



# Toward precision medicine in inflammatory breast cancer

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**Abstract:** Inflammatory breast cancer (IBC) is an aggressive, although infrequent form of invasive breast cancer. Despite some advances in systemic treatment, even in the early setting, with combined-modality approach being the current recommended standard of care, the prognosis of IBC still remains unfavorable and has not significantly improved over time. Thus, a better understanding of the biology of IBC is eagerly awaited in order to identify possible targets for new drug development. This paper aims to provide an overview on recent data on the molecular and biological features of IBC and on possible targetable pathways. Molecular subtypes of IBC, similarly to other forms of breast cancer, have both therapeutic and prognostic implications. Moreover, few activated pathways have been described in IBC, including angiogenesis, epidermal growth factor receptor (EGFR), Janus kinase/signal transducer of activation (JAK/STAT) signaling and phosphoinositide 3-kinase/Akt/mTOR (PI3K/AKT/mTOR) pathways. However, when tested in clinical trials, agents targeting these pathways have provided only small benefit. Several clinical trials are currently ongoing investigating combination of standard chemotherapeutics, new targeted agents and immunotherapy. Moreover, tumor microenvironment (TME) is likely to play a central role in the disease; targeting the components of the tumor stroma may represent an interesting therapeutic strategy.

**Keywords:** Inflammatory breast cancer (IBC); molecular subtypes; activated pathways; targeted agents

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## Introduction

Inflammatory breast cancer (IBC) is a particularly aggressive form of invasive breast cancer, being responsible for up to 10% of breast cancer deaths, despite its relatively infrequency (approximately 1–5% of all breast carcinomas) (1,2). Given the absence of specific histological and molecular criteria, the diagnosis of IBC relies on the clinical presentation, characterized by the rapid onset of erythema, inflammation, edema and ridging of the skin of the breast (i.e., *peau d'orange*), with or without an underlying palpable mass (3,4). Indeed, a clinically dominant breast mass may be radiologically assessed in about 50% of patients, whereas patients frequently present with multicentric disease (5).

A skin punch biopsy is recommended in cases of suspected IBC and may show dermal lymphatic involvement with tumor emboli in the papillary and reticular dermis of the breast, a typical—although not pathognomonic—histopathologic finding (6).

Due to the lack of definitive diagnostic criteria, the possible differential diagnoses (mastitis, bacterial infection, breast abscess, post radiation dermatitis) and the relatively rarity of this clinicopathologic entity, the diagnosis of IBC is frequently delayed. The vast majority of patients with IBC have locally advanced disease at presentation and about 33% of them are diagnosed with metastatic spread (7). Consequently, patients with IBC have a poor prognosis with a median overall survival (OS) of 4.2 years and a

5-year OS of less than 55% (8-10). Moreover, some data suggest a worse prognosis for patients with metastatic IBC at presentation as compared to patients with stage IV non-IBC (nIBC) (11). However, different molecular subtypes of IBC, similarly to other forms of breast cancer, have both therapeutic and prognostic implications (10,12,13). Although each subtype of breast cancer may present as IBC, some studies showed a higher rate of human epidermal growth factor receptor-2 (HER2) overexpression and faster growth kinetics (14,15). As for the nIBC counterpart, triple negative breast cancer showed poorer outcome than other subgroups, whereas luminal A breast cancers had a trend towards better OS (16). Despite some advances in the therapeutic approach to locally advanced IBC have been made and combined-modality treatment with chemotherapy, surgery, and radiation therapy is currently the recommended standard of care, the OS of patients with IBC remains poor and has not significantly improved over the last 30 years (8,17,18), partly due to the underuse of the trimodal therapy as largely documented (18). Thus, identification of the molecular signature of IBC and of possible targets for novel therapies is eagerly awaited.

The present review aims to provide an update on recent findings on the biology of IBC and on possible therapeutic targets as well as to summarize most relevant ongoing clinical trials in this setting.

## Biology of IBC

Up to date, several efforts have been made to identify significant biologic differences, including molecular and genetic alterations, between IBC and nIBC. Different molecular subtypes, similarly to nIBC counterpart, have shown to have therapeutic and prognostic implications (10,12,13). A deeper understanding of the biologic and molecular features of IBC may lead to identify possible pathways promoting IBC growth and progression, thus fostering new drug development.

### Breast cancer subtypes in IBC

Assessment of hormone receptor (HR) status and HER2 expression is part of the standard evaluations that drive therapeutic choices in breast cancer patients (19,20). In IBCs, several studies have been conducted in order to identify any significant difference compared to nIBC. The incidence of HR-positive subtype is lower in IBC than in nIBC, while HER2-positive and triple-negative

tumors are higher represented in IBC, being associated with worse outcome (21,22). On the other hand, another study reported a comparable incidence of triple negative subtype between IBC and nIBC tumors (23). Moreover, according to a retrospective analysis on 593 IBC patients, HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple-negative tumors were 231 (39.0%), 98 (16.5%), 112 (18.9%), and 152 (25.6%), respectively (24). When assessed by gene expression profiling, molecular subtypes showed similar distributions in IBCs as compared to nIBCs. Indeed, Van Laere *et al.* reported that all subtypes are represented in IBC (25). Notably, a lower incidence of luminal A tumors (19% in IBC versus 42% in nIBC) and a higher of HER2+ tumors (9% in nIBC versus 22% in IBC) were observed.

Triple-negative and HR+/HER2- IBCs presented significantly worse survival compared with HR+/HER2+ or HR-/HER2+ subtypes (10,23,24,26).

Since a high incidence of IBC was observed in young subjects, the impact of BRCA1/2 mutations in this subgroup has been evaluated. No significant association between BRCA pathogenic variants and incidence of IBC was found (27), however IBC patients carrying pathogenic BRCA mutations were diagnosed at younger age as compared to BRCA-carriers nIBC patients.

### Molecular profiling of IBC

A cornerstone work in IBC molecular profiling was performed by Van Laere *et al.*, who evaluated gene expression and molecular profile of samples from 137 IBC and 252 nIBC patients classified according to the molecular subtypes using the PAM50-algorithm. The authors showed that a 79-gene signature, characterized by the downregulation of the transforming growth factor- $\beta$  (TGF- $\beta$ ), was specific for IBC, regardless of tumor subtype (25). In addition, this 79-gene signature had a prognostic value in a cohort of 871 patients with nIBC. However, a subsequent analysis of more than 400 nIBCs samples available in The Cancer Genome Atlas (TCGA) database showed that—according to this signature—25% of the tumors appeared to be IBC-like (25,28).

Subsequently, Bertucci *et al.* showed that IFN $\alpha$  and IFN $\gamma$  pathways were upregulated in patients with IBC who achieved a pathological complete response (pCR) after neoadjuvant chemotherapy (29). In the same study, the hypoactivation of other molecules, such as epidermal growth factor receptor (EGFR), p53 and TGF- $\beta$ , also correlated with higher rate of pCR. However, this set of genes was able to predict outcome also in nIBC patients

treated with neoadjuvant chemotherapy, suggesting that it is not exclusive for IBC. Furthermore, Ross *et al.* evaluated genetic alterations in a cohort of 53 IBC patients using the hybrid capture-based FoundationOne™ assay. The most frequently mutated genes were *TP53* (62%), *MYC* (32%), *PIK3CA* (28%), *ERBB2* (26%), *FGFR1* (17%), *BRCA2* (15%), and *PTEN* (15%) (30). More recently, Hamm *et al.* reported a comprehensive genomic profiling analysis of 20 IBCs, revealing that missense mutations were the most common variant (73%), followed by frameshifts (8%), splice-site alterations (6%), nonsense mutations (5.5%), amplifications (5.5%), and in-frame insertions-deletions (3%) (31). In this study, next-generation sequencing was able to identify 391 genetic variants. The five most commonly altered genes were *TP53* (58%), *HER2* (amplified in 53%), *ATM* (53%), *APC* (37%), and *HER3* (26%).

Genetic alterations in IBC were also explored by evaluating cell free DNA (cfDNA) from plasma. In a preliminary analysis of 13 IBC patients, somatic mutations in cfDNA samples were detected in *TP53* (53%), *RBI* (15%), *GEN1* (15%), *EP300* (15%), *PIK3CA* (7%), *ERBB2* (7%), *PALB2* (7%), and *MUC16* (7%) (32). In this setting, studies on larger cohorts of patients are currently ongoing.

### Targetable molecular pathways involved in IBC

Despite few activated pathways have been described in IBC, agents targeting some of these pathways have been tested in preclinical and clinical trials providing only small benefit. Several clinical trials are currently ongoing testing combinations of standard chemotherapeutics, new targeted treatments and immunotherapy, as summarized in *Table 1*.

#### *Angiogenesis and vasculogenesis*

Angiogenesis—the mechanism that leads to the formation of new vessels from pre-existing vessels—plays a relevant role in the development and progression of malignant neoplasms. In particular, IBCs present an upregulation of angiogenic processes as compared to nIBCs, including high expression of several molecules involved in these processes such as vascular endothelial growth factor A (VEGF-A), VEGF receptor 2 (VEGFR-2), angiopoietin 1 and 2, Tie-1, and Tie-2 (33-35). Moreover, IBCs seem to display an increased expression of angiogenesis-related genes (36). The extensive vascular involvement observed in IBC led to the conduct of a number of clinical trials testing the use of antiangiogenic treatment.

In this setting, several randomized clinical trials investigated the role of bevacizumab, a monoclonal antibody targeting the VEGF, a key factor that regulates blood vessels formation and permeability. Data from clinical trials investigating the use of bevacizumab in addition to standard neo-adjuvant chemotherapy showed an overall response rate ranging from 61% to 91% (37,38). In a phase II trial with dose-dense doxorubicin and cyclophosphamide followed by weekly carboplatin and paclitaxel with bevacizumab in patients with HER2 negative IBC, 3 out of 10 patients had a pCR (39). Two trials investigating bevacizumab in association with anthracycline and taxane-based neoadjuvant regimens in HER2 negative IBC patients reported pCR rate of 19–21% (40,41). Moreover, in the SWOG S0800 trial, HER2 negative IBC patients receiving bevacizumab and nab-paclitaxel with dose-dense doxorubicin and cyclophosphamide had higher pCR rate (30% *vs.* 14%), although the difference was not statistically significant ( $P=0.61$ ), given the small number of patients (42).

Based on these results, the addition of bevacizumab to chemotherapy does not seem to improve significantly pCR rates in HER2 negative population. The greater expression of other angiogenic, lymphangiogenic, and vasculogenic factors in IBC is likely to make VEGF blockade by bevacizumab insufficient and targeting multiple vasculo-lymphatic pathways concurrently seems to be the most promising strategy.

Slightly better results were obtained with bevacizumab in the HER2+ population. A recent phase II study showed the efficacy and safety of the combination of bevacizumab with weekly carboplatin and paclitaxel plus oral metronomic cyclophosphamide, with or without trastuzumab according to HER2 status. The overall response rate was 88%, and the pCR rate was 29%; patients with HER2 positive IBC had higher pCR rates and prolonged survival (43). The BEVERLY-2 trial reported a 63.5% pCR rate among 52 patients with HER2+ IBC treated with neoadjuvant anthracycline and taxane-based chemotherapy associated with bevacizumab and trastuzumab (44). Similarly, pCR rate around 50% was reported with the combination of bevacizumab, trastuzumab and neoadjuvant chemotherapy in patients with HER2+ IBC (45-47). On the other hand, the combination of HER2 blockade with lapatinib and the angiogenesis-targeting agent pazopanib showed no improvement in progression free survival (PFS) compared with lapatinib alone, and toxicity was significantly higher (48). Overall, these controversial results have not led to incorporate bevacizumab as neoadjuvant treatment for IBC.

**Table 1** Ongoing clinical trials in IBC

Setting	Subtype	NCT number	Phase	Treatment	Patients	Status
Neoadjuvant	All	NCT03742986	II	Nivolumab + AC/paclitaxel +/- trastuzumab	52	NYR
	HER2-	NCT03515798 (PELICAN)	II	Pembrolizumab + (F)EC-paclitaxel	81	NYR
		NCT02623972	II	Eribulin → AC	25	R
		NCT01036087	II	Panitumumab, nab-paclitaxel and carboplatin	40	ANR
		NCT00820547 (BEVERLY-1)	II	Bevacizumab + FEC/docetaxel	100	ANR
	TNBC	NCT02876107	II	Panitumumab, carboplatin, paclitaxel → AC	72	R
		NCT02041429	II	Ruxolitinib (INCB018242)	24	ANR
		NCT01525966	II	Abraxane + carboplatin	69	ANR
NCT02876302		II	Ruxolitinib + AC/paclitaxel	64	R	
Adjuvant	HR+/HER2-	NCT02971748	II	Pembrolizumab + hormonal treatment	37	R
	All	NCT01477489	I	Veliparib + RT	33	C
		NCT03598257	II	RT + olaparib vs. RT alone	300	R
Metastatic	All	NCT03202316	II	Atezolizumab + cobimetinib + eribulin (ACE)	33	R
		NCT02658812	II	Talimogene laherparepvec	35	ANR
		NCT02227082	I	RT + olaparib	36	R
	TNBC	NCT03184558	II	Bemcentinib (BGB324) + Pembrolizumab	56	R
	HER2-	NCT01262027	II	Dovitinib	22	ANR
		NCT02411656	II	Pembrolizumab	36	R
		NCT02892734 (WIN)	II	Ipilimumab + nivolumab	29	R
	HER2+	NCT01325428	II	Afatinib +/- vinorelbine	26	C

IBC, inflammatory breast cancer; AC, doxorubicin and cyclophosphamide; ANR, active, not recruiting; C, completed; (F)EC, (fluorouracil) epirubicin and cyclophosphamide; HER2-/+ , HER2 negative/positive; HR+, hormone receptor positive; NYR, not yet recruiting, R, recruiting; RT, radiotherapy; TNBC, triple negative breast cancer.

### EGFR pathway

The EGFR family comprises four single-chain transmembrane glycoproteins, namely EGFR (ErbB1, HER1), ErbB2 (HER2, neu in rodents), ErbB3 (HER3) and ErbB4 (HER4) (49). With the exception of HER2—which has no recognized ligand—the other ErbB receptors bind to their ligands and are activated by homo-dimerization/hetero-dimerization. The subsequent tyrosine auto-phosphorylation prompts the activation of downstream signaling pathway components, including mitogen-activated protein kinase (MAPK), phosphoinositide phospholipase C/protein kinase C (PLC/PKC), phosphoinositide 3-kinase/AKT (PI3K/AKT), and Janus kinase/signal transducer of activation (JAK/STAT) pathways (50,51).

Traditionally, HER2 overexpression in breast cancer has

been associated with increased aggressiveness, recurrence rates, and mortality. However, in the last years anti-HER2 agents have significantly improved outcomes in this population (52,53). As previously described, a higher proportion of HER2-positive subtype was observed among IBC patients, compared to nIBC counterpart (14,15). A large body of evidence supported the use of trastuzumab in patients with IBC (54). The NOAH trial assessed the benefit of the addition of neoadjuvant trastuzumab to chemotherapy in 77 patients with IBC (55). The small number of IBC patients included in studies investigating the dual HER2 blockade with pertuzumab and trastuzumab in the neoadjuvant setting, as NeoSphere, BERENICE and TRYPHAENA trials, precluded definitive indication in this setting (56-59), although there is no reason to think

that these drugs should not improve outcome as they do in nIBC. The use of lapatinib, also, has been studied in patients with locally advanced HER2+ IBC (60,61). The neoadjuvant administration of lapatinib in combination with paclitaxel had a combined clinical response rate of 78% in IBC patients (62).

EGFR overexpression was detected in roughly 30% of IBC patients. EGFR-positive IBC was associated both with a worse 5-year OS rate and an increased risk of disease recurrence as compared to EGFR-negative IBC (22,31,63,64). Interestingly, the anti-EGFR tyrosine kinase inhibitor erlotinib was able to inhibit IBC tumor growth and spontaneous lung metastases in an IBC orthotopic xenograft model (63). Moreover, the small molecule EGFR inhibitor AZD8931 showed antitumor activity in IBC cell lines (65,66). A large number of monoclonal antibodies, including cetuximab, panitumumab, nimotuzumab, necitumumab, GA201, and TKI targeting EGFR as varlitinib, gefitinib, erlotinib, aderbisib, AE37, are currently under evaluation in breast cancer (67). Although these agents have been especially tested in triple negative breast cancer, preclinical evidence showed the efficacy of gefitinib in slowing tumor growth also in IBC models (68). In a recent phase II trial (69), panitumumab was tested in combination with neoadjuvant chemotherapy (nab-paclitaxel and carboplatin weekly and then 4 cycles of fluorouracil epirubicin and cyclophosphamide) in 40 patients with primary IBC. A 28% pCR rate was observed overall, with greater benefit obtained in a cohort of 19 patients with triple negative IBC (pCR 42%). Some biomarkers predictive of pCR were identified, including pEGFR and COX-2 expression. Also, afatinib with or without vinorelbine, showed activity in a small cohort of trastuzumab-naïve HER2-positive IBC patients (70). However, the small number of patients precluded further conclusion, as the trial was terminated early following the results of LUX-Breast 1 trial, showing shorter OS and higher toxicity of afatinib-vinorelbine combination compared to trastuzumab plus vinorelbine (71). Due to its toxicity profile and modest activity, no further development of afatinib for HER2-positive breast cancer is planned (72).

### **PI3K/AKT/mTOR pathway**

The PI3K/AKT/mTOR pathway was shown to be frequently altered in breast cancer across all tumor subtypes (73). As previously highlighted, Hamm *et al.* reported that genomic alterations in PI3K/mTOR pathway are frequent in IBC, including 21% of mutation in PIK3CA (31). Similarly,

Liang *et al.* reported PIK3CA mutations in 29% of IBC, which correlated with worse metastasis-free survival (74). In metastatic HR-positive breast cancer, the mTOR inhibitor everolimus provided significant clinical benefit in combination with the aromatase inhibitor exemestane (75). Given the scant specificity of everolimus as well as the high incidence of toxicities, new agents targeting PI3K/AKT/mTOR pathway have been tested in breast cancer patients; the alpha-selective PI3K inhibitor alpelisib, which has shown to improve PFS when added to endocrine therapy in HR+/HER2- metastatic breast cancer (76). Although mTOR signaling was shown to be overexpressed in HER2-amplified IBC (77), the combination of everolimus and trastuzumab produced only a modest improvement in PFS compared to placebo in the metastatic setting (78). No specific data for these agents in IBC patients are available so far, but some PI3K inhibitors are under clinical investigation for IBC.

### **JAK/STAT pathway**

The JAK/STAT pathway is involved in IBC survival and proliferation; in IBC cells with stem-like characteristics (CD44+/CD24-), higher levels of phosphorylated JAK2 have been described as compared to nIBC cells (79). Inhibition of JAK pathway reduced IBC cells proliferation *in vitro* and inhibited tumor growth in IBC xenograft models (80). Based on this result, the JAK1/JAK2 tyrosine kinase inhibitor ruxolitinib was tested as monotherapy in pSTAT3-positive triple negative breast cancer in a phase II clinical trial; however the study was early stopped due to ineffectiveness (81). Currently, a phase I/II trial is being testing the combination of ruxolitinib and paclitaxel in triple negative breast cancer and IBC patients (NCT02041429).

### **Targeting tumor microenvironment (TME) in IBC**

The interaction between tumor cells and non-malignant cells, which compose the TME, has being deeply investigated in order to recognize how this cooperation may influence tumor development and progression. TME consists of non-malignant cells, including cancer associated fibroblasts (CAFs), endothelial cells and pericytes composing tumor vasculature, immune and inflammatory cells, bone marrow derived cells, and the extracellular matrix (ECM), establishing a complex cross-talk with tumor (82). Accumulating evidence suggests a unique cell composition within the TME in IBC. Resident non-malignant cells,

including tumor-associated macrophages, dendritic cells, lymphocytes, mesenchymal stem cells, fibroblasts, and endothelial cells, create a fine-tuned interaction with IBC cells, also affecting immune response (83). A single-institution experience investigating associations between tumor immune microenvironment and early response to neoadjuvant dual HER2 blockade was recently presented at 2018 San Antonio Breast Cancer Symposium (84). Matched tumor biopsies from 23 patients with HER2 positive IBC were collected before and after one week of dual blockade. Immune activation as determined by gene expression signatures both at baseline and after one week of treatment predicted pathologic complete response. Upregulation of immune activation was evident only one week after treatment with dual blockade.

### Immune system in IBC

Despite its name, which derives from the clinical signs of inflammation present at onset, immune infiltration is not a distinguishing feature of IBCs. Overall, the rate of tumor infiltrating lymphocytes (TILs) in IBC samples was superimposable to that observed in nIBCs (85). Consistently, gene expression analyses did not show higher expression of inflammatory component in IBC compared with non-IBC group (14). On the other hand, IBC presented with higher PD-L1 expression compared to nIBC (38% *vs.* 10–30%), when evaluated by means both RNA expression and immunohistochemistry (86,87). In addition, PD-L1 was more frequently overexpressed in HR-negative status, basal and HER2-enriched subtypes (86), being also significantly associated with pCR after neoadjuvant chemotherapy (87).

Immunologic analysis revealed a subset of IBC tumors associated with high CD8(+)/PD-L1(+) lymphocyte infiltration. Immune infiltration positively correlated with an NGS-based estimate of neoantigen exposure derived from the somatic mutation rate and mutant allele frequency, iScore (31). Additionally, DNA mismatch repair alterations, which may contribute to higher iScores, occurred at greater frequency in tumors with higher immune infiltration (31).

Immunotherapy is currently under evaluation in breast cancer, after having shown efficacy and durable responses in different hematologic and solid malignancies (88,89). Recently, the combination of an immune-checkpoint blockade (i.e., atezolizumab) and a chemotherapeutic agent (nab-paclitaxel) demonstrated to be effective as first-line treatment in metastatic triple-negative breast cancer with PD-L1 expression (90). Based on these data, FDA has

recently approved this combination in this setting. This BC subtype is characterized by a greater genetic instability, higher tumor mutational load and tumor immune infiltrate. So far, no data are available on the use of immunotherapy in IBC. However, many trials with immune-checkpoint inhibitors are currently ongoing as summarized in *Table 1*.

### Conclusions

This overview of available biologic and molecular data shows that IBC is a different clinic-pathological entity with particular features that determine its aggressive behavior. Advances in loco-regional therapies and the increasing use of a multimodal therapeutic approach provided some benefit. However, the prognosis of IBC patients still remains poor and has not significantly improved over time. High-dose chemotherapy with hematopoietic stem cell support and hyper-fractionated accelerated radiation therapy have been evaluated for the treatment of IBC with controversial results and additional data from prospective randomized clinical trials are awaited (91). New strategies and development of targeted agents are strongly needed to improve outcomes. However, mainly due to the relatively rarity of the disease, there is paucity of data from large-scale, prospective, multicenter, randomized trials. A deeper understanding of the molecular and biologic features of IBC may enable the identification of new therapeutic targets and/or pathways, thus promoting new drug development, at the same time it may help identifying patients who are more likely to respond to such therapies, thus improving the selection of patients to be enrolled in clinical trials.

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