breast cancer measured by different methodological approaches, including gene-expression profiling, classical histopathology and genomic alterations. Despite the different classification systems derived from the different approaches, there are common themes emerging. These themes include an increased immunological infiltrate (red), a high proliferation rate (green) , an expression of androgen receptors (blue) and a homologous recombination deficiency (orange). The color coding indicates that these themes are observed in parallel in different classification approaches. Based on these molecular results, at least 4 important therapy strategies for TNBC are emerging, which are currently tested in clinical studies.

Figure 1:

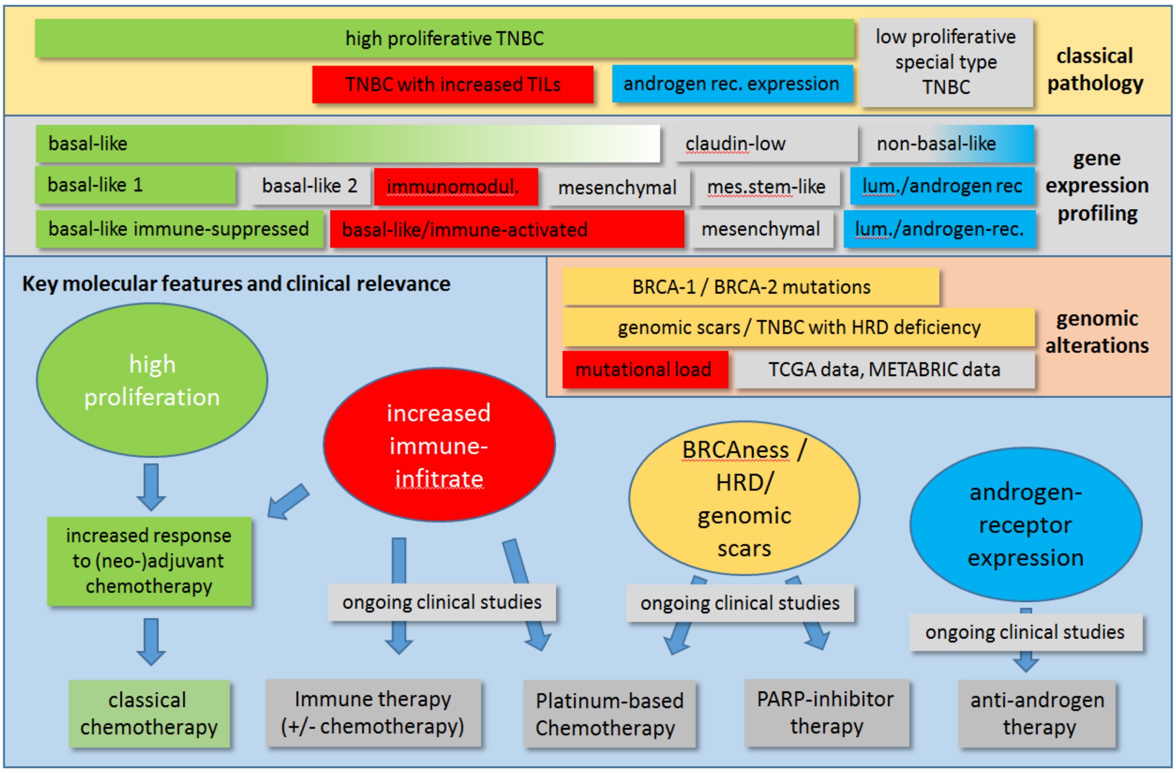

Table 1: Chemotherapy of TNBC – classical and new approaches: overview on relevant meta-analyses and clinical trials

Trial	Clincial cohort and therapeutic intervention	Main result	Reference
Selected meta-analyses			
Conventional adjuvant chemotherapy EBCTCG	Metaanalysis of 123 clinical studies (n=101000), different types of adjuvant chemotherapy	Anthracycline-taxane therapy; 30% risk reduction in all major subgroups, including ER-negative tumors	EBCTCG, Lancet 2012[10]
Conventional neoadjuvant chemotherapy CTNeoBC	12 clinical studies (n=11955), different types of neoadjuvant chemotherapy	Association between pCR and long-term outcomes was particularly large in TNBC	Cortazar et al, Lancet 2014[11]
Dose-dense adjuvant chemotherapy	Metaanalysis of 10 clinical studies (n=3337), Dose-dense vs.convent. chemoTx	Dose-dense chemotherapy results in better overall and disease-free survival, particularly in women with hormone receptor-negative BC	Bonilla et al. JNCI 2010 [15]
Platinum-therapy			
GEICAM/2006-03 Randomized phase 2 neoadjuvant multicenter study NCT00432172	Operable TNBC, basal-like subtype (negative for: ER,PR,HER2; positive for CK5/6+ or EGFR+) Neoadjuvant; 4 cycles EC followed by docetaxel (EC-D) vs docetaxel+carboplatin (EC-DCb) (n=94)	No difference in efficacy. pCR (breast) 35% with EC-D vs. 30% with EC-DCb	Alba et al. Breast Cancer Res Treat. 2012 [23]
GeparSixto Randomized neoadjuvant phase 2 trial NCT01426880	N=595, stage 2-3 TNBC or HER2+ BC, weekly paclitaxel and liposomal doxorubicin, with or without weekly carboplatin, all TNBC patients received bevacizimab	Therapy response: TNBC subgroup: pCR rate increased from 37% to 53% with carboplatin; Carboplatin effect was stronger in patients without BRCA mutations Survival: DFS in TNBC 85.8% with carboplatin and 76.1% without (hazard ratio = 0.56, *P* = .0350).	Von Minckwitz et al. Lancet Oncol, 2014 [17] von Minckwitz et al. 2015 San Antonio Breast Cancer Symposium, Abstract S2-04. [18]
CALGB 40603 Randomized 2x2 phase 2 trial	Stage 2-3 breast cancer (ER and PR>=10%, HER2 neg), (n=443); Neoadjuvant paclitaxel vs. paclitaxel+ bevacizumab vs. paclitaxel+ carboplatin	Therapy response: addition of either carboplatin or bevacizumab to NACT increased pCR rates; Survival: no outcome differences between therapy groups	Sikov et al., J. Clin. Oncol., 2015 [21] Sikov WM, 2015 San Antonio Breast Cancer

	vs. paclitacel+ carboplatin+ Bevacizumab		Symposium, Abstract S2-05. [22]
TNT trial Randomized phase 3 trial NCT00532727	Recurrent locally advanced or metastatic TNBC, n=376 Carboplatin vs. docetaxel	No difference in response rates to therapy arms in the complete cohort; Increased response rate to carboplatin (68% vs. 33% with docetaxel) in the subgroup of BRCA1/2 mutated tumors: HRD-assay: increased score linked to increased response in both therapy arms; PAM50 assay, non-basal subtype: higher response to docetaxel compared to carboplatin	Tutt et al. 2014 San Antonio Breast Cancer Symposium, Abstract S3-01 **Error! Bookmark not defined.**
NCT01611727 Phase 2 non-randomized single-arm trial	Metastatic breast cancer in patients with BRCA mutation (n=20)	Overall response rate: 80%; median time to progression:12 months.	Byrski et al. Breast Cancer Res. 2012 [27]
CBCSG006 open-label randomized phase 3	metastatic TNBC (n=240) cisplatin plus gemcitabine vs. paclitaxel plus gemcitabine	Improved progression-free survival with cisplatin/gemzitabine therapy in unselected advanced TNBC	Hu et al.[24]
PrECOG 0105 non-randomized single-arm neoadjuvant phase 2 study NCT00813956	stage 1-3A BC, either HER2neg; ER/PR>=5%; or BRCA1/2 mutated, any ER/PR, HER2-24% with BRCA1/2 mutation Neoadjuvant gemcitabine, carboplatin and iniparib (BSI-201) N=80 in intention-to-treat (ITT) cohort with six cycles Biomarkers: BRCA mutation analysis; HRD-LOH score	36% pCR in ITT group; higher pCR in: BRCA1/2 mutated tumors (47%): TNBC BRCA1/2 mutated tumors (56%); higher HDR-LOH observed scores in responders Comment: This trial used iniparib, which was later shown not to be a PARP inhibitor, therefore it is summarized here as a platinum-trial.[89]	Telli, JCO 2015 [28]
TBCRC009 Phase 2 non-randomized single-arm	metastatic TNBC (n=86), cisplatin or carboplatin monotherapy	Objective response rate: 26% (all patients); 55% (pts with BRCA1/2 mutation); 20% (pts without BRCA1/2 mutation); increased HRD score in responding patients (whole cohort and subcohort without BRCA mutation)	Isakoff, J. Clin. Oncol. 2015 [29]**Error! Bookmark not defined.**
Other chemotherapy approaches - postneoadjuvant therapy or adjuvant metronomic strategies			
CREATE-X	Patients with HER2neg	Interim analysis with improved	Toi M, 2015

UMIN000000843	breast cancer with non-pCR in the neoadjuvant setting, adjuvant capecitabine vs no adjuvant therapy, n=910, 37% TNBC	survival with post-NACT capecitabine; 2-year DFS 87% with capecitabine vs. 81% in control arm TNBC subgroup : HR of 0.58 in favor of postneoadjuvant capecitabine	San Antonio Breast Cancer Symposium, Abstract S1-07. [31]
IBCSG 22-00 Randomized phase 3 NCT00022516	ER/ PR neg BC (both >=10%), any HER2 status, completed surgery and adjuvant chemotherapy; randomized to 12 month metronomic cyclophosphamide methotrexate maintenance vs no maintenance therapy, n=1086	No significant reduction in DFS in the complete study cohort and in the TNBC group (n=814); Subanalysis for node-positive TNBC (n=340) showed a non-significant trend towards improved DFS in the experimental arm	Colleoni M et al., J Clin Oncol. 2016. [32]

Table 2: Targeted therapy of TNBC – overview on selected clinical trials of immune checkpoint inhibitors, PARP inhibitors, bevacizumab and anti-androgens

Trial	Clincial cohort and therapeutic intervention	Main result	Reference
Immune checkpoint inhibitors			
KEYNOTE-012 nonrandomized, multicohort, phase Ib study NCT01848834	Metastatic PD-L1-positive TNBC (all therapy lines) the PD-L1 inhibitor pembrolizumab given intravenously at 10 mg/kg every 2 weeks 32 patients with TNBC enrolled, 28 pts. wiith evaluable response	Efficacy: overall response rate: 18.5% median time to response: 17.9 weeks Safety: 15.6% incidence of grade 3 to 5 treatment-related AEs	Nanda et al. J Clin Oncol. 2016 [78]
NCT01375842 multicenter Phase Ia study	pts with pretreated metatatic PD-L1 positive TNBC enrolled (n=27) received the PD-L1 inhibitor atezolizumab (MPDL3280A) at 15 mg/kg, 20 mg/kg or 1200 mg flat dose IV q3w.	Efficacy: unconfirmed RECIST ORR 24%; Safety: Grade 3-5 related AE in 11% of pts	Emens et al. 2015 AACR Annual Meeting. Abstract 2859. [79]
GP28328 Phase Ib multicenter NCT01633970	metastatic TNBC treated with ≤ 3 prior lines of therapy (n=32) atezolizumab (MPDL3280A; 800 mg q2w (d1,15)) in combination with nab-paclitaxel (125 mg/m2 q1w (d1,8,15) q3 of 4 weeks)	Data from ongoing study presented at SABCS 2015: Efficacy: overall response rates were 1st line: 67% 2nd line 25% 3rd line 29% all patients: 42% Safety: 56% Grade 3-4 AEs	Adams et al. 2015 San Antonio Breast Cancer Symposium; Abstract P2-11-06 [81]
Androgen receptor inhibitors			
UCBG 12-1 Single arm open label multicenter Phase II NCT01842321	metastatic or locally advanced, triple negative and AR-positive BC (n=30) abiraterone acetate (AA, 1000 mg) once a day + prednisone (5 mg) twice a day	Clinical benefit rate (CBR) 20.0% [95%CI 7.7%-38.6%] ORR 6.7% (0.8%-22.1%) median PFS 2.8 months (1.7%-5.4%). Safety: 14.7% grade 3 AEs	Bonnefoi et al., Ann Oncol. 2016 [108]
MDV3100-11 phase 2 study NCT01889238	evaluating single agent enzalutamide in advanced AR+ TNBC (n=118 treaten, n=75 evaluated for response) evaluation of AR signature as possible biomarker	Clinical benefit rate (16 wks): 35% (all pts) 39% (AR signature +) Safety: 5% AE >= grade 3	Traina et al., ACO 2015, Abstr 1003 [109]
TBCRC 011	AR pos. ER/PRneg.	Efficacy: 6 month CBR: 19%	Gucalp

Phase 2 study NCT00468715	metastatic BC Bicalutamide 150 mg orally N=28 treated; N026 for resonse evaluation	Median PFS 12 weeks Safety: 14% grade 3 AEs	Clinical Cancer Res 2013 [107]
PARP inhibitor therapy			
NCT00494234 Phase 2 multicenter trial	Recurrent advanced breast cancer with BRCA1/2 mutations Subcohort 1 (n=27): olaparib (AZD2281) 400mg twice daily, 50% TNBC Subcohort 2 (n=27): olaparib 100mg twice daily, 64% TNBC	Objective response rates: 41% (subcohort 1) 22% (subcohort 2) Safety: grade 3-4 SAEs in 24% of pts.	Tutt et al. 2010 [85]
I-SPY 2 multicenter neoadjuvant, adaptively randomized phase 2 study NCT01042379	Stage 2-3 breast cancer, paclitaxel, doxorubicin, cyclophosphamide with or without veliparib (ABT888)-carboplatin (n=116, all TNBC)	Estimated pCR rates (Bayesian predicted probability) higher for veliparib–carboplatin Tx (51% vs. 26%); Probability of success in phase 3 trial: 88% in TNBC ; Higher rate of toxic effects in veliparib-carboplatin group	Rugo et al., NEJM 2016 [86]
Brightness Phase 3 randomized multicenter study NCT02032277	Planned N=624, T2-T4 TNBC Standard NACT vs. NACT+carboplatin vs. NACT+carboplatin+veliparib	Study under follow-up	von Minckwitz G, et al. ASCO 2014; abstr TPS1149 [87]
OlympiA Phase 3 randomized multicenter trial NCT02032823	adjuvant olaparib in high –risk TNBC and ER+/HER2-ve BC with germline BRCA1/2 mutation; planned n=1500	Recruitment ongoing	Tutt et al. ASCO 2015; abstr TPS1109 [88]
Bevacizumab			
GeparQuinto Neoadjuvant phase 3 multicenter study NCT00567554	Untreated HER2-neg breast cancer, (n=1948, TNBC subgroup n=663); neoadjuvant EC-D with or without bevacizumab; No postoperativ bev; bev discontinued in non-responders after 4 cycles EC	Therapy response: pCR rates (bev- vs. control-arm): all pts: 18% vs 15% (ns) TNBC: 39% vs. 28% (p=0.003) HR-pos BC: no difference Survival: no difference between Bev-arm and control	von Minckwitz et al NEJM 2015 [99] von Minckwitz et al. Ann. Oncol. 2014. [100]
NSABP-B40 Neoadjuvant phase 3 multicenter trial 3x2 factorial design NCT00408408	Primary operable HER2neg BC; Three different types of neoadjuvant chemotherapy, all with or without bevacizumab, Bev continued	Therapy response: pCR rates (bev- vs. control-arm): all pts: 35% vs 28% (p=0.02) TNBC: 52% vs. 47% (p=ns) HR-pos BC: 23% vs. 15% (p=0.007) Survival OS: improved overall	Bear et al, NEJM 2012 [103] Bear et al, Lancet oncology 2015 [104]

	postoperatively N=1206, 41% TNBC	survival with bev (HR 0.65, p=0.004) Survival DFS: not significant, but trend to better survival with bev (p=0.06) Survival effect mainly in the HRpos subcohort	
SWOG S0800 Randomized neoadjuvant phase 2 study NCI CDR0000636131	Stage 2b-3c untreated HER2-neg Breast cancer; n=212; nab-paclitaxel with concurrent bevacizumab followed by doxorubicin-cyclophosphamide (AC) vs. AC followed by nab-paclitaxel with concurrent bevacizumab vs. AC followed by NAB-paclitaxel	Therapy response: pCR rates (bev- vs. control-arm): all pts: 36% vs 21% (p=0.019) TNBC: 59% vs. 29% (p=0.014) HR-pos BC: no difference Survival: no difference between Bev-arm and control, trend in favor of bev in TNBC (p=0.06)	Nahleh ZA, Breast cancer research treatment, 2016 [101]
CALBG 40603	See above table 1 for details	Therapy response: addition bevacizumab to NACT increased pCR rates; Survival: no outcome differences between therapy groups	Sikov et al., J. Clin. Oncol., 2015 [21] Sikov WM, 2015 San Antonio Breast Cancer Symposium. Abstract S2-05. [22]
ARTemis Neoadjuvant phase 3 trial NCT01093235	HER2neg early BC D-FEC neoadjuvant therapy with or without bevacizumab; n=800; 31% ERneg	Therapy response: pCR rates (bev- vs. control-arm): all pts: 22% vs 17% (p=0.03) numerically stronger effect in ERneg and ER-weakly pos subgroups. No p-values for ER subgroups reported. Currently no survival data.	Earl et al. Lancet Oncol. 2015 [102]
BEATRICE Randomized multicenter adjuvant phase 3 trial NCT00528567	Operable HER2neg primary BC; Chemotherapy with or without bevacizumab; n=1290	No difference in invasive disease-free survival or in overall survival between treatment groups	Cameron et al. Lancet Oncol. 2013 [105]

Table 3: selected clinical trials of PD1 or PD-L1 inhibition that are currently recruiting patients

Trial number (Trial name)	Indication	Phase	Design
NCT02513472	MBC, (1st to 3rd line)	Phase 1b/2	Eribulin + Pembrolizumab* (single-arm)
NCT02499367 (TONIC)	MBC (2nd to 4th line)	Phase 2	Nivolumab** alone vs. nivolumab + • doxorubicin vs. • cyclophosphamide vs. • radiation vs. • cisplatin (five arms, open-label)
NCT02447003 (KEYNOTE-086)	MBC (all lines)	Phase 2	Pembrolizumab (single-arm)
NCT02819518 (KEYNOTE-355) **Part 1**	MBC / LABC (1st line)	Phase 3	Pembrolizumab + • Nab-Paclitaxel vs. • Paclitaxel vs. • Gemcitabine/Carboplatin
Part 2	MBC / LABC (1st line)	Phase 3	Pembrolizumab + chemotherapy Vs. pembrolizumab + placebo
NCT02555657 (KEYNOTE-119)	MBC (2nd or 3rd line)	Phase 3	Pembrolizumab vs. Physian's choice (capecitabine, eribulin, gemcitaine or vinorelbine)
NCT02425891 (IMpassion130)	MBC (1st line)	Phase 3	Nab-paclitaxel + azetolizumab vs. Nab-paclitaxel + placebo
NCT02489448	EBC (neoadjuvant)	Phase 1/2	MEDI4736 *** + weekly Nab-Paclitaxel followed by dose-dense doxorubicin / cyclophosphamide (single arm)
NCT02530489	EBC (neoadjuvant)	Phase 2	Azetolizumab + Nab-Paclitaxel
NCT02620280 (NeoTRIPaPDL1)	EBC (neoadjuvant)	Phase 3	Carboplatin + Nab-Paclitaxel + Azetolizumab vs. Carboplatin + Nab-Paclitaxel (open-label)
NCT02685059 GeparNuevo	EBC, TNBC (neoadjuvant)	Phase 2	Epirubicin + Cyclophosphamide + NAB-Paclitaxel + Durvalumab (MEDI4736) vs. Epirubicin + Cyclophosphamide + NAB-Paclitaxel + placebo

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