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Review

Triple-Negative Breast Cancer: The Progress of Targeted Therapies and Future Tendencies

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Abstract. *Triple-negative breast cancer (TNBC) is characterized by a lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) and unfortunately is not associated with good prognosis. Treatment of breast cancer mainly depends on chemotherapy, due to the lack of specifically approved targeted therapies for TNBC. It is of paramount importance to find new therapeutic approaches, as resistance to chemotherapy frequently occurs. Herein, we present clinical studies published within the last five years, in order to reveal possible targeted therapies against TNBC. We aimed to discuss factors against TNBC, such as tyrosine kinase inhibitors, anti-androgens, poly ADP-ribose polymerase-1 (PARP-1) inhibitors, anti-angiogenic factors, immune checkpoints and histone deacetylase inhibitors (HDACI). Furthermore, the PI3K/AKT/mTOR pathway seems to be a promising field for the development of new anti-TNBC targeted therapies. Data from 18 clinical trials with patients suffering from TNBC were summarized and presented descriptively.*

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Breast cancer is one of the most common cancers in females, comprising heterogeneous tumors with a variety of biological features, clinical course, prognosis and response to therapy (1, 2). In 2017, triple-negative breast cancer (TNBC) accounted for about 15% of all the new cases of breast cancer in the United States (3-7). Many different epidemiological studies have revealed that TNBC was more likely to arise among females characterized by early menarche, higher waist to hip ratio, higher parity, shorter duration of breast feeding, higher body mass index, and was more common among pre-menopausal patients (8). TNBC is a disease defined by the absence of human epidermal growth factor receptor 2 (HER2) and hormone receptors (HR), specifically the progesterone (PR) and the estrogen receptor (ER) (9) (Figure 1). There are at least 6 different subtypes, which demonstrate different biological behavior, including the basal-like 1 and 2 (BL-1 and BL-2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), luminal androgen receptor (LAR) and unstable subtype (7, 10).

TNBC is characterized by poorer diagnosis compared to the other types of breast cancer, with a more aggressive clinical behavior (11-14). Central nervous system and visceral metastases appear at higher incidence and in shorter period of time in this specific type of cancer (15-17). In addition, cerebral, hepatic and pulmonary metastases are more frequent in TNBC, than in other luminal subtypes (18, 19). The greatest risk of recurrent disease occurs in the first 2-3 years after diagnosis and is at minimal after 8 years (4, 20, 21). Cytotoxic chemotherapy still remains the main treatment for TNBC disease, along with surgery and/or radiotherapy, although 60% of TNBC patients show minimal or no response to the aforementioned treatment (22-24). Thus, various studies and clinical trials are being conducted, in order to provide new targets and improve prognosis. Androgen targeted therapy, anti-angiogenetic factors, histone deacetylase inhibitors, immune checkpoint inhibitors, PARP inhibitors and the PI3K/AMT/TOR pathway have been proposed as possible targets for the treatment of TNBC (25-34).

The present study provides an up-to-date review which focuses on the progress made in the field of targeted therapies for TNBC in the last five years.

Materials and Methods

A literature search was conducted in MEDLINE (*via* PubMed) and COCHRAINE library in order to retrieve articles published during the period between 2015-2019. The search strategy was based on the use of keywords such as triple-negative breast cancer, targeted therapies, clinical trials and metastases. The PRISMA approach was used for the selection of the publications included in the review. A total of 358 records were identified. Following removal of the duplicates 357 records remained. These were screened and 339 were excluded because they were only abstracts or did not include clinical trials. Furthermore, articles were excluded because TNBC patients were neither the only group included, nor were analyzed separately in the clinical study. The full-text articles assessed for eligibility were 18 and none of them was excluded. The inclusion process is presented in Figure 2.

Results

Anti-angiogenic factors. High expression of VEGF has been reported in TNBC (35, 36). VEGF has been shown to induce high tumor cell proliferation in mice models of breast cancer (37). As demonstrated in various clinical and experimental studies, the most significant angiogenic factor for breast cancer is VEGF (35). In human breast cancer, the combination of mutant p53 with high labels of VEGF, is associated with poor clinical outcome (38).

In 2016, Ferrero *et al*., reported a single-arm multicenter phase II study which included 64 patients with advanced TNBC (Table I, Entry 1). Patients received treatment with 4-week cycles with capecitabine (800 mg/m^2 twice on days 1-5, 8-12, 15-19), paclitaxel (80 mg/m^2 on days 1, 8 and 15 for maximum of 6 cycles) and bevacizumab (10 mg/kg on days 1 and 14) every 4 weeks until unacceptable toxicity or disease progression. It was shown that this triple regimen had efficient antitumor activity with acceptable levels of toxicity (39).

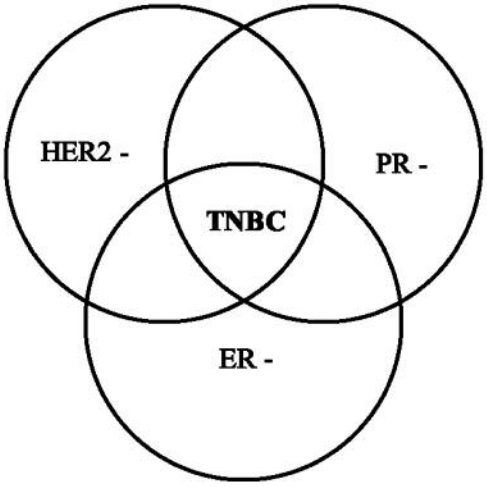

Figure 1. *Triple-negative breast cancer. HER2: Human epidermal growth factor receptor 2; PR: progesterone receptor; ER: estrogen receptor; TNBC: triple-negative breast cancer.*

In 2016, the results of an international randomized phase III trial of 2,591 female patients with centrally operable primary invasive TNBC was published (Table I, Entry 2). Chemotherapy alone or combined with bevacizumab at a dose equivalent to 5 mg/kg weekly was administrated to patients. Bell's study compared the two treatments and suggested that there is no significant benefit from the addition of bevacizumab in non-advanced TNBC (40).

One year later, a phase II study with 46 patients examined the efficacy of paclitaxel, carboplatin and bevacizumab 10mg/kg intravenous on day 1 and 15 of a 28-day cycle against metastatic TNBC (Table I, Entry 3). It was shown that this regimen offered clinical response without the serious adverse events associated to bevacizumab (24).

In 2018, a phase II clinical trial including 55 female patients, aged between 33 to 83 years old, with invasive TNBC was conducted (Table I, Entry 4). Nabpaclitaxel and 10 mg/kg IV bevacizumab at days 1 and 15, along with maintenance therapy with the same dose of bevacizumab with erlotinib was administered to patients. According to Symonds *et al*., the combination treatment described above did not increase progression-free survival, as expected, but the maintenance therapy offered a break from chemotherapy (41).

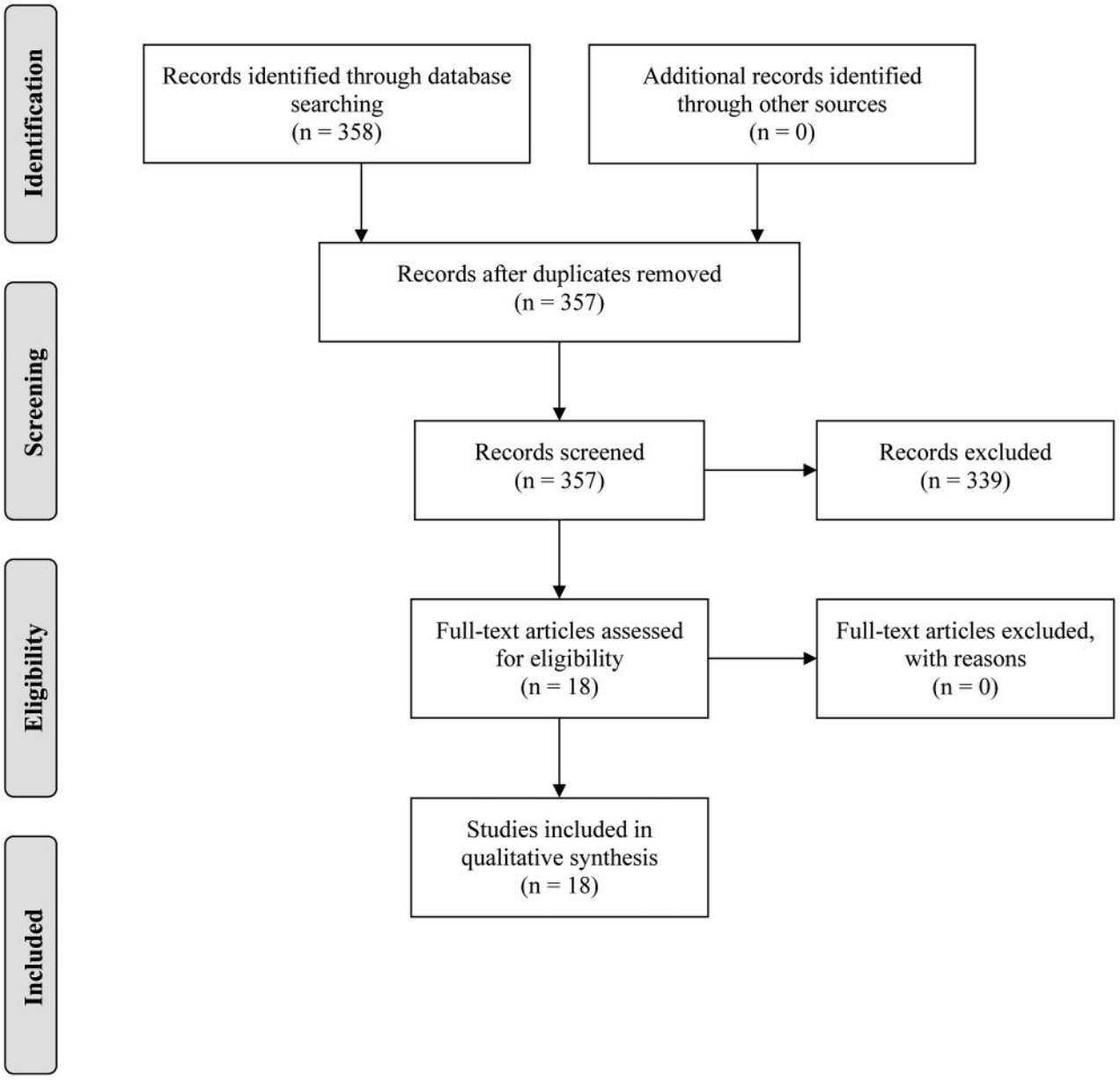

Figure 2. *Prisma flow diagram for the current literature review.*

Next year, Mery *et al*., treated 45 female TNBC patients with a median age of 62 years, with paclitaxel plus 10 mg/kg bevacizumab on days 1 and 15 (Table I, Entry 5). According to the results, bevacizumab proved to be beneficial to patients by prolonging median progression-free survival with limited toxicity (42).

Immune checkpoint inhibitors. PD-1 receptor is expressed on the surface of T-reg cells. Both lymphocytes and cancer cells bind to PD-1 *via* its ligand named PD-L1. PD-L1 is not found in normal epithelial cells (43, 44). Their binding leads to inhibition of T killer cell action against cancer cells and decreased production of inflammatory cytokines. Thus, T killer and cancer cells interact. The inhibitors of PD-1 and PD-L1 inhibit the immune checkpoints mentioned above and improve immune response induced by T killer cells (44).

TNBC expresses relatively high levels of PD-L1, mostly on immune [tumor infiltrating lymphocytes (TILs)] cells and less frequently on cancer cells (45). Thus, TNBC is a perfect candidate for trials with anti-PD-1/PD-L1 agents (46).

Table I. *Clinical trials with targeted therapies conducted in patients with Triple-Negative Breast Cancer.*

Entry	Author	Year	Study	Patients	Therapy	Conclusion
1	Ferrero *et al.* (39)	2016	Single-arm multicenter phase II study	62 patients with metastatic or locally advanced TNBC without previous treatment with chemotherapy	Paclitaxel, capecitabine and bevacizumab 10 mg/kg on days 1 and 14 every 4 weeks	This triple regimen showed antitumor efficacy with an OR 77% [95% Confidence interval (95%CI)=66-88%] and with acceptable toxicity
2	Bell *et al.* (40)	2017	International open-label randomized phase III trial	2591 female patients with operable primary invasive TNBC	Chemotherapy alone or combined with bevacizumab at dose equivalent to 5 mg/kg weekly	The combination of chemotherapy with bevacizumab did not demonstrate significant benefit IDFS 80% (95%CI=77-82%) compared to chemotherapy alone 77% (95%CI=75-79%)
3	Saloustros *et al.* (24)	2018	Phase II study	46 patients of median age 54 years old suffering from mTNBC	Paclitaxel, carboplatin and bevacizumab 10 mg/kg intravenous on day 1 and 15 of 28 days cycle	This regimen demonstrated efficient antitumor action with an ORR 65.2% (95%CI=52.9-80.4%)
4	Symonds *et al.* (41)	2018	Phase II clinical trial	55 female patients aging between 33 to 83 years old with invasive TNBC	Nab-paclitaxel and bevacizumab 10 mg/kg IV at days 1 and 15 and maintenance therapy with the same dose of bevacizumab with erlotinib	Even though PFS (9.1 months, 95%CI=7.2-11.1) did not increase as expected, these regimens demonstrated tolerable toxicity and similar efficacy with other regimens. The maintenance therapy offered a break from chemotherapeutic treatment
5	Mery *et al.* (42)	2019	Single-center retrospective study	45 female patients of median age 62 years old suffering from mTNBC	Paclitaxel plus bevacizumab 10 mg/kg on days 1 and 15	Bevacizumab offered significant benefit as the median PFS was 8.4 months (95%CI=6-9.6) with limited toxicity
6	Nanda *et al.* (47)	2016	Nonrandomized, multicohort, phase Ib study	32 women with positive PD-L1 TNBC aging between 29 to 72 years old	IV administration of pembrolizumab 10 mg/kg every 2 weeks	The use of pembrolizumab shows significant clinical antitumor activity with ORR=18.5% [95%CI=18.5 (6.3 to 38.1)] with mild toxicity
7	Dirix *et al.* (48)	2017	Open-label, international, phase I trial	168 female patients with metastatic breast cancer, including 58 with TNBC and ECOG performance status <2	IV administration of avelumab 10 mg/kg every 2 weeks	In the TNBC population, avelumab demonstrated antitumor activity with ORR=5.2%, [95%CI=5.2 (1.1 to 14.4)] with tolerable safety profile
8	Adams *et al.* (49)	2019	International, multicohort, open-label, phase II study	170 female patients between 28 to 85 years old with mTNBC having already received previous chemotherapy schemes	200 mg Pembrolizumab IV over 30 min every 3 weeks for maximum 2 years	Pembrolizumab demonstrated antitumor activity especially in patients with PD-L1-positive mTNBC with ORR=5.7% (95%CI=2.4-12.2)

Table I. *Continued*

Table I. *Continued*

Entry	Author	Year	Study	Patients	Therapy	Conclusion
9	Adams *et al*. (50)	2019	International, multicohort, open-label, phase II study	84 female patients aging between 26 to 91 years old, ECOG performance status <2 and diagnosed with positive PD-L1 mTNBC without previous systematic treatment	200 mg Pembrolizumab intravenous over 30 min every 3 weeks for maximum 2 years	Pembrolizumab used as monotherapy for positive PD-L1 mTNBC not previously treated showed a low incident rate for serious adverse events (grade 3, 9.5%). In addition, durable and effective antitumor activity was shown as the ORR was 21.4% (95%CI=13.9-31.4)
10	Connolly *et al*. (54)	2017	Single arm, multicenter, phase II study	40 female patients including 13 with TNBC and 27 with hormone resistant breast cancer	AZA and entinostat (7 mg orally, days 3 and 10) every 28 days (cycle)	There was no response to treatment provided in women with TNBC.
11	Kim *et al*. (60)	2017	Randomised, double-blind, placebo-controlled, phase I trial	124 women aged more than 18 years old suffering from metastatic or locally advanced TNBC with ECOG performance status <2	IV paclitaxel (day 1, 8, 15) plus ipatasertib 400 mg or placebo daily for days 1 to 21 every cycle (28 days)	The period of progression free survival was longer in patients treated with ipatasertib than those treated with placebo. ([HR] 0.60; 95%CI= 37-98%; p=0.037)
12	Basho *et al*. (61)	2017	Phase I study	52 female patients with mTNBC aging between 37-79 years old	On the first day of every cycle (21 days of duration) intravenous of both bevacizumab and liposomal doxorubicin combined with daily oral everolimus (DAE) or weekly intravenous temsirolimus (DAT)	The patients showed a CBR of 40% (95%CI= 27-55%) and an ORR of 21% (complete response [CR]=4 [8%]; partial response [PR]=7 [13%] (95%CI=11-35%). PI3K pathway aberration is related to improved objective response rate (31% *vs*. 0%; p=0.04)
13	Jovanovic *et al*. (62)	2017	Multicenter, double-blinded, randomized, placebo-controlled, phase II clinical trial	145 patients >18 years old, with clinical stage 2 or 3 of TNBC and ECOG performance status <2 divided in a placebo and in an everolimus administrated group	Cisplatin weekly for 12 weeks, paclitaxel weekly for 11 weeks (administration started 1 week after cisplatin initiation) and everolimus 5 mg orally daily or placebo orally daily for 12 weeks	The simultaneous use of cisplatin/paclitaxel and everolimus failed to improve PCR compared to the placebo group (36% compared to 49%) and; led to increased adverse events
14	Traina *et al*. (65)	2018	Prospective phase II study	118 patients (78 evaluated) with AR+ TNBC locally advanced or metastatic	160 mg of enzalutamide once daily until disease progression	There was significant clinical benefit with the use of enzalutamide as CBR was 25% (95%CI= 17-33%) and its adverse events were well tolerated
15	Bonnefoi *et al*. (66)	2016	Single-arm open-label phase II study	34 patients with AR+TNBC locally advanced or metastatic	1000 mg of AA (four tablets of 250 mg, daily) and prednisone 5 mg twice every day	The administration of abiraterone acetate demonstrated a 20% clinical benefit rate after 6 months of treatment (6/30; 95%CI=7.7-38.6%)

Table I. *Continued*

Table I. *Continued*

Entry	Author	Year	Study	Patients	Therapy	Conclusion
16	Llombart-Cussac *et al.* (73)	2015	Multicenter, randomized open-label phase II study.	141 patients with TNBC Stage II–IIIA	3 groups: a. PTX b. Paclitaxel plus iniparib weekly PWI c. PTI	PCR was similar in the three groups PTX: 10 (21%) patients, PWI: 10 (22%) patients, and PTI: 9 (19%) patients. The addition of iniparib increased neither antitumor activity nor toxicity.
17	Kummar *et al.* (74)	2016	Multicenter, open-label, randomized phase II study	45 patients with mTNBC	Cyclophosphamide alone or co-administered with veliparib at 60 mg per day in 21-day cycles	No improvement was observed to the response rate after the combination of both drugs compared to cyclophosphamide alone
18	Tolaney *et al.* (83)	2016	Single-arm, two-stage phase II study	35 women of median age 50 years with mTNBC and ECOG performance status <3	Cabozantinib 60 mg once per day for 3 weeks in each cycle	Cabozantinib demonstrated a clinical benefit rate of 34% after 15 weeks of treatment (95%CI=19-52%) although only 3 patients showed partial response (ORR, 9%) (95%CI=2-26)

PTX: Paclitaxel alone; PWI: paclitaxel plus iniparib weekly; PTI: paclitaxel plus iniparib twice a week; AA: abiraterone Acetate; IDFS: invasive disease-free survival; mTNBC: metastatic triple-negative breast cancer; TNBC: triple-negative breast cancer; ORR: objective response rate; PFS: progression-free survival; ECOG: Eastern Cooperative Oncology Group; IV: intravenous; CI: confidence interval; AZA: 5-azacitidine; CR: complete response; PR: partial response; CBR: clinical benefit rate; PCR: pathologic complete response; AR: androgen receptor.

In 2016, Nanda *et al.*, conducted a multicohort, nonrandomized, phase Ib study, in which 32 women with positive PD-L1 TNBC, aging between 29 to 72 years old, were enrolled (Table I, Entry 6). Intravenous administration of pembrolizumab at a dose of 10 mg/kg every 2 weeks was found to be clinically efficacious against cancer cells and to have a tolerable safety profile with limited toxicity (47).

One year later, a phase 1 trial evaluated the clinical response of 168 patients with metastatic breast cancer, including 58 patients with TNBC (Table I, Entry 7). Patients received pembrolizumab at a dose of 10 mg/kg every 2 weeks. It was pointed out that, especially in the TNBC population there was a greater antitumor activity without serious adverse events (48).

Next year, a group of 170 female individuals between 28 to 85 years old with metastatic TNBC, who had already received previous chemotherapy treatment, received 200 mg of pembrolizumab intravenously over 30 min every 3 weeks for maximum 2 years (Table I, Entry 8). Patients treated with pembrolizumab, showed significant clinical response with acceptable adverse events (49).

In addition, another phase II study aimed to examine the efficacy and the safety profile of pembrolizumab, as a first-line treatment in 84 individuals diagnosed with PD-L1 positive mTNBC (Table I, Entry 9). According to Adams's study, there was significant evidence that pembrolizumab led to a low incident rate of severe adverse events, with durable and effective antitumor activity (50).

Histone deacetylase inhibitors. Both histone acetylation and deacetylation demonstrate a great effect on chromatin structure and remodeling. According to functional criteria, histone deacetylases (HDAC) can be classified in four classes, which can be divided into two groups, the NAD-dependent class III and the Zn^{2+}-dependent classes of I, II and IV. These classes include a) hydroxamates, b) benzamides c) cyclic peptides and d) aliphatic acids (51). HDAC inhibitors (HDACI) affect a wider spectrum of cellular functions in cancer cells, such as cell proliferation, cell death, gene expression and cell migration (52). In addition, anti-angiogenesis and prevention of glycose metabolism are additional mechanisms of action against cancer cells (53). Importantly, normal cells seem to be relatively resistant to HDACI and be less affected by their actions, providing an opportunity to maximize results against cancer cells and minimize toxicity on healthy ones (52, 53).

In 2016, a multicenter phase II study tested the objective response rate of entinostat and 5-azacitidine (AZA) in 40 patients with advanced breast cancer, including 13 with TNBC (Table 1, Entry 10). The clinical results showed that there was no response to treatment provided in women with TNBC (54).

PI3K/AKT/mTOR pathway inhibitors. The aberrations in the PI3K/AKT/mTOR pathway are considered to be common in various subtypes of breast cancer including TNBC (55). In TNBC, overexpression of regulators, such as epidermal growth factor receptor (EGFR), the loss of function of phosphatase and tension homolog (PTEN) or the presence of mutations, which activate the PI3K subunit a, can trigger oncogenic activation of this pathway (56-58). Downstream of PI3K is AKT, which is inhibited by ipatasertib (59). In 2017, Kim *et al*., conducted a phase II trial, in which 124 women suffering from metastatic or locally advanced TNBC with ECOG performance status <2 participated (Table I, Entry 11). Patients were randomized to paclitaxel plus 400 mg oral ipatasertib or placebo on days 1 and 21 on each cycle (28-days). The period of progression-free survival was longer in patients treated with ipatasertib, than in those treated with placebo. Furthermore, the risk of adverse events grade ≥3 was slightly higher in patients receiving ipatasertib compared to those receiving placebo (60).

Concerning the mTOR inhibitors, in 2016, 52 female patients with metaplastic TNBC participated in a phase I study (Table I, Entry 12). On the first day of every cycle (of 21 days duration) both bevacizumab and liposomal doxorubicin, combined with daily oral everolimus (DAE) or weekly intravenous temsirolimus (DAT), were administered to participants. Both combinations showed remarkable activity against metaplastic TNBC. Additionally, PI3K pathway aberrations were related to improved objective response rate (61).

Next year, investigators tested the use of Cisplatin weekly for 12 weeks, paclitaxel weekly for 11 weeks (administration started 1 week after cisplatin initiation) and everolimus 5 mg orally daily or placebo orally daily for 12 weeks in 145 patients with Stage II/III TNBC and ECOG performance status <2 (Table I, Entry 13). The results revealed that the triple combination therapy, compared to cisplatin/paclitaxel, failed to improve the clinical outcome of patients. In addition, more adverse events occurred (62).

Androgen-targeted therapy. The androgen receptor (AR) is found in both malignant and normal breast tissue and its prevalence varies according to the histological subtype of breast cancer. Approximately 10-15% of TNBC expressing AR show a more benign course (63, 64). In 2018, Traina *et al*. tested 175 individuals with AR positive, locally advanced or metastatic TNBC. Patients received 160 mg of enzalutamide once daily until disease progression (Table I, Entry 14). The outcome of the prospective phase II study indicated that there was a significant clinical benefit from the use of enzalatumide (65).

Next year, a group of scientists evaluated the efficacy of 1,000 mg of Abiraterone Acetate (four tablets of 250 mg, daily) and 5 mg prednisone twice every day in 34 patients with AR positive, locally advanced or metastatic triple-negative breast cancer (Table I, Entry 15). They showed that administration of abiraterone acetate demonstrated significant clinical benefit after 6 months of treatment. Additionally, the majority of the adverse events were characterized as grade 1 and 2 (66).

Poly-ADP ribose polymerase (PARP) inhibitors. Poly-ADP-ribose synthesis consists one of the primary responses to DNA strand breaks. PARP1, as a stable element of chromatin, accelerates DNA repair *via* various mechanisms, such as attraction of other repairing proteins and binding to DNA breaks (67-71). PARP inhibitors induce apoptosis, by causing accumulation of damaged cellular DNA. Thus, the inhibition of PARP-1 can cease the procedure or repairment in a single-stranded intermediate state (69, 70, 72).

In 2015, 141 patients with TNBC Stage II-IIIa were evaluated in a phase II study (Table I, Entry 16). The patients were divided into three groups depending on the neoadjuvant regimen received. They were randomized to receive paclitaxel alone (PTX), paclitaxel plus iniparib weekly (PWI), and paclitaxel plus iniparib twice a week (PTI). The investigators demonstrated that pathologic complete response was similar in the three groups and the addition of iniparib increase neither antitumor activity nor toxicity (73).

One year later, a group of 45 patients with metastatic TNBC were enrolled in a randomized phase II study (Table I, Entry 17). They randomly received cyclophosphamide alone or co-administered with veliparib at 60 mg per day in 21-day cycles. According to the results, no improvement was observed to the response rate, after the combination of both drugs, compared to cyclophosphamide alone (74).

Tyrosine kinase inhibitors. MET is a tyrosine kinase receptor, which binds to its ligand hepatocyte growth factor (HGF) (75). Its activation leads to proliferation, survival and invasion of cancer cells and is associated with poor clinical outcome (76-81). Cabozantinib consists an inhibitor of various tyrosine kinases, such as MET and the vascular endothelial growth factor receptor 2 (VEGFR2) (82).

In 2016, Tolaney *et al*., conducted a phase II study, in which they tested 35 women of median age 50 years with metastatic TNBC (Table I, Entry 18). Cabozantinib 60 mg once per day for 3 weeks in each cycle was administered to participants. Via analysis of blood biomarkers during treatment, they showed that cabozantinib leads to immune

system activation and prevents angiogenesis. Thus, cabozantinib showed clinical benefit without adverse events grade >3 even though it did not reach the objective response rate in pre-treated metastatic TNBC patients (83).

Conclusion

TNBC is characterized by great metastatic ability and is associated with poor clinical result. Patients with the TNBC do not benefit from hormonal treatment or treatment with anti-HER2 antibodies (trastuzumab), since their tumors do not express the ER, PR, and HER2 receptors. Surgery, radiation therapy, and chemotherapy, used alone or in various combinations, are currently the primary reliable therapeutic options for patients with TNBC. Thus, it is necessary to conduct studies with specifically selected patient populations, as the TNBC is so heterogeneous. As it is shown in this review, numerous new therapeutic targets have emerged, such as tyrosine kinase inhibitors, antiandrogens, poly ADP-ribose polymerase-1 (PARP-1) inhibitors, anti-angiogenic factors, immune checkpoints and HDACI. In addition, the PI3K/AKT/mTOR pathway is regarded as another evolving field, concerning treatment of TNBC.

In conclusion, as new opportunities emerge from the development of all these potential new targeted therapies against TNBC, more clinical trials should be conducted in order to examine the toxicity profile and the efficacy of the new agents.

Conflicts of Interest

All the Authors declare that there is no conflict of interest regarding this study.

Authors' Contributions

CD and NG designed the study. CD, AG, KN and NG wrote the article. CD, AG, KN, MV, ED, AP, PF and NG collected the data. AN, DM, NN and KK offered scientific advice. DD, EAA and NG revised the manuscript. NG was the supervisor.

References

1 Adkins FC, Gonzalez-Angulo AM, Lei X, Hernandez-Aya LF, Mittendorf EA, Litton JK, Wagner J, Hunt KK, Woodward WA and Meric-Bernstam F: Triple-negative breast cancer is not a contraindication for breast conservation. Ann Surg Oncol *18(11)*: 3164-3173, 2011. PMID: 21947595. DOI: 10.1245/s10434-011-1920-z

2 Brenton JD, Carey LA, Ahmed AA and Caldas C: Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol *23(29)*: 7350-7360, 2005. PMID: 16145060. DOI: 10.1200/JCO.2005.03.3845

3 American Cancer Society. Cancer Facts and Figures 2017. Atlanta, GA: American Cancer Society; 2017.

4 Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P and Narod SA: Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res *13(15 Pt 1)*: 4429-4434, 2007. PMID: 17671126. DOI: 10.1158/1078-0432.CCR-06-3045

5 Bauer KR, Brown M, Cress RD, Parise CA and Caggiano V: Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer registry. Cancer *109(9)*: 1721-1728, 2007. PMID: 17387718. DOI: 10.1002/cncr.22618

6 Loibl S, Muller BM, von Minckwitz G, Schwabe M, Roller M, Darb-Esfahani S, Ataseven B, du Bois A, Fissler-Eckhoff A, Gerber B, Kulmer U, Alles JU, Mehta K and Denkert C: Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients treated with neoadjuvant chemotherapy. Breast Cancer Res Treat *130(2)*: 477-487, 2011. PMID: 21837479. DOI: 10.1007/s10549-011-1715-8

7 Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y and Pietenpol JA: Identification of human triple negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest *121(7)*: 2750-2767, 2011. PMID: 21633166. DOI: 10.1172/JCI45014

8 Smid M, Wang Y, Zhang Y, Sieuwerts AM, Yu J, Klijn JG, Foekens JA and Martens JW: Subtypes of breast cancer show preferential site of relapse. Cancer Res *68(9)*: 3108-3114, 2008. PMID: 18451135. DOI: 10.1158/0008-5472.CAN-07-5644

9 Diaz LK, Cryns VL, Symmans WF and Sneige N: Triple negative breast carcinoma and the basal phenotype: from expression profiling to clinical practice. Adv Anat Pathol *14(6)*: 419-430, 2007. PMID: 18049131. DOI: 10.1097/PAP.0b013e3181594733

10 Marmé F and Schneeweiss A: Targeted therapies in triple-negative breast cancer. Breast Care (Basel) *10(3)*: 159-166, 2015. PMID: 26557820. DOI: 10.1159/000433622

11 von Minckwitz G, Untch M, Nüesch E, Loibl S, Kaufmann M, Kümmel S, Fasching PA, Eiermann W, Blohmer JU, Costa SD, Mehta K, Hilfrich J, Jackisch C, Gerber B, du Bois A, Huober J, Hanusch C, Konecny G, Fett W, Stickeler E, Harbeck N, Müller V and Jüni P: Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat *125(1)*: 145-156, 2011. PMID: 21042932. DOI: 10.1007/s10549-010-1228-x

12 Gluz O, Liedtke C, Gottschalk N, Pusztai L, Nitz U and Harbeck N: Triple-negative breast cancer current status and future directions. Ann Oncol *20(12)*: 1913-1927, 2009. PMID: 19901010. DOI: 10.1093/annonc/mdp492

13 Bosch A, Eroles P, Zaragoza R, Viña JR and Lluch A: Triple-negative breast cancer: molecular features, pathogenesis, treatment and current lines of research. Cancer Treat Rev *36(3)*: 206-215, 2010. PMID: 20060649. DOI: 10.1016/j.ctrv.2009.12.002

14 de Ruijter TC, Veeck J, de Hoon JP, van Engeland M and Tjan-Heijnen VC: Characteristics of triple-negative breast cancer. J Cancer Res Clin Oncol *137(2)*: 183-192, 2011. PMID: 21069385. DOI: 10.1007/s00432-010-0957-x

15 Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O,

Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO and Botstein D: Molecular portraits of human breast tumours. Nature *406(6797)*: 747-752, 2000. PMID: 10963602. DOI: 10.1038/35021093

16 Rodriguez-Pinilla SM, Sarrio D, Honrado E, Hardisson D, Calero F, Benitez J, Palacios J: Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res *12(5)*: 1533-1539, 2006. PMID: 16533778. DOI: 10.1158/1078-0432.CCR-05-2281

17 Collignon J, Lousberg L, Schroeder H and Jerusalem G: Triple-negative breast cancer: treatment challenges and solutions. Breast Cancer (Dove Med Press) *8*: 93-107, 2016. PMID: 27284266. DOI: 10.2147/BCTT.S69488

18 Heitz F, Harter P, Lueck HJ, Fissler-Eckhoff A, Lorenz-Salehi F, Scheil-Bertram S, Traut A and du Bois A: Triple-negative and HER2-overexpressing breast cancers exhibit an elevated risk and an earlier occurrence of cerebral metastases. Eur J Cancer *45(16)*: 2792-2798, 2009. PMID: 19643597. DOI: 10.1016/j.ejca.2009.06.027

19 Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A and Winer EP: Sites of distant recurrence and clinical outcomes in patients with metastatic triple negative breast cancer: High incidence of central nervous system metastases. Cancer *113(10)*: 2638-2645, 2008. PMID: 18833576. DOI: 10.1002/cncr.23930

20 Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN and Pusztai L: Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol *26(8)*: 1275-1281, 2008. PMID: 18250347. DOI: 10.1200/JCO.2007.14.4147

21 Jatoi I, Anderson WF, Jeong JH and Redmond CK: Breast cancer adjuvant therapy: Time to consider its time-dependent effects. J Clin Oncol *29(17)*: 2301-2304, 2011. PMID: 21555693. DOI: 10.1200/JCO.2010.32.3550

22 Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE Jr, Pazdur R, Ditsch N, Rastogi P, Eiermann W and von Minckwitz G: Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet *384(9938)*: 164-172, 2014. PMID: 24529560. DOI: 10.1016/S0140-6736(13)62422-8

23 Fedele P, Orlando L and Cinieri S: Targeting triple negative breast cancer with histone deacetylase inhibitors. Expert Opin Investig Drugs *26(11)*: 1199-1206, 2017. PMID: 28952409. DOI: 10.1080/13543784.2017.1386172

24 Saloustros E, Nikolaou M, Kalbakis K, Polyzos A, Christofillakis C, Kentepozidis N, Pistamaltzian N, Kourousis C, Vamvakas L, Georgoulias V and Mavroudis D: Weekly paclitaxel and carboplatin plus bevacizumab as first-line treatment of metastatic triple-negative breast cancer. A multicenter phase II trial by the Hellenic oncology research group. Clin Breast Cancer *18(1)*: 88-94, 2018. PMID: 29153775. DOI: 10.1016/j.clbc.2017.10.013

25 O'Shaughnessy J, Osborne C, Pippen JE, Yoffe M, Patt D, Rocha C, Koo IC, Sherman BM and Bradley C: Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med *364(3)*: 205-214, 2011. PMID: 21208101. DOI: 10.1056/NEJMoa1011418

26 O'Shaughnessy J, Schwartzberg LS, Danso MA, Miller KD, Rugo HS, Neubauer M, Robert N, Hellerstedt B, Saleh M, Richards P, Specht JM, Yardley DA, Carlson RW, Finn RS, Charpentier E, Garcia-Ribas I and Winer EP: Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. J Clin Oncol *32(34)*: 3840-3847, 2014. PMID: 25349301. DOI: 10.1200/JCO.2014.55.2984

27 Miles DW, Diéras V, Cortés J, Duenne AA, Yi J and O'Shaughnessy J: First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol *24(11)*: 2773-2780, 2013. PMID: 23894038. DOI: 10.1093/annonc/mdt276

28 Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D and Davidson NE: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med *357(26)*: 2666-2676, 2007. PMID: 18160686. DOI: 10.1056/NEJMoa072113

29 Miles DW, Chan A, Dirix LY, Cortés J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chlistalla A and Romieu G: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol *28(20)*: 3239-3247, 2010. PMID: 20498403. DOI: 10.1200/JCO.2008.21.6457

30 Cameron D, Brown J, Dent R, Jackisch C, Mackey J, Pivot X, Steger GG, Suter TM, Toi M, Parmar M, Laeufle R, Im YH, Romieu G, Harvey V, Lipatov O, Pienkowski T, Cottu P, Chan A, Im SA, Hall PS, Bubuteishvili-Pacaud L, Henschel V, Deurloo RJ, Pallaud C and Bell R: Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol *14(10)*: 933-942, 2013. PMID: 23932548. DOI: 10.1016/S1470-2045(13)70335-8

31 Curigliano G, Pivot X, Cortés J, Elias A, Cesari R, Khosravan R, Collier M, Huang X, Cataruozolo PE, Kern KA and Goldhirsch A: Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer. Breast *22(5)*: 650-656, 2013. PMID: 23958375. DOI: 10.1016/j.breast.2013.07.037

32 Gradishar WJ, Kaklamani V, Sahoo TP, Lokanatha D, Raina V, Bondarde S, Jain M, Ro SK, Lokker NA and Schwartzberg L: A double-blind, randomised, placebo-controlled, phase 2b study evaluating sorafenib in combination with paclitaxel as a first-line therapy in patients with HER2-negative advanced breast cancer. Eur J Cancer *49(2)*: 312-322, 2013. PMID: 22954665. DOI: 10.1016/j.ejca.2012.08.005

33 Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, Blackwell K, Rugo H, Nabell L, Forero A, Stearns V, Doane AS, Danso M, Moynahan ME, Momen LF, Gonzalez JM, Akhtar A, Giri DD, Patil S, Feigin KN, Hudis CA, Traina TA and Translational Breast Cancer Research Consortium (TBCRC 011): Trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. Clin Cancer Res *19(19)*: 5505-5512, 2013. PMID: 23965901. DOI: 10.1158/1078-0432.CCR-12-3327

34 Costa RBL, Han SH and Gradishar WJ: Targeting the PI3K/AKT/mTOR pathway in triple-negative breast cancer: a review. Breast Cancer Res Treat *169(3)*: 397-406, 2018. PMID: 29417298. DOI: 10.1007/s10549-018-4697-y

35 Andre F, Job B, Dessen P, Tordai A, Michiels S, Liedtke C, Richon C, Yan K, Wang B, Vassal G, Delaloge S, Hortobagyi GN, Symmans WF, Lazar V and Pusztai L: Molecular characterization of breast cancer with high-resolution oligonucleotide comparative genomic hybridization array. Clin Cancer Res *15(2)*: 441-451, 2009. PMID: 19147748. DOI: 10.1158/1078-0432.CCR-08-1791

36 Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, Lehtiö J and Lewensohn R: Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. Ann Oncol *20(10)*: 1639-1646, 2009. PMID: 19549711. DOI: 10.1093/annonc/mdp062

37 Hervé MA, Buteau-Lozano H, Vassy R, Bieche I, Velasco G, Pla M, Perret G, Mourah S and Perrot-Applanat M: Overexpression of vascular endothelial growth factor 189 in breast cancer cells leads to delayed tumor uptake with dilated intratumoral vessels. Am J Pathol *172(1)*: 167-178, 2008. PMID: 18079435. DOI: 10.2353/ajpath.2008.070181

38 Linderholm BK, Lindahl T, Holmberg L, Klaar S, Lennerstrand J, Henriksson R and Bergh J: The expression of vascular endothelial growth factor correlates with mutant p53 and poor prognosis in human breast cancer. Cancer Res *61(5)*: 2256-2260, 2001. PMID: 11280795.

39 Ferrero JM, Hardy-Bessard AC, Capitain O, Lortholary A, Salles B, Follana P, Herve R, Deblock M, Dauba J, Atlassi M and Largillier R: Weekly paclitaxel, capecitabine, and bevacizumab with maintenance capecitabine and bevacizumab as first-line therapy for triple-negative, metastatic, or locally advanced breast cancer: Results from the GINECO A-TaXel phase 2 study. Cancer *122(20)*: 3119-3126, 2016. PMID: 27412268. DOI: 10.1002/cncr.30170

40 Bell R, Brown J, Parmar M, Toi M, Suter T, Steger GG, Pivot X, Mackey J, Jackisch C, Dent R, Hall P, Xu N, Morales L, Provencher L, Hegg R, Vanlemmens L, Kirsch A, Schneeweiss A, Masuda N, Overkamp F and Cameron D: Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer. Ann Oncol *28(4)*: 754-760, 2017. PMID: 27993816. DOI: 10.1093/annonc/mdw665

41 Symonds L, Linden H, Gadi V, Korde L, Rodler E, Gralow J, Redman M, Baker K, Wu V, Jenkins I, Kurland B, Garrison M, Smith J, Anderson J, Van Haelst C, Seattle Cancer Care Alliance Network Investigators and Specht J: Combined targeted therapies for first-line treatment of metastatic triple negative breast cancer-A phase II trial of weekly nab-paclitaxel and bevacizumab followed by maintenance targeted therapy with bevacizumab and erlotinib. Clin Breast Cancer *19(2)*: 283-296, 2019. PMID: 30737173. DOI: 10.1016/j.clbc.2018.12.008

42 Mery B, Rowinski E, Vallard A, Jacquin JP, Simoens X, Magné N and Doucey P: Advocacy for a new oncology research paradigm: The model of bevacizumab in triple-negative breast cancer in a French cohort study. Oncology *97(1)*: 1-6, 2019. PMID: 30939479. DOI: 10.1159/000499583

43 Kurozumi S, Inoue K, Matsumoto H, Fujii T, Horiguchi J, Oyama T, Kurosumi M and Shirabe K: Prognostic utility of tumor-infiltrating lymphocytes in residual tumor after neoadjuvant chemotherapy with trastuzumab for HER2-positive breast cancer. Sci Rep *9(1)*: 1583, 2019. PMID: 30733496. DOI: 10.1038/s41598-018-38272-1

44 Topalian SL, Taube JM, Anders RA and Pardoll DM: Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer *16(5)*: 275-287, 2016. PMID: 27079802. DOI: 10.1038/nrc.2016.36

45 Dill EA, Gru AA, Atkins KA, Friedman LA, Moore ME, Bullock TN, Cross JV, Dillon PM and Mills AM: PD-L1 expression and intratumoral heterogeneity across breast cancer subtypes and stages: An assessment of 245 primary and 40 metastatic tumors. Am J Surg Pathol *41(3)*: 334-342, 2017. PMID: 28195880. DOI: 10.1097/PAS.0000000000000780

46 Solinas C, Gombos A, Latifyan S, Piccart-Gebhart M, Kok M and Buisseret L: Targeting immune checkpoints in breast cancer: An update of early results. ESMO Open *2(5)*: e000255, 2017. PMID: 29177095. DOI: 10.1136/esmoopen-2017-000255

47 Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, Pusztai L, Pathiraja K, Aktan G, Cheng JD, Karantza V and Buisseret L: Pembrolizumab in patients with advanced triple-negative breast cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol *34(21)*: 2460-2467, 2016. PMID: 27138582. DOI: 10.1200/JCO.2015.64.8931

48 Dirix LU, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, Boccia R, Lippman ME, Somer R, Smakal M, Emens LA, Hrinczenko B, Edenfield W, Gurtler J, von Heydebreck A, Grote HJ, Chin K and Hamilton EP: Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. Breast Cancer Res Treat *167(3)*: 671-686, 2017. PMID: 29063313. DOI: 10.1007/s10549-017-4537-5

49 Adams S, Schmid IP, Rugo HS, Winer EP, Loirat D, Awada A, Cescon DW, Iwata H, Campone M, Nanda R, Hui R, Curigliano G, Toppmeyer D, O'Shaughnessy J, Loi S, Paluch-Shimon S, Tan AR, Card D, Zhao J, Karantza V and Cortés J: Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the Phase II KEYNOTE-086 study. Ann Oncol *30(3)*: 397-404, 2019. PMID: 30475950. DOI: 10.1093/annonc/mdy517

50 Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, Winer EP, Mukai H, Tamura K, Armstrong A, Liu MC, Iwata H, Ryvo L, Wimberger P, Rugo HS, Tan AR, Jia L, Ding Y, Karantza V and Schmid P: Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol *30(3)*: 405-411, 2019. PMID: 30475947. DOI: 10.1093/annonc/mdy518

51 Garmpis N, Damaskos C, Garmpi A, Kalampokas E, Kalampokas T, Spartalis E, Daskalopoulou A, Valsami S, Kontos M, Nonni A, Kontzoglou K, Perrea D, Nikiteas N and Dimitroulis D: Histone deacetylases as new therapeutic targets in triple-negative breast cancer: Progress and promises. Cancer Genomics Proteomics *14(5)*: 299-313, 2017. PMID: 28870998. DOI: 10.21873/cgp.20041

52 Damaskos C, Garmpis N, Valsami S, Kontos M, Spartalis E, Kalampokas T, Kalampokas E, Athanasiou A, Moris D, Daskalopoulou A, Davakis S, Tsourouflis G, Kontzoglou K, Perrea D, Nikiteas N and Dimitroulis D: Histone deacetylase inhibitors: An attractive therapeutic strategy against breast

cancer. Anticancer Res *37(1)*: 35-46, 2017. PMID: 28011471. DOI: 10.21873/anticanres.11286

53 Garmpi A, Garmpis N, Damaskos C, Valsami S, Spartalis E, Lavaris A, Patelis N, Margonis GA, Apostolou GK, Spartalis M, Andreatos N, Diamantis E, Tsivelekas K, Moschos MM, Nonni A, Tsourouflis G, Markatos K, Antoniou EA, Kontzoglou K, Nikiteas N and Dimitroulis D: Histone deacetylase inhibitors as a new anticancer option: How far can we go with expectations? J BUON *23(4)*: 846-861, 2018. PMID: 30358185.

54 Connolly RM, Li H, Jankowitz R C, Zhang Z, Rudek MA, Jeter SC, Slater SA, Powers P, Wolff AC, Fetting JH, Brufsky A, Piekarz R, Ahuja N, Laird PW, Shen H, Weisenberger DJ, Cope L, Herman JG, Somlo G, Garcia AA, Jones PA, Baylin SB, Davidson NE, Zahnow CA and Stearns V: Combination epigenetic therapy in advanced breast cancer with 5-azacitidine and entinostat: a phase II national cancer institute/stand up to cancer study. Clin Cancer Res *23(11)*: 2691-2701, 2017. PMID: 27979916. DOI: 10.1158/1078-0432.CCR-16-1729

55 Cancer Genome Atlas Network and Collaborators (357): Comprehensive molecular portraits of human breast tumours. Nature *490(7418)*: 61-70, 2012. PMID: 23000897. DOI: 10.1038/nature11412

56 Liu T, Yacoub R, Taliaferro-Smith LD, Sun SY, Graham TR, Dolan R, Lobo C, Tighiouart M, Yang L, Adams A and O'Regan RM: Combinatorial effects of lapatinib and rapamycin in triple-negative breast cancer cells. Mol Cancer Ther *10(8)*: 1460-1469, 2011. PMID: 21690228. DOI: 10.1158/1535-7163.MCT-10-0925

57 Cossu-Rocca P, Orru S, Muroni MR, Sanges F, Sotgiu G, Ena S, Pira G, Murgia L, Manca A, Uras MG, Sarobba MG, Urru S and De Miglio MR: Analysis of PIK3CA mutations and activation pathways in triple negative breast cancer. PLoS ONE *10(11)*: e0141763, 2015. PMID: 26540293. DOI: 10.1371/journal.pone.0141763

58 Ooms LM, Binge LC, Davies EM, Rahman P, Conway JR, Gurung R, Ferguson DT, Papa A, Fedele CG, Vieusseux JL, Chai RC, Koentgen F, Price JT, Tiganis T, Timpson P, McLean CA and Mitchell CA: The inositol polyphosphate 5-phosphatase PIPP regulates AKT1-dependent breast cancer growth and metastasis. Cancer Cell *28(2)*: 155-169, 2015. PMID: 26267533. DOI: 10.1016/j.ccell.2015.07.003

59 Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, Savage H, Guan Z, Hong R, Kassees R, Lee LB, Risom T, Gross S, Liederer BM, Koeppen H, Skelton NJ, Wallin JJ, Belvin M, Punnoose E, Friedman LS and Lin K: Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res *19(7)*: 1760-1772, 2013. PMID: 23287563. DOI: 10.1158/1078-0432.CCR-12-3072

60 Kim SB, Dent R, Im SA, Espié M, Blau S, Tan AR, Isakoff SJ, Oliveira M, Saura C, Wongchenko MJ, Kapp AV, Chan WY, Singel SM, Maslyar DJ and Baselga J; LOTUS investigators: Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol *18(10)*: 1360-1372, 2017. PMID: 28800861. DOI: 10.1016/S1470-2045(17)30450-3

61 Basho RK, Gilcrease M, Murthy RK, Helgason T, Karp DD, Meric-Bernstam F, Hess KR, Herbrich SM, Valero V, Albarracin C, Litton JK, Chavez-MacGregor M, Ibrahim NK, Murray JL 3rd, Koenig KB, Hong D, Subbiah V, Kurzrock R, Janku F and Moulder SL: Targeting the PI3K/AKT/mTOR pathway for the treatment of mesenchymal triple-negative breast cancer: Evidence from a phase 1 trial of mTOR inhibition in combination with liposomal doxorubicin and bevacizumab. JAMA Oncol *3(4)*: 509-515, 2017. PMID: 27893038. DOI: 10.1001/jamaoncol.2016.5281

62 Jovanovic B, Mayer IA, Mayer EL, Abramson VG, Bardia A, Sanders ME, Kuba MG, Estrada MV, Beeler JS, Shaver TM, Johnson KC, Sanchez V, Rosenbluth JM, Dillon PM, Forero-Torres A, Chang JC, Meszoely IM, Grau AM, Lehmann BD, Shyr Y, Sheng Q, Chen SC, Arteaga CL and Pietenpol JA: A randomized phase II neoadjuvant study of cisplatin, paclitaxel with or without everolimus in patients with stage II/III triple-negative breast cancer (TNBC): Responses and long-term outcome correlated with increased frequency of DNA damage response gene mutations, TNBC subtype, AR status, and Ki67. Clin Cancer Res *23(15)*: 4035-4045, 2017. PMID: 28270498. DOI: 10.1158/1078-0432.CCR-16-3055

63 Niemeier LA, Dabbs DJ, Beriwal S, Striebel JM and Bhargava R: Androgen receptor in breast cancer: expression in estrogen receptor-positive tumors and in estrogen receptor-negative tumors with apocrine differentiation. Mod Pathol *23(2)*: 205-212, 2010. PMID: 19898421. DOI: 10.1038/modpathol.2009.159

64 Barton VN, D'Amato NC, Gordon MA, Christenson JL, Elias A and Richer JK: Androgen receptor biology in triple negative breast cancer: a case for classification as AR+ or quadruple negative disease. Horm Cancer *6(5-6)*: 206-213, 2015. PMID: 26201402. DOI: 10.1007/s12672-015-0232-3

65 Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, Gradishar W, Schmid P, Winer E, Kelly C, Nanda R, Gucalp A, Awada A, Garcia-Estevez L, Trudeau ME, Steinberg J, Uppal H, Tudor IC, Peterson A and Cortes J: Enzalutamide for the treatment of androgen receptor-expressing triple-negative breast cancer. J Clin Oncol *36(9)*: 884-890, 2018. PMID: 29373071. DOI: 10.1200/JCO.2016.71.3495

66 Bonnefoi H, Grellety T, Tredan O, Saghatchian M, Dalenc F, Mailliez A, L'Haridon T, Cottu P, Abadie-Lacourtoisie S, You B, Mousseau M, Dauba J, Del Piano F, Desmoulins I, Coussy F, Madranges N, Grenier J, Bidard FC, Proudhon C, MacGrogan G, Orsini C, Pulido M and Gonçalves A: A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1). Ann Oncol *27(5)*: 812-818, 2016. PMID: 27052658. DOI: 10.1093/annonc/mdw067

67 De Vos M, Schreiber V and Dantzer F: The diverse roles and clinical relevance of PARPs in DNA damage repair: current state of the art. Biochem Pharmacol *84(2)*: 137-146, 2012. PMID: 22469522. DOI: 10.1016/j.bcp.2012.03.018

68 Krishnakumar R and Kraus WL: The PARP side of the nucleus: molecular actions, physiological outcomes, and clinical targets. Mol Cell *39(1)*: 8-24, 2010. PMID: 20603072. DOI: 10.1016/j.molcel.2010.06.017

69 Eustermann S, Wu WF, Langelier MF, Yang JC, Easton LE, Riccio AA, Pascal JM and Neuhaus D: Structural basis of detection and signaling of DNA single-strand breaks by human PARP-1. Molecular Cell *60(5)*: 742-754, 2015. PMID: 26626479. DOI: 10.1016/j.molcel.2015.10.032

70 Dawicki-McKenna JM, Langelier MF, DeNizio JE, Riccio AA, Cao CD, Karch KR, McCauley M, Steffen JD, Black BE and Pascal JM: PARP-1 activation requires local unfolding of an

autoinhibitory domain. Mol Cell *60(5)*: 755-768, 2015. PMID: 26626480. DOI: 10.1016/j.molcel.2015.10.013

71 Satoh MS and Lindahl T: Role of poly(ADP-ribose) formation in DNA repair. Nature *356(6367)*: 356-358, 1992. PMID: 1549180. DOI: 10.1038/356356a0

72 Lord CJ and Ashworth A: PARP inhibitors: synthetic lethality in the clinic. Science *355(6330)*: 1152-1158, 2017. PMID: 28302823. DOI: 10.1126/science.aam7344

73 Llombart-Cussac A, Bermejo B, Villanueva C, Delaloge S, Morales S, Balmaña J, Amillano K, Bonnefoi H, Casas A, Manso L, Roché H, Gonzalez-Santiago S, Gavilá J, Sánchez-Rovira P, Di Cosimo S, Harbeck N, Charpentier E, Garcia-Ribas I, Radosevic-Robin N, Aura C and Baselga J: SOLTI NeoPARP: a phase II randomized study of two schedules of iniparib plus paclitaxel versus paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer. Breast Cancer Res Treat *154(2)*: 351-357, 2015. PMID: 26536871. DOI: 10.1007/s10549-015-3616-8

74 Kummar S, Wade JL, Oza AM, Sullivan D, Chen AP, Gandara DR, Ji J, Kinders RJ, Wang L, Allen D, Coyne GO, Steinberg SM and Doroshow JH: Randomized phase II trial of cyclophosphamide and the oral poly (ADP-ribose) polymerase inhibitor veliparib in patients with recurrent, advanced triple-negative breast cancer. Invest New Drugs *34(3)*: 355-363, 2016. PMID: 26996385. DOI: 10.1007/s10637-016-0335-x

75 Gherardi E, Birchmeier W, Birchmeier C and Vande Woude G: Targeting MET in cancer: rationale and progress. Nat Rev Cancer *12(2)*: 89-103, 2012. PMID: 22270953. DOI: 10.1038/nrc3205

76 Beviglia L, Matsumoto K, Lin CS, Ziober BL and Kramer RH: Expression of the c-Met/HGF receptor in human breast carcinoma: Correlation with tumor progression. Int J Cancer *74(3)*: 301-309, 1997. PMID: 9221809. DOI: 10.1002/(sici)1097-0215(19970620)74:3<301::aid-ijc12>3.0.co;2-e

77 Jin L, Fuchs A, Schnitt SJ, Yao Y, Joseph A, Lamszus K, Park M, Goldberg ID and Rosen EM: Expression of scatter factor and c-met receptor in benign and malignant breast tissue. Cancer *79(4)*: 749-760, 1997. PMID: 9024713. DOI: 10.1002/(sici)1097-0142(19970215)79:4<749::aid-cncr12>3.0.co;2-#

78 Lengyel E, Prechtel D, Resau JH, Gauger K, Welk A, Lindemann K, Salanti G, Richter T, Knudsen B, Vande Woude GF and Harbeck N: C-Met overexpression in node-positive breast cancer identifies patients with poor clinical outcome independent of Her2/neu. Int J Cancer *113(4)*: 678-682, 2005. PMID: 15455388. DOI: 10.1002/ijc.20598

79 Raghav KP, Wang W, Liu S, Chavez-MacGregor M, Meng X, Hortobagyi GN, Mills GB, Meric-Bernstam F, Blumenschein GR Jr and Gonzalez-Angulo AM: cMET and phospho-cMET protein levels in breast cancers and survival outcomes. Clin Cancer Res *18(8)*: 2269-2277, 2012. PMID: 22374333. DOI: 10.1158/1078-0432.CCR-11-2830

80 Tuck AB, Park M, Sterns EE, Boag A and Elliott BE: Coexpression of hepatocyte growth factor and receptor (Met) in human breast carcinoma. Am J Pathol *148(1)*: 225-232, 1996. PMID: 8546209.

81 Yamashita J, Ogawa M, Yamashita S, Nomura K, Kuramoto M, Saishoji T and Shin S: Immunoreactive hepatocyte growth factor is a strong and independent predictor of recurrence and survival in human breast cancer. Cancer Res *54(7)*: 1630-1633, 1994. PMID: 8137271.

82 Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC and Joly AH: Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther *10(12)*: 2298-2308, 2011. PMID: 21926191. DOI: 10.1158/1535-7163.MCT-11-0264

83 Tolaney SM, Ziehr D R, Guo H, Ng MR, Barry WT, Higgins MJ, Isakoff SJ, Brock JE, Ivanova EV, Paweletz CP, Demeo MK, Ramaiya NH, Overmoyer BA, Jain RK, Winer EP and Duda DG: Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients. Oncologist *22(1)*: 25-32, 2016. PMID: 27789775. DOI: 10.1634/theoncologist.2016-0229

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