

Current Treatment Options of Metastatic Breast Cancer

Subjects: **Oncology**

Contributor: Pauline H. Lin , George Laliotis

breast cancer subtypes and classifications are well-characterized and personalized for each patient group. To this extent, given the distinct classification of breast cancer, the therapeutic decision and algorithms of metastatic disease is largely dependent on its molecular subclassification and on HR and HER-2 expression status.

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1. Treatment of Hormone Receptor Positive mBC

The treatment of HR⁺ mBC is defined by numerous clinical factors. These factors include the menopausal status (pre- or post-) at the time of metastatic disease, the recurrence of metastatic disease, the time interval between each recurrence episode, the status of specific concurrent mutations (e.g., *PIK3CA* and *BRCA* mutations), the presence of bone or visceral metastatic disease and the overall performance status. It is also worth mentioning that in clinical practice, de novo metastatic disease, recurrence after more than 12 months of adjuvant therapy and bone metastasis, fall into the endocrine-sensitive subgroups of patients [1]. Lastly, it is important to note that clinicians should obtain clinical tumor samples at baseline and at the treatment naive stage, since the therapeutic decisions depend on Next Generation Sequencing, transcriptomic and mutational characteristics of the tumor. This allows the researchers to compare the biological development of the early stage versus the metastatic tumor, to better guide clinical decisions [2].

The main clinical first line recommendation depends on the recurrence time interval and the menopausal status (**Figure 1**). In estrogen-sensitive cases, the administration of CDK4/6 with an aromatase inhibitor, should be considered the standard-of-care option in these patients [3][4]. CDK4/6 inhibitors have been approved more than 6 years ago for metastatic ER⁺ metastatic disease, based on the findings of PALOMA-1 trial [4]. Furthermore, the combination of CDK4/6i, ribociclib plus estrogen therapy significantly improved overall survival (OS) relative to estrogen therapy alone, according to the important phase III MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials [5]. On the other hand, regarding the estrogen-resistant cases or in cases with no suitability for aromatase inhibitors, CDK4/6 inhibitors should be combined with fulvestrant, an estrogen degrader [6][7][8].

HR+/HER2- Metastatic Breast Cancer

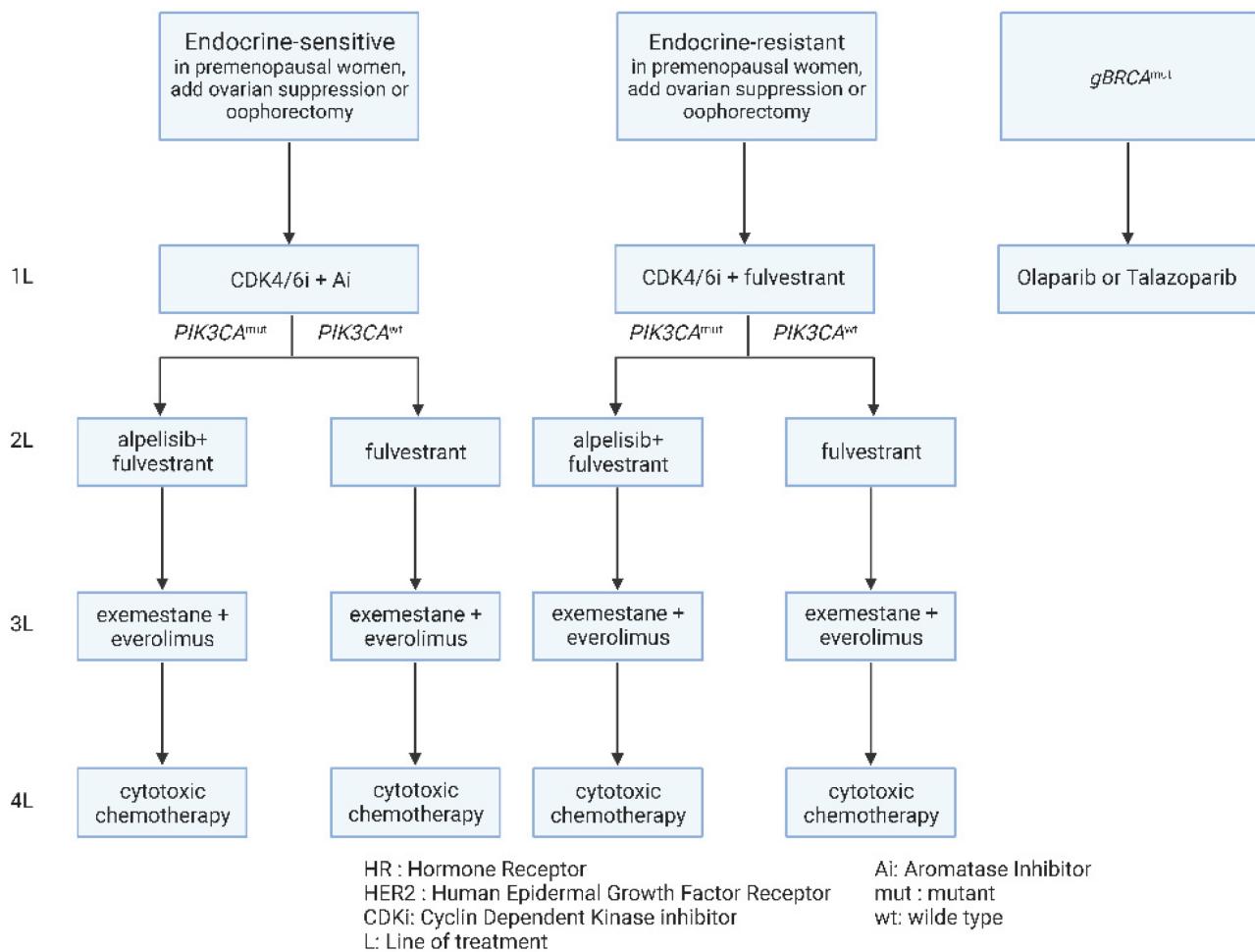


Figure 1. Current therapeutic algorithm for the management of HR+/HER-2- mBC. Proposed therapeutic algorithm for patients with HR+/HER-2- metastatic breast cancer [9]. The abbreviations of the terms used in the figure are outlined in the lower part of the algorithm.

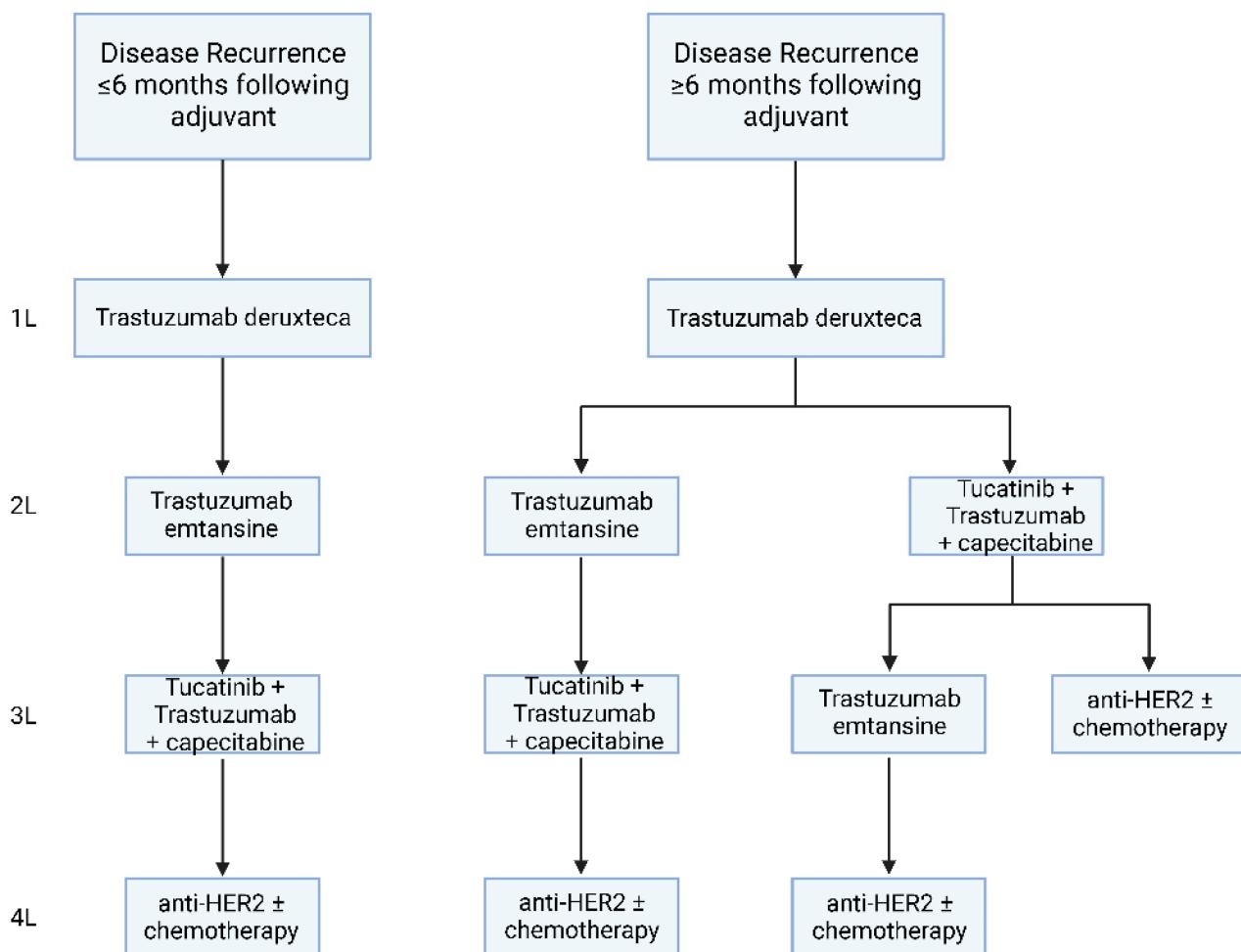
Following disease progression upon first-line treatment, in the case of the estrogen-resistant groups, *PIK3CA* mutational status defines the therapeutic decisions. In patients harboring *PIK3CA* mutations, fulvestrant can be combined with alpelisib, a PIK3α specific inhibitor [10]. Alpelisib has been approved as a combination therapy with fulvestrant for *PIK3CA* mutated ER+/HER-2- metastatic breast cancer, upon the findings of SOLAR-1 clinical trial [11]. On the other hand, the estrogen-sensitive patients with recurrence on CDK4/6 inhibitors, can be treated with an aromatase inhibitor in combination with the mTOR inhibitor, everolimus [10] (Figure 1). Beyond these therapeutic strategies, subsequent lines of therapy include cytotoxic chemotherapy for all patients [12][13][14] (Figure 1). On a different note, the administration of the same chemotherapeutic regimen upon recurrence, is not recommended, with the exemption of taxanes that can be used upon early and metastatic disease [1][12][13].

2. Treatment of HER-2 Positive mBC

Traditionally, the HER-2⁺ breast cancer has been a more aggressive clinical subtype compared to the HR⁺ subtype, with poorer clinical outcomes [15][16]. Nevertheless, due to advancements in drug development and introduction of HER-2 targeting therapies, such as trastuzumab and trastuzumab-emtansine (T-DM1), the median survival of these patients has been increased to 5 years, and up to 8 years in 30–40% of the cases [16][17].

As far as the therapeutic strategies of HER-2⁺ metastatic breast cancer are concerned, the main clinical factor that determines the first-line therapy option is the time of recurrence after adjuvant therapy (**Figure 2**). To begin with, based on recent guidelines and experts' opinion, the combination of trastuzumab and pertuzumab with a single chemotherapeutic reagent, should be considered as the first-line of treatment in patients with recurrence after 6 months of adjuvant treatment [18] (**Figure 2**). The usage of pertuzumab with the widely used trastuzumab, has been validated through the large phase III CLEOPARTA trial, which compared the addition of pertuzumab versus placebo, in HER-2⁺ mBC patients that have received trastuzumab, and docetaxel [19][20]. Specifically for CLEOPATRA trial, the OS in the pertuzumab receiving group was 56.5 months (95% CI, 49.3 to not reached), compared to 40.8 months (95% CI, 35.8 to 48.3) in the group receiving the placebo combination (HR = 0.68; 95% CI, 0.56 to 0.84; $p < 0.001$) [19][20]. The therapeutic regimen of pertuzumab, is a monoclonal antibody that inhibits the dimerization of HER-2 by binding the extracellular domain II of the protein [21]. Due to its targeting of HER-2, the trastuzumab-pertuzumab combination provides a multi-level inhibition against these tumors, radically increasing therapeutic responses [22][23][24].

HER2⁺ Metastatic Breast Cancer



HER2 : Human Epidermal Growth Factor Receptor

L: Line of treatment

Mets: Metastatic sites

Figure 2. Current therapeutic algorithm for the management of HER-2⁺ mBC. Proposed therapeutic algorithm for patients with HER-2⁺ metastatic breast cancer [16]. The abbreviations of the terms used in the figure are outlined in the lower part of the algorithm.

For patients that were presented with a recurrence in less than 6 months or progressed on trastuzumab and/or pertuzumab-based chemotherapy, the administration of T-DM1 should be considered as the second-line of choice (Figure 2). The FDA-approved T-DM1 regimen consists of the anti-HER-2 antibody trastuzumab, stably linked with microtubule-inhibitory agent DM1, in a 1:3.5 ratio [25][26]. This chemical structure allows specific drug delivery to HER2-overexpressing breast cancer cells intracellularly. The efficacy and safety profiling of T-DM1, is based on the results of EMILIA [25] and TH3RESA [26][27] phase III clinical trials, which compared T-DM1 with lapatinib plus capecitabine or chemotherapy plus trastuzumab, respectively.

Beyond targeted anti-HER-2 therapies, there are several drug regimens that have been FDA approved for patients that have progressed upon trastuzumab, pertuzumab and T-DM1. Nevertheless, there is no definite clinical algorithm for the management of these patients and the optimal sequence of drug administration remains largely unclear, depending mainly on the clinical characteristics, site of progression and toxicity profile. As far as these therapeutic regimens are concerned, tucatinib is a Tyrosine Kinase Inhibitor (TKI) with biochemical high specificity against HER-2 kinase domain [28]. The efficacy of tucatinib in combination with trastuzumab and capecitabine, was addressed in the phase II HER2CLIMB trial [29][30], leading to approval of this combination in 2020, for patients with advanced or metastatic HER-2⁺ mBC and have previously received anti-HER-2 based therapies. Notably, based on the results of this trial, on the arm of patients with brain metastasis, the 1-year PFS was 24.9%, compared to 0% in the placebo group [31][32], with subsequent increase in the reported quality of life [33], making this combination preferred for the brain metastatic disease (Figure 2). At this point, it is important to mention the recent developments in HER-2 low mBC. HER-2 low expression is generally defined as a IHC score of 1+ or as an IHC score of 2+ with negative results on in situ hybridization [32]. Based on the DESTINY-Breast04 clinical phase III trial, trastuzumab deruxtecan was compared with chemotherapy of physician's choice. In this cohort, the PFS in the trastuzumab deruxtecan group was 9.9 months and 5.1 months in the physician's choice group (HR = 0.50; $p < 0.001$), while the OS was 23.4 months and 16.8 months, respectively (HR = 0.64; $p = 0.001$) [33][34]. Based on these results, trastuzumab deruxtecan has been approved for the treatment of HER2-Low mBC. Furthermore, based on a recent clinical phase III trial, DESTINY-Breast03, trastuzumab deruxtecan achieved significantly longer progression free survival compared to trastuzumab emtansine (TDM-1) (HR = 0.55; 95% CI, 0.36 to 0.86), in HER-2⁺ mBC patient who progressed following treatment with anti-HER2 antibodies and a taxane [35][36].

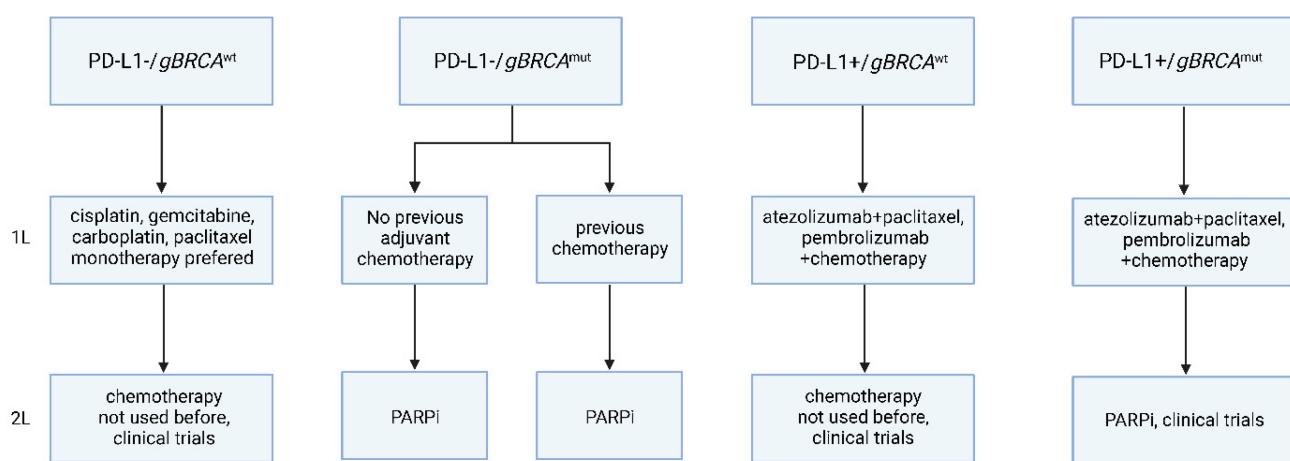
Another FDA-approved oral TKI, neratinib, irreversibly inhibits HER-1, HER-2 and HER-4, promoting cell death through ferroptosis induction [37]. NALA phase III clinical trial addresses the combination of neratinib with capecitabine with lapatinib plus capecitabine [38][39]. Overall, the neratinib plus capecitabine treatment significantly prolonged PFS and reduced the percentage of patients with brain metastatic disease that required CNS intervention [38][39]. Based on these results, neratinib plus capecitabine combination is approved for patients with advanced or metastatic HER-2⁺ mBC after two or more anti-HER-2 lines of therapy. Nevertheless, neratinib was characterized from grade 3 diarrhea, even though the patients received mandatory anti-diarrheal prophylaxis during the research. More importantly, the researchers need to mention that this clinical observation has been radically improved with the new dose escalation approaches, based on the CONTROL trial [40]. Last but not least, lapatinib is another FDA-approved oral TKI, reversibly inhibiting HER-1, HER-2 and EGFR. The results of a phase III clinical trial assessing the efficacy of lapatinib plus capecitabine compared to capecitabine alone, demonstrated that lapatinib treatment prolongs the progression interval, without increasing the observed side effects [41]. These results led to the FDA approval of lapatinib plus capecitabine for patients with HER-2⁺ mBC who had progressed upon treatment with anthracycline, taxanes, and trastuzumab (Figure 2).

3. Treatment of Triple Negative mBC

Compared to the two latter subtypes of breast cancer, Triple Negative Breast Cancer (TNBC) is characterized with significantly high risk of recurrence after treatment. Even though the majority of the patients presented with metastatic manifestations over the course of the disease in the past, in recent years the approval of new emerging therapies has significantly prolonged the survival and the pathological complete response (pCR) in this subgroup [42]. To begin with, the researchers need to mention several recent landmark clinical trials that have shaped the clinical management of TNBC mBC. Firstly, based on the ASCENT clinical trials [43] for the treatment of TNBC mBC, patients were treated with sacituzumab govitecan versus single-agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine). Sacituzumab govitecan is an antibody–drug conjugate composed of SN-38 (topoisomerase I inhibitor) and an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), coupled through a linker. Based on this research, the median progression-free survival in patients treated with sacituzumab govitecan was 5.6 months (95% CI, 4.3 to 6.3) and 1.7 months (95% CI, 1.5 to 2.6) compared with those treated with chemotherapy alone (HR = 0.41; 95% CI, 0.32 to 0.52; $p < 0.001$) [43].

Nevertheless, TNBC is also characterized by extensive chemo-sensitivity with high rates of pathological complete response after chemotherapy among the other breast cancer subtypes [44]. Based on recent advancements in molecular target identification, Programmed death-ligand 1 (PD-L1) and germline Breast Cancer gene (gBRCA) mutational status have been identified as main determinants of therapeutic approaches (Figure 3). To begin with, in patients with negative PD-L1 expression and wild type BRCA status, cytotoxic chemotherapy agents are considered the treatment of choice [44][45][46], especially in patients who have not received this chemotherapy class before [44][45][46]. Even though chemotherapy is associated with higher clinical response rates, and it is preferred in patients with extensive visceral disease, it has not been proved to prolong the overall and progression-free survival [12][13].

TNBC Metastatic Breast Cancer



TNBC : Triple Negative Breast Cancer

L: Line of treatment

PD-L1 : Program Death-Ligand 1

gBRCA : germline BRCA mutation

wt : wild type

BRCA: Breast Cancer Gene

mut : mutated

PARPi : Poly Adenosine Diphosphate-

Ribose Polymerase inhibitor

Figure 3. Current therapeutic algorithm for the management of TNBC mBC. Proposed therapeutic algorithm for patients with Triple Negative metastatic breast cancer [43][44]. The abbreviations of the terms used in the figure are outlined in the lower part of the algorithm.

In patients harboring germline *BRCA* mutations, the therapeutic approach includes the usage of platin-based chemotherapy and/or PARP inhibitors. The *BRCA* genes (*BRCA1*, *BRCA2*) encode proteins that participate in the DNA double-stranded breaks and homologous recombination, with their mutations to induce significant impairment in the DNA repair system [47]. On the one hand, platin-based chemotherapy introduces multiple single-stranded breaks in DNA, leading to synthetic lethality and apoptosis in *gBRCA^{mut}* tumors, due to their inability to repair DNA breaks [47]. On the other hand, Polyadenosine Diphosphate-Ribose Polymerase (PARP) complex maintains cellular homeostasis through a plethora of biological functions, that include the DNA repair system [48]. Similar to platin, PARP inhibitors interfere with the DNA damage response, leading to synthetic lethality in *gBRCA^{mut}* patients [49][50]. The effectiveness of platinum-based chemotherapy in *HR⁺/HER-2⁻* and TNBC patients was proved in the TNT phase III clinical trial, in which carboplatin significantly enhanced the response rates (68% vs. 33%) and prolonged the PFS (6.8 vs. 4.4 months), compared to docetaxel [51]. In the case of PARP inhibitors, two large phase III clinical trials, namely the OLYMPIAD and EMBRACA studies, demonstrated significantly prolonged PFS in the PARP inhibitor group, compared to chemotherapy (7.0 vs. 4.2 months in OLYMPIAD and 8.6 vs. 5.6 months in EMBRACA) [52][53]. Notably, in both trials, PARP inhibition was associated with grade 3 hematological toxicities. These studies led to the FDA approval of talazoparib and olaparib for patients with *gBRCA^{mut}/HER-2⁻* metastatic breast cancer in 2018.

On the other hand, due to its unique biological background, TNBC is considered highly immunogenic, a characteristic linked with its high tumor mutational burden (TMB), among the other breast cancer subtypes [54]. To this extent, given that high TMB is associated with the generation of neoantigens and immune cell infiltration in the tumor-microenvironment [55], the effectiveness of immune checkpoint inhibitors in the clinical outcomes of TNBC patients has been previously investigated. In the large stage III clinical trial Impassion 130, the combination of nab-paclitaxel with atezolizumab was compared to nab-paclitaxel alone in patients with metastatic TNBC. Based on the results of this trial, the atezolizumab/nab-paclitaxel combination significantly prolonged the PFS compared to nab-paclitaxel alone (7.2 vs. 5.5 months, HR = 0.8, *p* = 0.002), without demonstrating any benefit in the OS (21.3 vs. 17.6 months, HR = 0.84, *p* = 0.08) [56]. Notably, specifically in the PD-L1⁺ patient subgroup, the investigated combination achieved prolonged PFS (7.5 vs. 5.0 months, HR = 0.62, *p* < 0.001) and OS (25.0 vs. 15.5 months, HR = 0.62, *p* < 0.001), compared to monotherapy, with parallel toxicity profiling [56][57]. It is important to mention that regardless of these results, the atezolizumab/nab-paclitaxel combination approval for metastatic TNBC has been withdrawn by the FDA. More importantly, according to the KEYNOTE-355 clinical phase III, the addition of pembrolizumab to chemotherapy led to significantly longer PFS than chemotherapy alone, in patients with PD-L1⁺ (CPS > 10) mBC TNBC (HR = 0.73; 95% CI, 0.55 to 0.95; *p* = 0.0185) [57][58]. Further clinical studies with a larger patient cohort are needed to address its effectiveness in PD-L1⁺ TNBC patients [58] (Figure 3). Given that TNBC has a higher frequency metastasizing in the brain, a summary of proposed therapeutic choices and indications for brain metastasis mBC are outlined in Table 1.

Table 1. Summary of Brain Metastasis Treatment.

Indication	Therapy
Single, surgically accessible metastasis with favorable prognosis	Surgical resection [59][60][61][62][63][64] Whole brain radiotherapy (WBRT) [65]
Single, surgically inaccessible metastasis with favorable prognosis	Stereotactic Radiosurgery (SRS) with WBRT [66][67][68][69]
Multiple < 3 cm brain metastases, with favorable prognosis	SRS alone [70] Adjunctive WBRT [71]
Poor prognosis/PS	WBRT vs. SRS [72][73]
Patients with progressive extracranial disease or no feasible local therapy option	Systemic therapy based on subtypes [74]

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