

Hormonal and Targeted Therapies for Premenopausal Hormone Receptor Positive (HR+), HER2 Negative (HER2-) Women

The sequence of providing hormonal (endocrine) therapy for premenopausal, HR+ HER2- patients is as follows, based upon NCCN 2020 Guidelines.*

Upon diagnosis, an **LHRH agonist** (Luteinizing Hormone-Releasing Hormone agonist) **such as Zoladex** (Goserelin), **Lupron** (Leuprolide) or **Trelstar** (Triptorelin) is recommended along with hormonal (endocrine) therapy. LHRH agonists work by telling the pituitary gland located in the brain to stop producing luteinizing hormone, which in women stimulates the ovaries to release estrogen. This process of limiting the production of estrogen is referred to as “**ovarian suppression.**” (*Instead of initially taking an LHRH agonist, some patients may opt to undergo an oophorectomy, which involves the surgical removal of both ovaries (referred to as “**ovarian ablation**”) at which point they become postmenopausal and follow the guidelines for postmenopausal women.*

As you can see below, you have a choice of taking single drugs or a combination of drugs, with combination drugs generally causing more side effects but potentially being more effective. You'll want to discuss these options with your doctor and check your insurance coverage, since it's possible that some of the combination drug regimens listed below may not be covered by your insurance, or they may be expensive.

First Line Hormonal and Targeted Treatment Options:

- **The combination of a CDK4/6 inhibitor such as Ibrance** (Palbociclib), **Kisqali** (Ribociclib) **or Verzenio** (Abemaciclib) **with either an Aromatase Inhibitor (Letrozole [Femara], Arimidex [Anastrozole], or Aromasin [Exemestane]) or with Faslodex** (Fulvestrant) **is the current standard-of-care as initial treatment, along with an LHRH agonist.**
- **An Aromatase Inhibitor** alone (but **with an LHRH agonist**).
- **Faslodex with either Letrozole or Arimidex (with an LHRH agonist).**
- **Faslodex** alone (but **with an LHRH agonist**).
- **Tamoxifen** (Nolvadex) **or Fareston** (Toremifene) **with an LHRH agonist** is also a first line therapeutic option.

After progression if you still have your ovaries, **an oophorectomy** may be appropriate because it will remove a key source of estrogen from being produced by your body. At that point, you would be considered postmenopausal and would follow the hormonal therapy guidelines for postmenopausal patients. If you decide against an oophorectomy, the therapies below can be considered.

Second Line Hormonal and Targeted Treatment Options depend upon what endocrine therapy you have previously taken:

- **Possibly any of the above therapies.**
- **Piqray** (Alpelisib) **in combination with Faslodex and an LHRH agonist if your cancer has a PI3K mutation** (*if you were initially premenopausal when diagnosed, you must be deemed postmenopausal to be eligible for Piqray. More about Piqray below*).
- **Talzenna** (Talazoparib) or **Lynparza** (Olaparib) if you have a germline (inherited) BRCA1 or BRCA2 mutation (*more about this below*).

- **With an LHRH agonist, Afinitor (Everolimus) can be taken in combination with either Aromasin, Faslodex, or Tamoxifen.**

Later-Line Hormonal and Targeted Treatment Options:

- **Possibly any of the above therapies** (although not all options are widely used in a third- or later-line setting).
- **Verzenio alone** (after disease progression on endocrine therapy and prior chemotherapy for MBC).

You may want to reconsider having an oophorectomy and possibly taking different endocrine-based therapy. Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva** (Denosumab) or **Zometa** (Zoledronic acid) in addition to your other therapy.

If your cancer has progressed on first-line hormonal therapy and has a PI3K mutation, then you are eligible to take **Piqray** (Alpelisib) tablets along with **Faslodex** and an **LHRH agonist** if you are now deemed to be postmenopausal through ovarian suppression. *(If you had your ovaries removed, you're officially postmenopausal and should refer to the section "Hormonal and Targeted Therapies for Postmenopausal Hormone Receptor Positive (HR+), HER2 Negative (HER2-) Women."* Piqray is a PI3K inhibitor that has shown a clinically meaningful benefit in treating patients with this type of breast cancer. A diagnostic test called "Therascreen PI3KCA RGQ PCR Kit," has been FDA-approved to detect the mutation in a tissue and/or a liquid biopsy.

If you have a germline BRCA mutation, you may want to speak with your doctor about taking a PARP inhibitor such as **Talzenna** (Talazoparib) or **Lynparza** (Olaparib), which are FDA-approved for HER2 negative MBC patients with a BRCA mutation. Talzenna or Lynparza is generally prescribed for hormone receptor positive, HER2 negative MBC patients with a BRCA mutation after first- or second-line therapy has failed.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you've progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda** (Pembrolizumab) is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you've progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi** (Larotrectinib) and **Rozlytrek** (Entrectinib) – oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

**The above hormonal treatment options are recommended for patients who are not experiencing "visceral crisis" (severe organ dysfunction and rapid progression of disease). For patients who have visceral crisis, chemotherapy may be used straightaway to control the disease, after which endocrine-based therapy may be a viable option.*

Hormonal and Targeted Therapies for Postmenopausal Hormone Receptor Positive (HR+), HER2 Negative (HER2-) Women

The sequence of providing hormonal (endocrine) therapy for postmenopausal, HR+ HER2- patients will vary, since much of it depends upon what - if any - hormonal therapy drugs you've previously taken and how recently you've taken them.*

As per NCCN 2020 guidelines, you have a choice of taking single drugs or a combination of drugs, with combination drugs generally causing more side effects but potentially being more effective. You'll want to discuss these options with your doctor and check your insurance coverage, since it's possible that some of the combination drug regimens listed below may not be covered by your insurance, or they may be expensive.

First Line Hormonal and Targeted Treatment Options:

- **The combination of a CDK4/6 inhibitor such as Ibrance (Palbociclib), Kisqali (Ribociclib) or Verzenio (Abemaciclib) with either an Aromatase Inhibitor (Letrozole [Femara], Arimidex [Anastrozole], or Aromasin [Exemestane]) or with Faslodex (Fulvestrant) is the current standard-of-care as initial treatment.**
- **An Aromatase Inhibitor** alone.
- **Faslodex (Fulvestrant) with either Letrozole or Arimidex.**
- **Faslodex** alone.
- **Tamoxifen (Nolvadex) or Fareston (Toremifene) alone (*rarely used as a first-line therapy*).**

Second Line Hormonal and Targeted Treatment Options depend upon what endocrine therapy you have previously taken:

- **Possibly any of the above therapies.**
- **Piqray (Alpelisib) in combination with Faslodex if your cancer has a PI3K mutation (*more about this below*).**
- **Talzenna (Talazoparib) or Lynparza (Olaparib) if you have a germline (inherited) BRCA1 or BRCA2 mutation (*more about this below*).**
- **Afinitor (Everolimus) with either Aromasin, Faslodex, or Tamoxifen.**

Third and Fourth Line Hormonal and Targeted Treatment Options depend upon what endocrine therapy you have previously taken:

- **Possibly any of the above therapies** (although not all options are widely used in a third- or later-line setting).
- **Verzenio alone (*after disease progression on endocrine therapy and prior chemotherapy for MBC*).**
- **Either Ethinyl Estradiol, Megace (Megestrol Acetate), or Halotestin (Fluoxymesterone).**

Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has

regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva** (Denosumab) or **Zometa** (Zoledronic acid) in addition to your other therapy.

If your cancer has progressed on first-line hormonal therapy and has a PI3K mutation, then you are eligible to take **Piqray** (Alpelisib) tablets along with **Faslodex**. Piqray is a PI3K inhibitor that has shown a clinically meaningful benefit in treating patients with this type of breast cancer. A diagnostic test called “Therascreen PI3KCA RGQ PCR Kit,” has been FDA-approved to detect the mutation in a tissue and/or a liquid biopsy.

If you have a germline BRCA mutation, you may want to speak with your doctor about taking a PARP inhibitor such as **Talzenna** (Talazoparib) or **Lynparza** (Olaparib), which are FDA-approved for HER2 negative MBC patients with a BRCA mutation. Talzenna or Lynparza is generally prescribed for hormone receptor positive, HER2 negative MBC patients with a BRCA mutation after first- or second-line therapy has failed.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you’ve progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda** (Pembrolizumab) is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you’ve progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi** (Larotrectinib) and **Rozlytrek** (Entrectinib) – oral tyrosine kinase inhibitors that act as an “on” or “off” switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

**The above hormonal treatment options are recommended for patients who are not experiencing “visceral crisis” (severe organ dysfunction and rapid progression of disease). For patients who have visceral crisis, chemotherapy may be used straightaway to control the disease, after which endocrine-based therapy may be a viable option.*

Hormonal and Targeted Therapies for Hormone Receptor Positive (HR+), HER2 Negative (HER2-) Men

The sequence of providing hormonal (endocrine) therapy for male HR+ HER2- patients may vary, since much of it depends upon what - if any - hormonal therapy drugs you've previously taken and how recently you've taken them.*

An **LHRH agonist** (Luteinizing Hormone-Releasing Hormone agonist - also known as a Gonadotropin-Releasing Hormone [GnRH] agonist) such as **Zoladex** (Goserelin), **Lupron** (Leuprolide) or **Trelstar** (Triptorelin) is **recommended for men who will be taking an Aromatase Inhibitor or Faslodex**. The agonist works by suppressing the production of testosterone and estrogen.

As per NCCN 2020 guidelines, you have a choice of taking single drugs or a combination of drugs, with combination drugs generally causing more side effects but potentially being more effective. You'll want to discuss the various options with your doctor and check your insurance coverage, since it's possible that some of the combination drug regimens listed below may not be covered by your insurance, or they may be expensive. In general, the therapies available to men with HR+, HER2- MBC closely resemble those for postmenopausal women.

First Line Hormonal and Targeted Treatment Options:

- **The combination of a CDK4/6 inhibitor such as Ibrance (Palbociclib), Kisqali (Ribociclib) or Verzenio (Abemaciclib) with either an Aromatase Inhibitor (Letrozole [Femara], Arimidex [Anastrozole], or Aromasin [Exemestane]) or with Faslodex (Fulvestrant) and with an LHRH agonist is the current standard-of-care as initial treatment.** *In April 2019, the FDA specifically approved Ibrance in combination with an Aromatase Inhibitor or Faslodex as initial therapy for male HR+, HER2- MBC patients..*
- An Aromatase Inhibitor without a CDK4/6 inhibitor (but with an LHRH agonist).
- Faslodex with either Letrozole or Arimidex.
- Faslodex either in combination with a CDK4/6 inhibitor or alone (but with an LHRH agonist).
- Tamoxifen (Nolvadex) or Fareston (Toremifene) with an LHRH agonist.

Second Line Hormonal and Targeted Treatment Options depend upon what endocrine therapy you have previously taken:

- Possibly any of the above therapies.
- **Piqray** (Alpelisib) in combination with Faslodex and an LHRH agonist if your cancer has a **PI3K mutation** (*more about this below*).
- **Talzenna** (Talazoparib) or **Lynparza** (Olaparib) if you have a germline (inherited) BRCA1 or BRCA2 mutation (*more about this below*).
- An LHRH agonist with **Afinitor** (Everolimus) and either Aromasin, Faslodex, or Tamoxifen.

Third and Fourth Line Hormonal and Targeted Treatment Options depend upon what endocrine therapy you have previously taken:

- Possibly any of the above therapies (although not all options are widely used in a third or later line setting).
- **Verzenio alone** (*after disease progression on endocrine therapy and prior chemotherapy for MBC*).

- **Either Ethinyl Estradiol, Megace (Megestrol Acetate), or Halotestin (Fluoxymesterone).**

Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva** (Denosumab) or **Zometa** (Zoledronic acid) in addition to your other therapy.

If your cancer has progressed on first-line hormonal therapy and has the PI3K mutation, then you are eligible to take **Piqray** (Alpelisib) tablets along with **Faslodex and an LHRH agonist**. Piqray is a PI3K inhibitor that has shown a clinically meaningful benefit in treating patients with this type of breast cancer. A diagnostic test called “Therascreen PI3KCA RGQ PCR Kit,” has been FDA-approved to detect the mutation in a tissue and/or a liquid biopsy.

If you have a germline BRCA mutation, you may want to speak with your doctor about taking a PARP inhibitor such as **Talzenna** (Talazoparib) or **Lynparza** (Olaparib), which are FDA-approved for HER2 negative MBC patients with a BRCA mutation. Talzenna or Lynparza is generally prescribed for hormone receptor positive, HER2 negative MBC patients with a BRCA mutation after first- or second-line therapy has failed.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you’ve progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda** (Pembrolizumab) is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you’ve progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi** (Larotrectinib) and **Rozlytrek** (Entrectinib) – oral tyrosine kinase inhibitors that act as an “on” or “off” switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

**The above hormonal treatment options are recommended for patients who are not experiencing “visceral crisis” (severe organ dysfunction and rapid progression of disease). For patients who have visceral crisis, chemotherapy may be used straightaway to control the disease, after which endocrine-based therapy may be a viable option.*

Therapies for Hormone Receptor Negative (HR-), HER2 Positive (HER2+), MBC Patients

First-Line Treatment:

- A “triplet” combination of **Herceptin** (Trastuzumab) (or an approved biosimilar, or a subcutaneous injection called **Herceptin-Hylecta**) along with **Perjeta** (Pertuzumab) and a **Taxane** chemotherapy is recommended for first-line treatment unless you have congestive heart failure or significantly compromised left ventricular ejection fraction (since Herceptin and Perjeta can cause heart damage).* **Alternatively, Phesgo** (an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf) can be given **with a Taxane**.

Second Line Treatment:

- **Kadcyla** (TDM-1/Ado-trastuzumab emtansine) alone. This is the recommended second-line treatment.
- **Tukysa** (Tucatinib) with **Xeloda** (capecitabine) and **Herceptin** (or **Herceptin Hylecta** or a biosimilar) is another option (*approved for HER2 positive MBC patients - including those with brain metastases - who have received 1 or more HER2-directed therapies in the metastatic setting*).

Third-and Later-Line Treatment Options depend upon what treatments you’ve previously taken:

- A third- (or later-) line treatment is **Enhertu** (Trastuzumab Deruxtecan/DS-8201), which was FDA-approved in Dec. 2019 for HER2-positive MBC patients who have received two or more prior anti-HER2 based regimens in the metastatic setting.
- Another third- (or later-) line treatment is the **combination of Nerlynx (Neratinib) plus Xeloda (capecitabine)**, which has been FDA-approved in Feb. 2020 for HER2-positive MBC patients who have received two or more prior anti-HER2 based regimens in the metastatic setting.
- Another option is **Margenza (Margetuximab) in combination with chemotherapy** for HER2-positive MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Other options include:

- **Herceptin** (or **Herceptin Hylecta** or a biosimilar) and **Perjeta**, with or without chemotherapy (*if the patient has previously taken Herceptin and chemotherapy without Perjeta*). **Alternatively, Phesgo**, an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf, can be given **with or without chemotherapy**.
- **Herceptin** (or **Herceptin Hylecta** or a biosimilar) **with chemotherapy**.
- **Herceptin** (or **Herceptin Hylecta** or a biosimilar) **with Tykerb** (Lapatinib).
- **Tykerb with chemotherapy**.
- **A clinical trial**.

**Frontline treatment for HER2+ MBC patients was researched in the Phase 2 PERNETTA trial, which randomized 210 previously-untreated HER2+ MBC patients to receive either Herceptin, Perjeta, and chemotherapy (“Group 1”) vs. Herceptin and Perjeta without chemotherapy (“Group 2”). Patients whose disease progressed were given Kadcyla in the second-line setting. Results announced in July 2019 indicated that the 2-year Overall Survival (OS) was similar in both Groups, although the Progression Free Survival (PFS) was better in Group 1. For HER2+, hormone receptor negative patients in Group 1, the median PFS was 22.2 months vs. 8.8 months for Group 2, and the OS was very close – 79.5% vs. 81.1%. The researchers indicated that frontline Herceptin and Perjeta without chemotherapy may be considered for patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably reduced.*

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva** (Denosumab) or **Zometa** (Zoledronic acid) in addition to your other therapy.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you've progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda** (Pembrolizumab) is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you've progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi** (Larotrectinib) and **Rozlytrek** (Entrectinib) – oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

Therapies for Hormone Receptor Positive (HR+), HER2 Positive (HER2+) (“Triple Positive”) MBC Patients

NCCN 2019 Guidelines stated that hormonal (endocrine) therapy without HER2-targeted therapy may be considered if your cancer is only in the bones (or if it’s in an organ and there are no symptoms), and it appears that you are likely to respond to endocrine therapy due to a long disease-free interval, have limited sites of disease, a slow disease progression (“indolent disease”), and/or you are older in age. However, NCCN 2020 Guidelines made no mention of this option.

Hormonal therapy options for eligible triple positive patients are listed immediately below with the understanding that **premenopausal women - as well as men - should also take an LHRH agonist** (Luteinizing Hormone-Releasing Hormone agonist) **such as Zoladex** (Goserelin), **Lupron** (Leuprolide) or **Trelstar** (Triptorelin) to suppress the production of specific hormones in the body (this is optional when taking Tamoxifen or Fareston). If the cancer progresses on initial endocrine therapy, another type of endocrine therapy may be considered, or a HER2-targeted therapy (with or without hormonal therapy) may be taken.

- **An Aromatase Inhibitor** (AI) such as **Letrozole** (Femara), **Arimidex** (Anastrozole), or **Aromasin** (Exemestane).
- **Faslodex** (Fulvestrant) with either **Letrozole** or **Arimidex**.
- **Faslodex** alone.
- **Tamoxifen** (Nolvadex) or **Fareston** (Toremifene).

HER2-TARGETED THERAPY FOR TRIPLE POSITIVE PATIENTS MAY BE TAKEN ALONE, OR IN COMBINATION WITH EITHER CHEMOTHERAPY OR HORMONAL THERAPY AS DESCRIBED BELOW. A CLINICAL TRIAL IS ALSO AN OPTION.

HER2 Targeted Therapy Options with or without Chemotherapy:

- **Herceptin** (Trastuzumab) (or a biosimilar), or **Herceptin Hylecta** (the subcutaneous injectable form of Herceptin) **with Perjeta** (Pertuzumab) and a **Taxane** chemotherapy. (*According to NCCN 2019 Guidelines, this “triple” is the preferred therapy for triple positive patients. Once chemotherapy is stopped, hormonal therapy should be added to Herceptin and Perjeta as maintenance therapy.*)* **Note:** **Phesgo** (an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf) can be given **with a Taxane** instead of Herceptin and Perjeta..

Additional lines of HER2-Targeted Therapy include:

- **Kadcyla** (TDM-1/Ado-trastuzumab emtansine) alone. This is the recommended HER2-directed second-line treatment.
- **Tukysa** (Tucatinib) **with Xeloda** (capecitabine) and **Herceptin** (or **Herceptin Hylecta** or a biosimilar) is another option (*approved for HER2 positive MBC patients - including those with brain metastases - who have received 1 or more HER2-directed therapies in the metastatic setting*).

Third-and Later-Line HER2 Treatment Options depend upon what treatments you’ve previously taken:

- A third- (or later-) line HER2-directed treatment is **Enhertu** (Trastuzumab Deruxtecan/DS-8201), which was FDA-approved in Dec. 2019 for HER2-positive MBC patients who have received two or more prior anti-HER2 based regimens in the metastatic setting.

- Another third- (or later-) line treatment is the **combination of Nerlynx (Neratinib) plus Xeloda (capecitabine)**, which has been FDA-approved in Feb. 2020 for HER2-positive MBC patients who have received two or more prior anti-HER2 based regimens in the metastatic setting.
- Another option is **Margenza (Margetuximab) in combination with chemotherapy** for HER2-positive MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Other HER2-directed Options Include:

- **Herceptin (or Herceptin Hylecta or a biosimilar) and Perjeta, with or without chemotherapy** (*if the patient has previously taken Herceptin and chemotherapy without Perjeta*). **Alternatively, Phesgo**, an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf, can be given **with or without chemotherapy**.
- **Herceptin (or Herceptin Hylecta or a biosimilar) with chemotherapy.**
- **Herceptin (or Herceptin Hylecta or a biosimilar) with Tykerb (Lapatinib).**
- **Tykerb with chemotherapy.**

HER2-Targeted Therapy Options with Hormonal Therapy:

As mentioned above, premenopausal women - as well as men - should take a Luteinizing Hormone-Releasing Hormone agonist while taking hormonal therapy, although this is optional when taking Tamoxifen or Fareston.

- **An Aromatase Inhibitor with Herceptin (or Herceptin Hylecta or a biosimilar).**
- **An Aromatase Inhibitor with Tykerb, with or without Herceptin (or Herceptin Hylecta or a biosimilar).**
- **Faslodex with Herceptin (or Herceptin Hylecta or a biosimilar).**
- **Tamoxifen or Fareston with Herceptin (or Herceptin Hylecta or a biosimilar).**

**Frontline treatment for HER2+ MBC patients was researched in the Phase 2 PERNETTA trial which randomized 210 previously-untreated HER2+ MBC patients (some of whom were triple positive) to receive either Herceptin, Perjeta, and chemotherapy ("Group 1") vs. Herceptin and Perjeta without chemotherapy ("Group 2"). Patients whose disease progressed were given Kadcyca in the second-line setting. Results announced in July 2019 indicated that the 2-year Overall Survival (OS) was similar in both Groups, although the Progression Free Survival (PFS) was better in Group 1. For HER2+, hormone receptor positive patients in Group 1, the median PFS was 23.7 months vs. 8.3 months for Group 2, and the OS was very close – 74.2% vs. 75%. The researchers indicated that frontline Herceptin and Perjeta without chemotherapy (but with endocrine therapy) may be considered for triple positive patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably reduced.*

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva (Denosumab)** or **Zometa (Zoledronic acid)** in addition to your other therapy.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you've progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda (Pembrolizumab)** is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you've progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi (Larotrectinib)** and **Rozlytrek (Entrectinib)** – oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

Therapies for Triple Negative (HR-, HER2-) “TNBC” MBC Patients

If your tumor has immune cells on or near it that are PD-L1 positive, then you should receive **Tecentriq** (Atezolizumab) **in combination with Abraxane** (nab-Paclitaxel). Atezolizumab is an immunotherapy drug that works well in combination with chemotherapy. The FDA has specifically approved the VENTANA PD-L1 (SP142) Assay as a companion diagnostic for selecting TNBC patients for this therapy.

Another option for TNBC MBC patients whose tumors are PD-L1 positive is the combination of **Pembrolizumab** (Keytruda) **and chemotherapy**. A test called PD-L1 IHC 22C3 pharmDx has been FDA-approved as a companion diagnostic for selecting patients with TNBC to be eligible for the Keytruda plus chemotherapy regimen.

If your tumor-related immune cells are PD-L1 negative, then your first line of treatment should be **sequential single agent chemotherapy** (combination chemotherapy should only be given in the event of visceral crisis). However, if you have a BRCA1 or BRCA2 mutation, it is recommended that you take a PARP inhibitor (**Talzenna** or **Lynparza** described below), as first-line therapy. A clinical trial may also be an option.

Third-line therapy and beyond for all TNBC MBC patients:

Third- or later-line therapy for TNBC patients should be **Trodely** (**Sacituzumab Govitecan-hziy**), which was FDA-approved in April 2020 for the treatment of adult TNBC MBC patients who have received at least two prior therapies for their metastatic disease.

DID YOU KNOW?

If you have **bone metastases**, you should receive a bone-directed therapy such as **Xgeva** (Denosumab) or **Zometa** (Zoledronic acid) in addition to your other therapy.

If you have a germline BRCA mutation, you may want to speak with your doctor about taking a PARP inhibitor such as **Talzenna** (Talazoparib) or **Lynparza** (Olaparib), which are FDA-approved for HER2 negative MBC patients with BRCA mutations. If a TNBC MBC patient has a germline BRCA mutation and is PD-L1 negative, either Talzenna or Lynparza is generally recommended as first-line treatment instead of chemotherapy.

Although very rare, if your cancer has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) characteristics, or is Tumor Mutational Burden-High (TMB-H), and if you've progressed on prior therapy and have no satisfactory treatment options, then the PD-1 inhibitor **Keytruda** (Pembrolizumab) is an FDA-approved option.

If your cancer has a Neurotrophic Receptor Tyrosine Kinase (NTRK) gene fusion without a known acquired resistance mutation, and if you've progressed on prior therapy and have no satisfactory treatment options, **Vitrakvi** (Larotrectinib) and **Rozlytrek** (Entrectinib) – oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. NTRK fusions are extremely rare, occurring in only about 0.5–1% of common cancers.

A Few Notes About Invasive Lobular Metastatic Breast Cancer

Invasive Lobular Cancer (ILC), which is usually hormone receptor positive and HER2 negative, may appear more like a spider web or filmy “sheets” than a solid tumor. Therefore, ILC it can be difficult to diagnose and track because it doesn’t always appear on scans.

When it’s metastatic, ILC may often spread to the ovary, abdomen/stomach, peritoneum (the tissue that lines the abdominal wall and covers organs in the abdomen), and omentum (a membranous double layer of fatty tissue that covers the intestines and organs in the lower abdomen). Sometimes the function of the ureters and bile ducts can also be impacted.

On occasion, excess fluid called “ascites” may build up in the abdominal area. Some people with metastatic ILC experience significant issues such as fatigue, weight loss, nausea, abdominal pain or enlargement (“looking pregnant”), diarrhea, loss of appetite, and /or a feeling of premature fullness while eating. If you’re experiencing any of these symptoms, you should report them to your doctor.