

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Breast Cancer

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Introduction

On April 2, 2015, FDA held a public meeting to hear perspectives from people living with breast cancer about their disease, its impact on their daily life, and currently available therapies. FDA conducted the meeting as part of the agency's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings over a five-year period, each focused on a specific disease area.

More information on this initiative can be found at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Overview of Breast Cancer

Breast cancer is cancer that forms in the tissues of the breast. Breast cancer is the most commonly diagnosed malignancy among women. The American Cancer Society estimates that 232,000 new cases of invasive breast cancer will be diagnosed in US women in 2015, and about 40,000 women will die from breast cancer, making it the second leading cause of death in American women. The exact cause of breast cancer is not known; however, some known risk factors for breast cancer include older age, family history, genetic alterations, hormone therapy, and obesity. A majority of patients will have breast cancer localized to the breast and/or regional lymph nodes at the time of diagnosis. In less than 5% of patients, the breast cancer will have spread to distant sites at the time of diagnosis. About 20-30% of patients that initially present with localized disease will develop metastasis to other parts of the body, including the liver, brain, lungs, and bones. Common types of breast cancer include ductal carcinomas and lobular carcinomas; uncommon types include Paget's disease and inflammatory breast cancer.

Breast cancer may or may not have symptoms at the time of diagnosis. Many patients are diagnosed following routine screening imaging exams with no symptoms. The most common symptom of breast cancer is a lump or mass, which may or may not cause pain. Symptoms of metastatic breast cancer depend on where the cancer has spread; for example, brain metastasis may cause seizures or worsening headaches. In some cases, the cancer can grow for years before symptoms are felt. Other possible symptoms include swelling in part of the breast, skin irritation or dimpling, breast or nipple pain, nipple retraction, nipple discharge, or redness or scaling of the nipple or breast skin. Imaging modalities such as ultrasound, mammogram, computerized tomography scan, and magnetic resonance imaging, may be used to identify suspicious breast lesions or metastases. Ultimately, a biopsy is required to definitively diagnose breast cancer.

Breast cancer is treated in several ways, depending on the type and stage of the cancer. In most cases, treatment is multi-modal including as a combination of surgery, chemotherapy, biological therapy, radiation therapy, and/or hormonal therapy. Supportive care therapies include pain management, complementary and alternative therapies.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients, caregivers, and advocates about their perspectives on breast cancer and its treatments. The discussion focused on two key topics: (1) disease symptoms and daily impacts that matter most to patients, and (2) patients' perspectives on current approaches to treating breast cancer. The questions for discussion (*Appendix 1*) were published in a [Federal Register Notice](#) that announced the meeting. For each topic, a panel of patients (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. The discussion was led by an FDA facilitator, and a panel of FDA staff (*Appendix 2*) asked follow-up questions. Participants who joined the meeting via live webcast were invited to submit comments throughout the discussion. Additionally, in-person and web participants were periodically invited to respond to polling questions (*Appendix 3*), which provided a sense of the demographic makeup of participants and how many participants shared a particular perspective on a given topic.

Approximately 22 breast cancer patients and patient representatives attended the meeting in person, and about 30 web participants provided input through the live webcast and polling questions. Based on their responses to the polling questions, in-person and web participants represented a range of experiences with breast cancer, with a higher proportion of women who had been diagnosed more than 5 years ago. Within the in person participants, there was an approximately equal number of patients with metastatic cancer versus those that no longer had evidence of the disease. There were a higher proportion of women between the ages of 51-60 in person and on the webcast. Although participants may not fully represent all of the population living with breast cancer, FDA heard experiences and perspectives on breast cancer and its treatments, across a spectrum of patient ages and times since diagnosis.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments on the topic to a public docket, which was open until June 2, 2014. Twenty docket comments were submitted to the public docket², the majority by individual breast cancer patients. FDA also received comments from two breast cancer advocacy groups.

More information on the meeting, including the archived webcast recording and meeting transcript, is available on the meeting website:

<http://www.fda.gov/Drugs/NewsEvents/ucm421313.htm>

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting or through the webcast. It also includes a summary of comments submitted to the public docket. To the extent possible, the terms used in this report to describe specific breast cancer symptoms,

² A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

impacts and treatment experiences reflect the words used by in-person attendees, web participants, or docket commenters. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

The input from the meeting and docket comments underscore the diversity in patients' experiences with breast cancer, the debilitating side effects of treatment, and the physical, emotional, and social impacts the disease can exert on patients' lives. Several key themes emerged from this meeting:

- It can be difficult to distinguish between breast cancer symptoms and impacts of treatments. Fatigue and weakness, pain, and depression or anxiety were among the most commonly mentioned symptoms identified as having the greatest impact patients' daily lives. Other symptoms discussed included cognitive impacts, neuropathy, lymphedema, and gastrointestinal issues. The effects of breast cancer may continue long after treatment has stopped.
- While many participants clearly appreciated the advances in breast cancer treatments, it was evident that the side effects of treatments can take a tremendous toll on all aspects of a patient's life. Patients described a range of medications and types of therapies to manage their symptoms and treatment side effects, with mixed effectiveness. Many participants said that they value the benefits they see in non-drug therapies, such as diet changes, vitamins and supplements, acupuncture, yoga, and supportive interaction.
- Breast cancer and its treatment impact all aspects of patients' lives. Participants described limitations in physical activity due to fatigue or pain, the burden of frequent doctor or hospital visits, the impact on sexual intimacy and relationships, and the worry of the future. Participants also noted the significant emotional burden of the disease. The impact that breast cancer has on patients' lives varies widely and depends on a number of factors, including the disease manifestation, side effects of treatments, and other responsibilities in the person's life.
- Breast cancer treatment decisions are highly individual and personal. Treatment considerations include the effectiveness of the treatment to prolong life, prevent spread, and minimize side effects. While some patients identified that they were willing to live with many or severe side effects, others noted that quality of life was paramount and was the primary consideration.

The sections that follow detail the views shared by patients and patient representatives. The patient input generated through this Patient-Focused Drug Development meeting and public docket strengthens FDA's understanding of the burden of breast cancer on patients and the treatments currently used to treat breast cancer and its symptoms. FDA staff will carefully consider this input as it fulfills its role in the drug development process; including advising sponsors on their drug development programs and assessing benefit-risk for products under review for marketing approval (see Appendix 4). This input may also be of value to the drug development process more broadly. Specifically, it may be particularly useful to drug developers as they explore potential areas of unmet need for breast cancer patients, for example with regards to fatigue or controlling metastasis. It could also point to the potential need for development and qualification of new outcome measures in clinical trials.

Topic 1: Disease Symptoms and Daily Impacts That Matter Most to Patients

The first discussion topic focused on patients' experiences with their breast cancer symptoms and the resulting effects on their daily lives. FDA was particularly interested in hearing about specific activities that patients can no longer do at all, or as fully as they would like, because of their condition. Patients shared a similar perspective that the most significant daily impacts were primarily the result of treatments, rather than an underlying symptom of the disease.

Four panelists (Appendix 2) provided comments to start the dialogue. They included: a woman who was diagnosed with stage IV metastatic breast cancer 19 years after her initial diagnosis; a woman with HER2 positive breast cancer who shared the difference in her experiences with primary cancer versus metastatic cancer; a woman who described being "cancer-free" for 6 years; and a patient advocate and cancer survivor who shared her individual perspective and a broader perspective based on her experience working with patients.

The panelists' testimonies provided a vivid description of what it is like to live with breast cancer. They described their challenges with diagnosis, their experiences with treatment, and the day to day impact of breast cancer. They also described the significant psychological, physical, and social impacts they have experienced because of their condition. In the large-group facilitated discussion that followed the panel discussion, nearly all patients and patient representatives in the audience indicated by a show of hands that their experiences (or those of loved ones) were reflected in the panelists' comments. The range of symptoms discussed by in-person and web participants is described in more detail below.

Perspectives on most significant symptoms

Many patients acknowledged that the most significant symptoms of living with breast cancer were a result of both short term and long term side effects as a result of therapy. Participants were able to describe and compare these effects based on the stage of the breast cancer. Some participants described how symptoms or side effects were experienced upon diagnosis years ago to how they experience these effects in the present day with advanced stage breast cancer.

Fatigue / Weakness

The most frequently discussed impact of breast cancer by participants was fatigue or weakness. While some participants commented on the fatigue they felt during a specific treatment, many noted a constant, pervasive fatigue which, as one participant noted, "has become a part of my daily life." As one patient advocate explained, "[Patients] can rest and rest and rest and the fatigue doesn't go away." This patient advocate also noted the difference between fatigue and weakness, noting that her patient population experienced persistent weakness (and not tiredness). A few participants shared that fatigue has been the most lingering effect of treatment, lasting for years after treatments were completed. As one participant summarized, "All the treatments and the lack of sleep contributed to an extremely high level of fatigue I had never before experienced." Several participants also noted that fatigue worsened during the course of treatment. Finally, one participant noted, "The only side effect that hasn't been addressed through drugs or alternative therapy is fatigue. I am always so tired."

A few participants noted that fatigue prevented them from performing daily activities. As one participant commented, “there are a lot of times in the evening where I feel like it's just too much energy to open up my computer”. Participants noted that many activities were harder to do because of pervasive fatigue, such as gardening, walking, and household activities. One participant noted, “This is not the type of tiredness that will go away after a few nights of good sleeping and good eating. [It] is always there...you just can't get rid of that”. Finally, one participant with chronic anemia noted fatigue was especially “frustrating” for her, sharing that she had to pace herself to, “only plan on one big thing a day.”

Pain

Pain with breast cancer was primarily identified as a lingering effect of treatment. The descriptions of pain ranged from “minor and annoying” to “severe and debilitating”. Pain was described in unique ways: “sharp, skewer”, “dull and throbbing”, “head to toe,” constant, and pain that comes and goes. Participants also noted that pain can manifest in different ways: headaches, joint and muscle aches, bone, breast, and back pain, pain as a result of surgery, and pain that “moves all over” the body. One participant mentioned that bone pain increased fatigue. Other participants mentioned that pain worsens when they are fatigued. As one participant shared, “when I'm extremely tired, the pain is greater... the two are intertwined.”

Participants provided various thoughts on pain. One participant noted that her pain was so severe, she felt as if it was “jumping out of my skin.” Another shared her experiences pain that was specific to her fingers, “In the beginning, I had very mild arthritis or either carpal tunnel syndrome... my fingers are sort of now lumping up and on some days, it's excruciating with the pain or there are days that my hand is in so much pain that I literally have to pry my fingers open.”

One patient advocate noted that the experience of pain can be confusing to patients, who have to wonder if the pain is “a recurrence of their cancer or progression of their cancer, or is it just a natural sort of aging kind of thing?” This comment resonated with other participants.

Pain associated with specific treatments was mentioned throughout the meeting. These experiences are presented in the Topic 2 discussion.

Depression or Anxiety

When asked to identify other symptoms of their condition that have a significant impact on daily life, several participants identified anxiety, depression, fear, and stress. Participants commented that they felt these symptoms upon diagnosis and throughout treatment. Many participants described that anxiety was the result of the unknown: how treatments would impact their lives, when side effects would start, and the severity of side effects. As one participant noted that upon diagnosis, “I thought I was going to go on a roller coaster ride but instead I did the straight drop down and it was not fun.” She continued, “I became hopelessly depressed in spite of counseling and antidepressants.” Another participant shared, “There aren't words to describe the horror of depression. Suffice it to say, had it not been for my... child at home who I believe still needed me, I would not be here today.”

Several participants commented that other symptoms, such as pain fatigue or swelling, could lead to depression.

Other symptoms

In addition to fatigue, pain, and depression or anxiety, participants described a number of other symptoms that have a significant impact on their daily lives:

- Many participants shared that they experience cognitive issues or “chemo brain”, which resulted in not being able to recall things quickly or difficulty finding words. As one participant commented, “I can't get the word from my brain to come out my mouth... something is blocking that from coming out.” Another participant noted, “I can think of the letter that the word starts with but I can't think of the word, like it's just so close but it's not there.” A few participants mentioned that cognitive impairment has resulted after years of cancer treatments.
- A few participants described peripheral neuropathy as a painful and scary symptom. Participants described frequent falls due to loss of feeling in their feet. One participant shared that she experiences a burning feeling in her feet and noted that when climbing stairs, “it's one stair at a time and I hold onto the handrail with a death grip so I won't fall and risk breaking any bones.” Another participant noted of a similar experience of neuropathy in her feet sharing, “It's like... my toes [are] reminding me that I had breast cancer.”
- Several participants noted that lymphedema is a painful and troublesome symptom with constant pain that, “intrudes into your life.” Some participants shared that lymphedema was the result of surgery, and noted that due to painful swelling and bandaging that restricted the types of clothes they could wear. One participant noted that swelling in her arm due to lymphedema makes it very difficult to shop for clothes, sharing “To fit my left arm, it's a woman's size 22 to 24. The rest of my body is a size 12.”
- Several participants shared the severe emotional impact of the loss of sexual intimacy, primarily as a result of treatments. As one participant shared, “... being young... I lost the ability to want to be intimate or sexual with anyone, and that's something that's very important to me.” Another noted, “I, like nearly every woman that has taken an aromatase inhibitor, finds that the traditional position of sexual intercourse is extremely painful and uncomfortable.” One patient advocate reported on behalf of her patient organization that fatigue, pain, vaginal dryness, and nausea make it difficult for patients to be intimate and creates stress on relationships. Other participants noted that early menopause and severe hot flashes were physically and emotionally difficult to deal with.
- Other symptoms identified included gastrointestinal issues (e.g., nausea, queasy stomach, diarrhea, constipation, acid reflux), heightened sensitivity to smells, dental issues, dry skin, weight gain, mouth sores, anemia, sleep difficulties or insomnia, acne, mania, edema, loss of taste, and hair loss. Participants noted that many of these symptoms were the result of treatments. One participant noted the increased risk of serious infections were a common symptom, while others noted that bone density loss has resulted in osteoporosis.

Overall impact of breast cancer on daily life

Both in-person and web participants described in rich detail the impact that their condition has on daily life, including:

- **The ability to perform activities.** Participants shared the difficulties that breast cancer and its treatments posed on their ability to care for themselves, their family, and household. Participants noted that, “intense fatigue,” among other effects, made it difficult to leave their homes and care for loved ones, such as parents or children. Several participants shared that the burden of the disease and its treatments left them unable to continue working. One participant summarized that being unable to continue work and care for herself left her feeling “increasingly isolated.”
- **The impact on relationships.** Participants shared their challenges with social relationships due to the impact of breast cancer. As one participant related, “I lost interest in being with friends who were living normal happy lives compared to the nightmare I was now experiencing.” She continued, “Many days I didn't get out of bed, instead watching hours of TV to distract myself.” Another participant noted the psychological impacts of surgery, sharing that the removal of her breasts and ovaries significantly impacted the relationship with her husband. Participants also noted the difficulty in participating in physical activities, such as household chores and hobbies. One patient advocate shared perspectives from her patient organization noting that being unable to participate in activities in family, “you begin to see yourself as someone less important in the family.”
- **The significant emotional burden.** Participants shared their perspectives on the emotional challenges of diagnosis and treatments. Several participants described diagnosis and disease progression to be a “lonely time,” and a period during which, “my body immediately went into flight or fight mode in an extended period of extreme fear and high stress.” One participant noted the time spent on doctor visits saying, “... in the six years and two months since I was diagnosed metastatic, I have had 193 visits with my oncologist. That's not scan time, treatment time, any other doctor time. That's just with my oncologist.”
- **Worry about the future.** Several participants noted their worry for the future. As one participant shared, “I do not make any long-term plans. It's 6 to 12 months or less because I never know what the future is going to bring.” Participants worried not only about the prognosis of their disease, but also how they would respond to treatments. One web participant noted that she harvested her eggs due to potential fertility issues resulting from treatments.

Topic 2: Patient Perspectives on Treatments for Breast Cancer

The second discussion topic focused on patients’ experiences with therapies used to treat their breast cancer. Four panelists provided comments to start the dialogue: a 34 year old mother with stage four breast cancer who weighed the importance of prolonging her life much higher than side effects of treatments; a woman who was diagnosed at the onset with metastatic breast cancer who described her experience with targeted chemotherapy treatments; a woman who had no sign

of cancer in her body after liver metastasis; and a woman who was diagnosed with breast cancer 24 years ago and has lived with metastatic breast cancer for the last 11.5 years. The panelists shared their experiences on not only the treatments they used, but how they made decisions on what treatments to pursue.

In the large group facilitated discussion that followed, several of the patients and patient representatives indicated by a show of hands, that their experiences (or those of loved ones) were reflected in the panelists' comments. The facilitated discussion included experiences with prescription drugs, surgery, over-the-counter, non-drug, and alternative therapies. Participants' perspectives on the benefits and downsides of these treatments are summarized below. This section ends with participants' perspectives on what considerations come to mind regarding treatment decisions.

Perspectives on breast cancer treatments

According to the polling question (Appendix 3, Q8), near all in-person and web participants reported having had chemotherapy and or surgery to treat their breast cancer. Radiation therapy, hormone therapy, and target drug therapy followed closely as other treatments used to help reduce or control the spread of breast cancer. Other therapies were also identified, which are discussed in further detail below.

Participants were clear in their appreciation for current therapies for breast cancer; many shared that treatment therapies have improved their chances of survival, as well as their quality of life while living with breast cancer. The primary types of treatment therapies are described below.

Chemotherapy was one of the most frequently mentioned treatments, and many participants described the debilitating side effects of their chemotherapy, even after years of treatment. One participant shared, "While I read and was told about all the possible side effects, nothing could prepare me for the emotional and mental upheaval I would experience. I literally felt like I was dying and I questioned my decision to do the chemotherapy. Every day I contemplated quitting."

Surgery, such as a lumpectomy, mastectomy, or oophorectomy, was also frequently mentioned. Some participants also mentioned the removal of lymph nodes due to metastasis. Some participants described the heavy burden of decision making regarding surgical treatment options. One participant described the lingering effects of surgery, noting, "Never did I realize that my decision for a double mastectomy and oophorectomy would have much deeper psychological implications than just the loss of physical feeling."

Radiation therapy was also identified by several participants. As described in topic 1, some participants spoke of the pain which resulted from radiation therapy. One participant shared that despite side effects, she continued with whole brain radiation, targeted, and local radiation. Another participant noted the fatigue and skin blistering which resulted from her radiation therapy.

Hormone therapy, such as aromatase inhibitors, was identified by a few participants who primarily spoke of the resulting pain from treatment. One participant noted pain during sexual intercourse, while another commented that the, "... initial bone pain was excruciating... while some of that bone pain has subsided, I still feel it in my lower back on a regular basis." Other participants noted specific hormone therapies, such as leuprolide and exemestane.

Other prescription therapies described included targeted drug therapy, lymphedema therapy, Procrit (epoetin alfa) injections to treat anemia, CyberKnife technology, and in one case, the insertion of a Greenfield filter.

Perspectives on drug therapies

In most cases, participants were taking a combination of treatments; in some cases, however, participants felt able to attribute specific symptoms or side effects to specific treatments. Participants described in detail the complexity of taking multiple therapies and weighing the benefits versus downsides of specific treatment therapies. Participants also noted that when treatments stopped working, or side effects were intolerable or potentially life threatening, treatments were added, removed, or switched to another medication.

In several cases, participants noted that treatment therapies were effective in managing their breast cancer. One participant noted that a targeted therapy drug worked well for her, commenting that it was, “amazing... it’s been phenomenal.” A few participants noted that chemotherapy alone was effective in treating their breast cancer, while others noted that they required a combination of therapies. Participants identified minor side effects associated with certain therapies. One participant noted that although she experienced, “hair loss, nausea, fatigue, [and] infusion reactions... [it] was one of the more gentle drugs for me.” Another shared of her targeted therapy, “I had some sinus issues. I had some fatigue. That was about it.”

Some participants commented that they continued with a specific therapy, despite difficult side effects. For example, one participant noted, “I experienced minor fatigue, mild neuropathy, acid reflux, minor constipation, elevated liver enzymes, and lowered platelets. My oncologist has reduced the dosage a few times to minimize [the side effects] but the treatment... is continuing to work.” Other participants described that despite “bad joint pain,” “extreme neuropathy,” “increased blood pressure, red face and neck,” and nail deterioration, they continued treatment with their combination treatment regimen.

Finally, some participants noted that in some cases, side effects were intolerable and required changing the medication. One participant expressed disappointment and shared that it was, “horribly discouraging [that] I had to suspend my treatment” with a targeted therapy drug. Another participant experienced, “very bad hot flashes, depression for the first time in my life, bloating, abdominal pain that would have me sometimes double over,” and chose to stop taking that treatment. Other participants also noted that severe pain led to stopping a particular treatment.

Supportive Care Therapies

Participants mentioned a range of supportive therapies used to manage side effects of treatment. These included antidepressants, bisphosphonates, steroids, hyperbaric oxygen treatments, opioid pain management medications (including OxyContin, Percocet, Fentanyl patches), ibuprofen, and sleep medications. Some participants shared that they use antidiarrheal medications, stool softeners, and medications to control indigestion. Similar to above, participants noted downsides to supportive care therapies, including: trouble falling asleep on antidepressants, impairment on pain medications, and the burden of having to drive for hyperbaric oxygen treatment sessions.

Many participants agreed that it was beneficial to use a holistic approach to managing the effects of breast cancer. Participants noted that diet modifications (such as stopping alcohol consumption) and vitamin supplements were an important part of their treatment regimen. Others mentioned that light exercise helped to manage pain and fatigue. Finally, participants also mentioned yoga, acupuncture, massage, nerve ablation, cognitive therapy, and support group therapy.

Consideration on treatment decisions

A key topic of discussion focused on understanding the factors that patients take into account when making decisions about using breast cancer treatments. To help guide the discussion, participants were asked to imagine a scenario (see full text in Appendix 3) in which they (or a loved one) were had the opportunity to consider participating in an experimental treatment for breast cancer. This hypothetical treatment is a chemotherapy drug which prolonged survival on average 2 months longer than standard of care alone. This treatment was associated with diarrhea, rash, and rarer but more serious toxicities such as liver injury and lung inflammation, in addition to the toxicities of standard of care chemotherapy.

Participants were asked to comment on first thoughts that came to mind as they heard this scenario. A few participants identified immediately the need for more information. The below excerpts illustrate the perspectives that came to mind:

- “Is it a first line treatment or is it something for metastatic patients who've undergone prior treatments? I think that makes a difference.”
- “It shouldn't matter whether it's early stage or advanced stage. Only two months more, that's, to me, not enough to warrant the added cost.”
- “What if you're not the average person? What if you're the outlying person? [There] may be an 80 percent chance that you won't go [live] longer but what if you're in that 20 percent chance that you can live longer? Then it's worth that.”
- “My first question would be who's in the clinical trial and how do they compare to me?”

Participants were next asked (Appendix 3, Q10) to identify factors that would be most important to them in making decisions about using treatments to reduce or control the spread of their breast cancer. The majority of in-person and web participants selected, “how long the treatment *would* probably prolong my life”, followed by “how long the treatment *could* probably prolong my life” (in person participants) and, “the expected side effects of treatments, such as nausea, loss of appetite, etc.” (web participants). One participant noted that she relied on her treating physician to decide if surgery was the best option for her.

Finally, participants were asked (Appendix 3, Q11) to identify which factors were least important to them in making decisions about using breast cancer treatments. The majority of in person and web participants selected “how the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.”

Several participants provided additional perspectives on how they make individual decisions regarding treatment. A few participants noted that prolonging life was the primary consideration in choosing

treatment options. As one participant summarized, “I weigh the importance of prolonging my life much higher than improving the symptoms I experience due to breast cancer. I will take on many more side effects if I get to stay on a particular drug longer. This is one more month I get to participate in the raising of my children, one more day I get to see their smiles, hear their laugh, and show them my love.” One participant shared, “young women out there, particularly those that are raising families that are metastatic -- they are willing to put up with so much more toxicity just for the sake of being there as long as they possibly can for their children.”

Others shared that quality of life outweighed other considerations in choosing treatment. One participant commented, “As long as I can live my life and continue to work full-time, that is my goal. My goal is to stay away from systemic chemo. That's just my preference due to their extreme side effects for me and their disabling qualities.” One 34 year-old participant noted that she had chosen not to continue on aromatase inhibitors sharing, “... my quality of life is more important to me than living with something that makes me feel less like a woman... I lost the ability to want to be intimate or sexual with anyone, and that's something that's very important to me. I would rather go through chemotherapy and other treatments again if the cancer comes back...”

Finally, one participant commented that fear of the unknown can impact the decision to pursue treatments, sharing, “the fear factor is very pervasive, because they've [women] heard everybody in their neighborhood say all of the horrible things about it. They rarely hear the benefits of undergoing any type of cancer treatment.” She also noted a similar perspective, commenting that some women may fear getting an initial mammogram. Other participants mentioned that fear of side effects, such as severe neuropathy or pain, can weigh into treatment decision making. One participant noted, “I would rather my oncologist reduce the dosage on a treatment and risk the cancer growing than to continue on a higher dosage and risk permanent neuropathy.”

Perspectives on an ideal treatment for breast cancer

Participants provided feedback on what they would look for in an ideal treatment for breast cancer. One participant noted that she hoped for treatments that would prevent spread of metastatic cancer. She highlighted that this was different to her than the reduction in tumor size, sharing, “...we are willing to live with this disease if it doesn't spread any further... as long as we can keep it from attacking organs, that's the type of drug that metastatic patients would like.”

Another participant noted that it was critical to provide patients with more research evidence and validity through access to patient reported outcomes data so that patients could make treatment decisions with more confidence. Similarly, a few participants shared that they wanted to see an increase in the use of genomic sequencing to identify how individuals may respond to treatments. One participant emphasized the importance of diversity in clinical trials saying, “I'd really to see more people of color in clinical trials.”

FDA asked participants to share perspectives on experiences (including risk, anxiety, frequency, and uncertainty) with biopsies to determine mutation or biomarker status. A few participants stressed the importance of physicians to explain the value of the biopsy to the patient so that they can feel more confident about the decision to undergo a biopsy. One participant shared that she was willing to undergo biopsies so that her oncologist could understand her tumor first before making treatment recommendations.

Summary of Comments Submitted to the Public Docket

20 comments were submitted to the public docket that supplemented the Patient Focused Drug Development meeting on breast cancer. The majority of comments were submitted by women with breast cancer. Two comments were submitted by breast cancer advocacy organizations. The Metastatic Breast Cancer Alliance submitted a survey of patient perspectives on symptoms and side effects of metastatic breast cancer and additional perspectives from its patient group, and the Breast Cancer Action organization provided its comments on clinical trials and drug approval process for breast cancer.

Overall, the comments received in the docket reflected the experiences and perspectives of shared during the April 2015 public meeting. They further emphasized and elaborated upon the themes identified during the meeting. The following is a summary of comments provided on breast cancer symptoms (or impacts from treatments), impacts on daily life, treatments, and decision making around treatments. Similar to the public meeting, it was difficult to distinguish symptoms from treatment burden.

In the summaries that follow, particular focus is placed on experiences or perspectives that were not raised or addressed in detail at the meeting.

Submitted comments on symptoms of breast cancer

- Pain was the most commonly mentioned symptom in the docket. Commenters identified bone pain, joint pain, pain due to reconstruction, and pain during intercourse. One commenter noted, “I had shooting pains and muscle spasms all over my body 24/7.” One patient noted, however, that her bone pain has diminished with time. Several participants noted the debilitating impact of neuropathy. As one commenter summarized, “Because of the neuropathy, I am unable to use my hands to perform clerical activity (job), sew, glass hobby activities. I am unable to stand or walk for extended periods. I drive much less than before as I now lack confidence - I fear that I won't notice something critical.”
- Fatigue and weakness were also mentioned frequently in the docket comments. Participants noted that fatigue has impacted many aspects of their lives, including the ability to do any activities. As one commenter shared, “Fatigue was, and is, has the most significant impact on my daily life. It seems that I cannot get enough rest, and sleep.” One commenter shared, “Just driving to the grocer could take all of my stamina before I even reached the door.”
- Several commenters shared that lymphedema was a painful, debilitating aspect of breast cancer. One participant shared, “Lymphedema is by far the most impactful, and will be for the rest of my life. I have never regained my previous level strength and stamina, and have gained 30 pounds.”
- A few commenters mentioned sexual problems, including pain during sexual intercourse and loss of sex drive.
- A range of other symptoms of breast cancer were identified. Others symptoms included cognitive impairments (or “chemo brain”), gastrointestinal issues (such as nausea and diarrhea), rash, hand-foot syndrome, and weight fluctuation.

Submitted comments on the overall impact of breast cancer on daily life

The docket comments reflected the input received during the meeting related to the debilitating impact of breast cancer on patients' daily lives, and its significant toll on patients and their families.

Most commenters shared that participating in physical activity has become very limited due to the impact of breast cancer. Commenters reiterated the impact on personal and family life, including difficulty with managing their household. As one commenter shared, "Lymphedema very much limits my physical activity, especially repetitive motion. I can't sweep or vacuum for any more than a few minutes." Another shared that she was unable to exercise. Several participants noted that they were unable to perform their job due to pain, fatigue, and other impacts of breast cancer. One commenter described, "While in treatment the fatigue is debilitating and I was unable to take care of my home, cook meals, shop."

Commenters also identified a range of other impacts of breast cancer on their lives, including the impact on sexual intimacy and relationships, the anxiety and depression associated with diagnosis and prognosis, and financial concerns. A few commenters also noted that the frequency of doctor visits was also a burden on daily life.

Submitted comments on current treatments for breast cancer

The submitted comments about experiences with treatments were similar to those expressed at the public meeting. Chemotherapy, radiation therapy, surgery (such as lumpectomy, mastectomy, and oophorectomy), and hormonal therapy were the most common types of treatment that commenters discussed. One commenter shared her experiences with a radiosurgical technology, Cyberknife. Commenters noted the debilitating and painful effects of treatment; however, as one commenter shared, "I knew treatment was my best chance to save my life. Chemo and radiation [were] the only thing I could do for myself, so I did it." Many commenters noted the downsides to treatments, and but as one summarized, "As long as the side effects are manageable, I will continue my treatment."

Similar to the public meeting, many docket commenters noted that their treatment regimen resulted in a range of side effects, some of which were too intolerable to continue treatment. One commenter shared that her experience with a 3-month course of chemotherapy drug that resulted in such severe side effects that she, "could barely leave the house" while she was on the medication. Others noted the long term effects of their treatment. One commenter shared, "I now have early onset arthritis in [my] knees and ankles. It made my skin change in terms of texture and aging with itching and dryness which I never had before, and it never went away." Another commenter shared that severe neuropathy left her unable to, "fully practice my profession, after years of training and practice. This is demoralizing."

Other side effects mentioned included: hand/foot syndrome, peeling hands, blistering feet, fatigue, irritability, cognitive deficits (such as loss of memory and ability to concentrate), arthralgia, sleep disturbances, hot flashes, bone deterioration, osteoporosis, gastrointestinal issues (such as constipation, nausea, and diarrhea), and burns from radiation. As one commenter shared, "it's not the meds as much as the side effects that take both your health and your spirit."

A range of nondrug therapies were mentioned in the docket comments as well. These included diet modification and dietary supplements, exercise (such as yoga and tai chi), acupuncture, massage, homeopathic creams, physical therapy, and compression garments for lymphedema.

Considerations on treatment decisions

Similar to the perspectives heard during the public meeting, docket commenters raised several important considerations impacting treatment decisions. Nearly all commenters shared that prolonging life, while balancing quality of life, was of critical importance. As one commenter noted, “I am willing to try anything that will prolong my life without my life being completely miserable as well as the life of my family.” Another commented, “I have a 16-year-old daughter so prolonging life to see her graduate from high school and college is paramount. I’ll deal with a thousand side effects to achieve those goals!” A few commenters noted that preventing recurrence, minimizing symptoms (such as pain), and managing side effects were significant in their decision making.

Submitted comments on ideal treatments for breast cancer

Several perspectives were provided on ideal treatments for breast cancer. Aspects of ideal treatments included improvements in diagnostic imaging, better treatments to manage the side effects of medications (such as nausea, fatigue, pain), treatments to manage lymphedema, treatments with minimal to no side effects, and treatments and procedures that control metastatic cancer. Commenters also noted the affordability of treatments and the importance of ensuring a range of treatments were covered by insurance.

Conclusion

Breast cancer is a debilitating disease that can severely affect a patient’s day-to-day functioning and have a devastating impact on a patient’s life. FDA recognizes that patients have a unique ability to contribute to our understanding of the broader context of this disease, which is important to our role, and that of others, in the drug development process. This Patient-Focused Drug Development meeting provided FDA with the opportunity to hear from patients first-hand about the significant emotional and physical toll that breast cancer has on their lives. FDA is especially grateful to have heard the patients’ voice on what symptoms, impacts, and aspects of treatments matter most to them, in addition to what factors are considered in making treatment decisions.

The meeting highlighted the difficulty that patients face through diagnosis and treatment of breast cancer. Participants’ sense of community and their desire to support other patients “so when they make a decision, it will be an educated one” was strikingly clear. We are thankful to all of the participants who so thoughtfully and generously shared their brave personal stories and perspectives. FDA shares the patient community’s desire and commitment to furthering the development of safe and effective drug therapies.

Appendix 1: Meeting Agenda and Discussion Questions



Breast Cancer Public Meeting on Patient-Focused Drug Development



April 2, 2015

12:00 – 1:00 pm	Registration
1:00 – 1:05 pm	Welcome Soujanya Giambone, MBA <i>Office of Strategic Programs (OSP), Center for Drug Evaluation and Research (CDER), FDA</i>
1:05 – 1:10 pm	Opening Remarks Amna Ibrahim, MD <i>Deputy Director, Division of Oncology Products 1 (DOP 1), CDER, FDA</i>
1:10 – 1:20 pm	Overview of FDA's Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, OSP, CDER, FDA</i>
1:20 – 1:30 pm	Background on Disease Area and Treatment Suparna Wedam, MD <i>Medical Officer, DOP 1, CDER, FDA</i>
1:30 – 1:40 pm	Overview of Discussion Format Soujanya Giambone, MBA <i>OSP, CDER, FDA</i>
1:40 – 2:10 pm	Panel #1 Comments on Topic 1 Topic 1: Disease symptoms and daily impacts that matter most to patients. A panel of patients and patient representatives will provide comments to start the discussion.
2:10 – 2:45 pm	Large-Group Facilitated Discussion on Topic 1 Patients and patient representatives in the audience are invited to add to the dialogue.
2:45 – 2:55 pm	Break
2:55 – 3:25 pm	Panel #2 Comments on Topic 2 Topic 2: Patient perspectives on current approaches to treating breast cancer. A panel of patients and patient representatives will provide comments to start the discussion.
3:25 – 4:25 pm	Large-Group Facilitated Discussion on Topic 2 Patients and patient representatives in the audience are invited to add to the dialogue.
4:25 – 4:55 pm	Open Public Comment
4:55 – 5:00 pm	Closing Remarks Amy McKee, MD <i>Team Lead, DOP 1, CDER, FDA</i>

Discussion Questions

Topic 1: Symptoms and daily impacts that matter most to patients

1. For context, how long ago was your diagnosis of breast cancer? Is your cancer currently in only one area or has it spread to other parts of the breast or lymph nodes or outside of the breast?
2. Of all the symptoms that you experience because of your breast cancer, which one to three symptoms have the most significant impact on your daily life? (Examples may include breast pain, swelling, bone pain, and fatigue.)
3. Are there specific activities that are important to you but that you cannot do at all, or as fully as you would like, because of breast cancer? (Examples may include exercise, sexual activity/intimacy, etc.)

Topic 2: Patient perspectives on current approaches to treating breast cancer

1. Are you currently undergoing any cancer treatments to help reduce or control the spread of your breast cancer? Please describe.
 - a) What do you consider to be the most significant downsides of these treatments? (Examples of downsides may include side effects, going to the hospital for treatment, frequent blood tests, etc.)
 - b) How do these downsides affect your daily life?
2. What supportive care treatments, if any, are you taking to help improve or manage the symptoms you experience because of your breast cancer? Please include any prescription medicines, over-the-counter products, and other therapies including non-drug therapies (such as pain medication, acupuncture, massage therapy, and dietary supplements).
 - a) What specific symptoms do your treatments address?
 - b) How well do these treatments manage these symptoms?
 - c) Are there symptoms that your current treatment regimen does not address at all, or does not treat as well as you would like?
3. When thinking about your overall goals for treatment, how do you weigh the importance of prolonging your life versus improving the symptoms you experience because of your breast cancer?
4. What factors do you take into account when making decisions about using treatments to help reduce or control the spread of your breast cancer? In particular:
 - a) What information on the potential benefits of these treatments factors most into your decision? (Examples of potential benefits from treatments may include shrinking the tumor, delaying the growth of the tumor, prolonging life, etc.)
 - b) How do you weigh the potential benefits of these treatments versus the common side effects of the treatments? (Common side effects could include nausea, loss of appetite, fatigue, diarrhea, rash.)
 - c) How do you weigh the potential benefits of these treatments versus the less common but serious risks associated with the treatments? (Examples of less common but serious risks are developing a hole in the stomach or intestine, liver failure, kidney failure, lung inflammation, blood clot, stroke, heart attack, serious infections, etc.)

Docket Information

We encourage you to submit your written comments to the docket by June 2, 2015:

<http://www.regulations.gov/#!documentDetail;D=FDA-2014-N-2137-0001> or go to www.regulations.gov and search for: **breast cancer patient-focused drug development**.

Appendix 2: FDA and Patient Panel Participants

Patient Panel, Topic 1

- Karen Durham – Patient
- Katy McRae - Patient
- Debbie Drake Dunne – Patient
- Sandy Finestone – Patient and Patient Advocate

Patient Panel, Topic 2

- Colleen Duffy – Patient
- Susan Faris – Patient
- Elizabeth Cappel – Patient
- Shirley Mertz – Patient

FDA Panel

- Geoffrey Kim (Division of Oncology Products (DOP) 1, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER))
- Amna Ibrahim (DOP1, OHOP, OND, CDER)
- Suparna Wedam (DOP1, OHOP, OND, CDER)
- Amy McKee (DOP1, OHOP, OND, CDER)
- Theresa Mullin (Office of Strategic Programs, CDER)
- Ashley Slagle (OND, CDER)
- Jonca Bull (Office of Minority Health, Office of the Commissioner, FDA)

Appendix 3: Meeting Polling and Scenario Questions

The following questions were posed to in-person and web meeting participants at various points throughout the April 2, 2015, Breast Cancer Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Where do you live?
 - a. Within the Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area

2. Have you ever been diagnosed as having breast cancer?
 - a. Yes
 - b. No

We asked that the remainder of the questions be answered by people who responded “yes” to Question 2 above.

3. What is your age?
 - a. Younger than 30
 - b. 31 – 40
 - c. 41 – 50
 - d. 51 – 60
 - e. 61 – 70
 - f. 71 or greater

4. Are you:
 - a. Female
 - b. Male

5. What is the length of time since your diagnosis?
 - a. Less than 1 year ago
 - b. 1 years ago to 2 years ago
 - c. 2 years ago to 5 years ago
 - d. More than 5 years ago
 - e. I’m not sure

6. Which of the following best describes your current condition?
 - a. My cancer is localized and has not spread outside my breasts and/or local lymph nodes

- b. My cancer has spread (metastasized) to the rest of my body
- c. I have been treated for my cancer and currently have no evidence of disease
- d. I'm not sure

Question for Topic 1

7. Of all the symptoms you have experienced because of your breast cancer, which do you consider to have the most significant impact on your daily life? **Please choose up to three symptoms.**
- a. Pain, such as breast pain, or bone pain
 - b. Swelling
 - c. Fatigue or lack of energy
 - d. Depression or anxiety
 - e. Cognitive dysfunction, such as memory loss
 - f. Numbness/tingling in hands and/or feet
 - g. Fertility issues
 - h. Menopausal symptoms
 - i. Other symptoms/side effects of cancer treatments not mentioned

Questions for Topic 2

8. Have you ever used any of the following cancer treatments to help reduce or control the spread of your breast cancer? Include any current treatment.
- a. Prescription medicines
 - b. Over-the-counter products (for example, a lubricant)
 - c. Physical therapy, massage, or acupuncture
 - d. Dietary supplements or diet changes
 - e. Lifestyle changes, such as exercise or avoiding stressful situations
 - f. Behavioral therapies or couples sex therapy
 - g. Support group
 - h. Other
 - i. I am not doing or taking any therapies
9. Besides your cancer treatments, what therapies have you taken to help manage any symptoms you have experienced because of your breast cancer or your breast cancer medication? Check all that apply.
- a. Pain medications
 - b. Dietary supplements or diet changes
 - c. Complementary or alternative therapies, such as massage, acupuncture
 - d. Herbal remedies, such as soy supplements
 - e. Other therapies
 - f. I am not doing or taking any therapies to treat symptoms

10. Of the following factors, which two would you rank as most important to your decisions about using treatments to help reduce or control the spread of your breast cancer? Please select up to two responses.

- a. Whether the treatment is expected to help relieve the symptoms I experience because of my cancer
- b. The small but significant risk of serious side effects associated with treatment, such as blood clots or kidney failure
- c. How long the treatment would probably prolong my life
- d. How long the treatment could possibly prolong my life (for longer than expected)
- e. The expected side effects of the treatment, such as nausea, loss of appetite, etc.
- f. How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.

11. Of the following factors, which one would you rank as least important to your decisions about using treatments to help reduce or control the spread of your breast cancer?

- a. Whether the treatment is expected to help relieve the symptoms I experience because of my cancer
- b. The small but significant risk of serious side effects, such as blood clots or kidney failure
- c. How long the treatment would probably prolong my life
- d. How long the treatment could possibly prolong my life (for longer than expected)
- e. The expected side effects of the treatment, such as nausea, loss of appetite, etc.
- f. How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.

Scenario Questions

12. What thoughts and questions come to mind?

Drug X is a chemotherapy drug being developed for patients with breast cancer.

- It was studied in a clinical trial comparing “standard of care” chemotherapy plus Drug X versus standard of care alone.

Clinical trial results showed that:

- The addition of Drug X **prolonged survival on average 2 months longer** (median survival was 12 months on Drug X + standard of care, versus 10 months on standard of care alone)
- In addition to toxicities related to standard of care chemotherapy, patients treated with Drug X had **more diarrhea and rash**, and had **more rare but serious toxicities** such as liver injury and lung inflammation.

Appendix 4: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Breast Cancer

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics³. The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the Breast Cancer Patient-Focused Drug Development meeting and docket comments will inform our understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information in the top two rows of the sample framework for Breast Cancer below draws from various sources, including what was discussed at the Breast Cancer Patient-Focused Drug Development meeting held on April 2, 2015. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for Breast Cancer. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

³ Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Dimensions	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> - Breast cancer forms in the tissues of the breast. Common types of breast cancer include ductal carcinomas and lobular carcinomas. Approximately 20-30% of patients that present with early stage breast cancer, develop metastasis to the brain, lungs, bones, liver, or other parts of the body. - The American Cancer Society estimates that 232,000 new cases of invasive breast cancer will be diagnosed in US women in 2015, and about 40,000 women will die from breast cancer, making it the second leading cause of death in the country for women. - Breast cancer may or may not be symptomatic. Possible symptoms include a breast lump or mass, swelling in part of the breast, skin irritation or dimpling, breast or nipple pain, nipple retraction, nipple discharge, or redness or scaling of the nipple or breast skin. - Breast cancer and its treatments can have a significant physical, emotional, and social impact on a patients' quality of life. - <i>See the Voice of the Patient report for a more detailed narrative.</i> 	<p>Breast cancer is a serious, potentially life threatening disease. While prognosis is dependent on the stage of the cancer, the disease and its treatments can have a debilitating impact on a patient's life.</p>
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> - The standard of care for breast cancer depends on the type and stage of cancer, a patient's overall health, age, and medical issues, and personal preferences. - Treatments for breast cancer include some combination of surgery, chemotherapy, radiation, hormone, and/or targeted therapies. - There are a range of FDA approved chemotherapy drugs for breast cancer, including drugs for early or locally advanced cancer (ex. doxorubicin, paclitaxel, and cyclophosphamide) and drugs for metastatic breast cancer (ex. capecitabine, ixabepilone and eribulin). Side effects include pain, nausea and vomiting, fatigue, hair loss, myelosuppression and cognitive impairments. - FDA-approved targeted therapies include trastuzumab, pertuzumab, ado-trastuzumab emtansine, and lapatinib. Side effects include heart problems, hand-foot syndrome, and diarrhea. - FDA-approved hormone therapies include tamoxifen, anastrozole, letrozole, fulvestrant, goserelin, exemestane, and leuprolide. Side effects include bone/joint pain, nausea, vomiting, hot flashes, fatigue, and dry skin. - Many patients use multiple medical or non-drug supportive care therapies to manage pain and other side effects of cancer treatment. - <i>See the Voice of the Patient report for a more detailed narrative.</i> 	<p>There is a continued need for additional therapies to treat breast cancer. While many effective treatments exist, most are dependent on the stage of the cancer. Most treatments are toxic, and the severity of side effects can have a significant impact on patients' lives. Patients' treatment decisions often require making difficult tradeoffs between increasing the chance to prolong life and preserving quality of life.</p> <p>Improved therapies are needed both to prevent the recurrence of early stage breast cancer and to better control the spread and growth of metastatic breast cancer.</p>

