State-of-the-Art Treatment for Triple Negative Breast Cancer:

Talking With the Experts

A Question and Answer Session

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Introduction: Why Is Triple Negative Breast Cancer Different?

All breast cancer begins in the breast tissue, and this leads many people to assume that breast cancer is one disease.

However, researchers have found that breast cancer can differ among women in a number of important characteristics. These characteristics, such as **stage** (how much the cancer has spread), **histopathology** (what the cells look like under the microscope), **grade** (how much the cancer has progressed), DNA (genetic) type, and **receptor status**, are used by physicians to determine what treatment would be the most effective.

Triple negative breast cancer is different from other types of breast cancers in the last characteristic, receptor status.

Receptors are proteins on the surface of cancer cells that receive signals and cause the cells to grow.

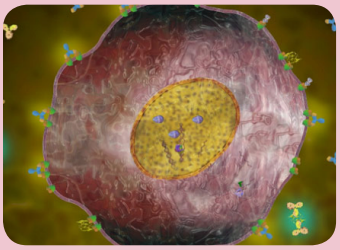
Targeted therapies block signals from reaching the receptors. Without these signals, the cancer cells do not grow.

Targeted therapies have been developed for 2 types of receptors:

1. Hormone receptors. These receptors receive growth signals from the hormones estrogen and progesterone.

2. Human epidermal growth factor (HER2) receptors. These receptors receive signals that stimulate the growth of breast cancer cells. The more HER2 receptors the cancer cells have, the more likely the breast cancer is to grow.

When tested for receptor status, many breast cancer cells test positive for estrogen, progesterone, or HER2 receptors. In other words, the tests show the breast cancer cells have receptors that will receive signals from estrogen, progesterone, HER2, or a combination of these.



To the left is an illustration of a HER2-positive breast cancer cell. This type of cell has more receptors than are normal for the protein HER2, and the more HER2 it receives, the more it will grow. The abnormal growth signals are shown in green.(http://www.webmd.com/breast-cancer/slideshow-breast-cancer-overview)

Tumor cells that have a positive receptor status can be treated with targeted therapies, which will prevent the cells from receiving signals that stimulate growth.

However, in some cases, breast cancer cells will test negative for all 3 receptors. This is known as ***triple negative breast cancer***. When the cancer cells test negative for all 3 receptors, the cancer's growth is not likely to be fueled by estrogen, progesterone, or by HER2. This means that the targeted therapies currently used to treat many other types of breast cancer will not be effective.

Although there is no targeted therapy for triple negative breast cancer yet, patients have other treatment options. Additionally, researchers are working to better understand triple negative breast cancer and develop new treatments.

In December 2010, a panel of breast cancer experts was assembled as part of an educational program for doctors and nurses about triple negative breast cancer. What follows are excerpts from that discussion. Topics ranged from risk factors to diagnosis and from surgery to treatment options for advanced disease.

Risk Factors: Genetic Mutations

Dr. Winer:
We know that triple negative breast cancer accounts for somewhere in the range of 10% to 15% of all breast cancer, at least in the United States. It seems to be more common in young women, more common in women of African ancestry, and more common in individuals who have BRCA1 mutations.

BRCA1 and BRCA2 are genes that normally work to prevent cancer from developing. A mutation is a change in the gene that can prevent its normal function. People who have inherited BRCA1 or BRCA2 mutations have a higher risk of certain cancers [such as breast and/or ovarian cancer] developing during their lifetime.

We know that unlike estrogen-receptor-positive and HER2-positive breast cancer, there are currently no targeted therapies for triple negative breast cancer. In addition, overall, stage-for-stage, the prognosis (chance for recovery) associated with triple negative breast cancer is a little worse than for some of the other subtypes of breast cancer.

For women who have BRCA1 and BRCA2 mutations, how common is triple negative breast cancer, and is there a difference between the 2 mutations?

Dr. Ford:
It is very common in BRCA1 mutation carriers (women who have inherited the mutation), and is not as common in BRCA2 carriers. Of those BRCA1 carriers in whom breast cancer develops, three quarters of the breast cancers will be of the triple negative type. Development of triple negative breast cancer in BRCA2 carriers seems to reflect patterns seen more often in the general population, 15% to 20% perhaps.

Notably, the National Comprehensive Cancer Network Breast Cancer Guidelines are going to be changed in this next year to recommend that a woman with triple negative breast cancer younger than 60 years of age, even in the absence of significant family history, could be considered for BRCA mutation testing.

Dr. Winer:
Other than being younger than age 60 years, what other features would make you think that a woman with triple negative breast cancer has a BRCA1 mutation?

Dr. Ford:
Certainly a family history of breast or ovarian cancer on either side of her family (because this is passed through males as well as females), a young age, the pathology (what the tumor cells looks like when viewed under a microscope), certain ***radiologic features*** (what the tumor looks like on a mammogram, MRI, or ultrasound image), all contribute to that decision.

Summary: Relationship Between BRCA1 and BRCA2 Mutations and Triple Negative Breast Cancer

- Approximately 75% of patients who have a BRCA1 mutation and in whom breast cancer develops will have the triple negative type.
- Approximately 15%-20% of patients who have a BRCA2 mutation and in whom breast cancer develops will have the triple negative type.
- Patients with triple negative breast cancer should consider BRCA testing if they:
  - Have relatives with ovarian or breast cancer
  - Are diagnosed with breast cancer younger than 60 years of age
  - Have suspicious pathology or radiologic test results

From:

Kandel MJ, et al. *J Clin Oncol.* 2006;24(18s):Abstract 508.
Somer R, et al. *Cancer Res.* 2009;(suppl 3):Abstract 4075.

Dr. Winer:
How are you defining "young age"?

Dr. Ford:
We often see women in their 30s and 40s with triple negative breast cancer who turn out to be BRCA carriers.

Dr. Winer:
How common is breast cancer in women with BRCA1 mutations?

Dr. Ford:
For a known carrier of a BRCA mutation, the risk starts to go up substantially in the mid 30s or younger, and over a lifetime can be up to a 60% or 70% chance for breast cancer developing; the risk for ovarian cancer is 40% to 50%. With BRCA2, the risk is slightly lower but still way above the general population risk — in the 40% to 50% range. This is what we do in genetics clinics: try to help identify risk and develop plans for screening.

Dr. Winer:
Do women who have BRCA2 mutations still have some elevated risk for ovarian cancer?

Dr. Ford:
They do, although it is less of a risk, about 10% to 12% over a lifetime. That is still way above population risk. Screening for breast cancer is incredibly important, and screening for ovarian cancer is even more challenging, given our lack of good tools.

Summary: Risk for Developing Cancer in Women With BRCA 1 and 2 Mutations

For BRCA1 mutations

- Lifetime risk for breast cancer: 60%-70%
  - Risk begins to increase starting at 30 years of age
- Lifetime risk
  - Breast cancer: 60%-70%
  - Ovarian cancer: 40%-50%

For BRCA2 mutations

- Lifetime risk
  - Breast cancer: 40%-50%
  - Ovarian cancer: 10%-12%

From:

PDQ® Cancer Information Summary. Bethesda, Md: National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/healthprofessional
National Cancer Institute. SEER Cancer Statistics Review, 1975-2005. Available at: http://seer.cancer.gov/csr/1975_2005/index.html

Detecting Triple Negative Breast Cancer

Dr. Winer:
Let's start with how to screen women who have known BRCA1 or BRCA2 mutations. How easy are these cancers to find using our current screening techniques?

Dr. Newman:
The data on use of MRI for screening are strongest for following women who have a hereditary susceptibility for breast cancer, including women who are BRCA1 mutation carriers. These mutation carriers require screening mammography in addition to breast MRI. I agree with Dr. Ford about recommending or referring for genetic counseling any woman who has been diagnosed with triple negative breast cancer, even up to the age of 60. Typically, we consider genetic counseling for any woman younger than age 40 who has been diagnosed with breast cancer. However, if a woman is diagnosed with triple negative breast cancer, I think it's quite appropriate to refer her for genetic counseling even if her cancer was diagnosed up to age 60.

Triple negative breast cancers in general have a higher likelihood of being found as interval cancers — lumps in the breast — between screening mammograms. Mammograms are appropriate, but you still have to be cautious about doing clinical breast examinations in these patients as well.

Dr. Winer:
Are investigators looking at other ways of screening for these cancers?

Dr. Newman:
The triple negative breast cancers are less likely to be associated with microcalcifications (calcium deposits within breast tissue that are often benign) and less likely to be associated with ***DCIS*** (ductal carcinoma in situ, an early form of breast cancer that develops in the milk duct but has not invaded the breast tissue), compared with the more typical ***sporadic*** (not hereditary) invasive ductal (occurring within the milk duct) cancers. They can easily be detected on ultrasound. Ultrasound is a very good way to identify and evaluate palpable lumps (ie, lumps that can be felt through the skin by the woman or her doctor).

Standard screening recommendations would be mammography on a yearly basis, but with a high threshold for workup if a lump develops in between those screening mammograms.

If a lump develops in between mammograms, a woman should undergo appropriate imaging and testing to rule out the potential presence of cancer.

Summary: Current Methods of Screening for Triple Negative Breast Cancer

- Magnetic resonance imaging (MRI) is valuable for screening individuals with known BRCA1 mutations
- Mammograms should be performed each year
- Clinical examinations are important to identify cancer that can occur between mammograms
- Ultrasound is useful in gathering more information about lumps detected by touch

From:
Warner E, et al. *J Clin Oncol.* 2001;19:3524-3531.

Special Populations

Dr. Winer:
Now let's focus on special populations, meaning those at higher risk for triple negative breast cancer. First, what about women of African ancestry?

Dr. Newman:
It has been very clearly demonstrated that African American women have about a twofold higher incidence of triple negative breast cancers compared with Caucasian American breast cancer patients. On a population basis (compared with other populations), these incidence curves are higher for African American women as well.

Individuals at highest risk for developing triple negative breast cancers are of African heritage in the premenopausal (before menopause takes place) age range. This clearly has relevance to the whole debate about when women should initiate screening mammograms (ie, either at age 40 or at age 50). Starting screening at age 50 may put African American women at greater risk for delays in diagnosis; delayed detection of triple negative breast cancer is especially dangerous.

Dr. Winer:
What about the Ashkenazi Jewish population and the frequency of gene mutations?

Dr. Ford:
What has been very interesting is the discovery that within the Ashkenazi population there was a bottleneck in history at some point that resulted in 3 founder mutations in the BRCA1 and BRCA2 genes: 2 mutations in BRCA1 and 1 mutation on the BRCA2 gene. These mutations confer risk just like any other BRCA mutation except that they are seen at a higher incidence — about 10 times higher — among Ashkenazi women than in the general Western population. Up to 1 in 40 women of clear Ashkenazi heritage may have a BRCA1 or BRCA2 mutation.

Any possibly Ashkenazi woman who has breast cancer or any family history of breast or ovarian cancer should undergo genetic testing. There is an **Ashkenazi panel** [ie, assay or test] that can be ordered.

Instead of sequencing the entire gene, the Ashkenazi panel is a test for the 3 BRCA mutations specifically known to occur in people of Ashkenazi heritage.

It is important to remember that if the woman does not have that mutation but has a compelling family history, she may still have another mutation and should be fully evaluated.

Summary: Special Populations at Risk for Triple Negative Breast Cancer

- African American women are twice as likely to develop triple negative breast cancer than Caucasian American women
  - African American women are at highest risk for triple negative breast cancer before menopause
  - The recent (but controversial) recommendation for yearly mammograms starting at age 50 years may result in delayed diagnoses for younger African American women
- Jewish women of Ashkenazi heritage are up to 10 times more likely to have a BRCA1 or BRCA2 mutation than other women of Western countries
  - Women of Ashkenazi heritage with breast cancer or a family history of breast or ovarian cancer should have genetic testing
    - A special "Ashkenazi panel" is available to test for BRCA mutations

From:

Stark A, et al. *Cancer.* 2010;116:4926-4932.
Stead LA, et al. *Breast Cancer Res.* 2009;11:R18.
Screening for Breast Cancer, Topic Page, July 2010, US Preventive Services Task Force. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspsbrca.htm
Roa BB, et al. *Nat Genet.* 1996;14:185-187.
Levy-Lahad E, et al. *Am J Hum Genet.* 1997;60:1059-1067.

Defining Triple Negative Breast Cancer

Dr. Winer:
Is triple negative breast cancer one disease, or is there variability? We know, for example, that patients with triple negative breast cancers do not always demonstrate similar responses to treatment.

Dr. Sledge:
Correct. I think we are still learning a lot about what constitutes triple negative breast cancer. You start off with the term "triple negative," which means estrogen receptor negative, progesterone receptor negative, HER2 negative -- it's a negative definition.

It appears that the triple negative type of breast cancer is probably a collection of subdiseases (types of breast cancer).

Dr Winer:
Compared with other breast cancers, triple negative breast cancers tend to be genetically unstable. To what extent is that different from other high-grade cancers?

Dr. Sledge:
There are certainly published studies suggesting a greater degree of chromosomal rearrangement in triple negative breast cancers than in most other sub-types of breast cancer. This has led to the suggestion that these cancers have a higher mutational load (the burden/problems created by growing numbers of genes that do not function properly). Not only are they more likely to be drug resistant, but they are also likely to have more pathways that are activated and therefore more difficult to "turn off."

Summary: What We Know About Triple Negative Breast Cancer…Now

- Triple negative breast cancer is currently defined by characteristics it does not have (hormone- or HER2-positive receptor status).
- Research about triple negative breast cancer is relatively new.
- Researchers suspect that there are not one but several types of triple negative breast cancers.
- The results of studies suggest that in triple negative breast cancer, chromosomes actively rearrange, altering the genes
  - These genetic changes may make it difficult for scientists to develop a drug that will be effective for the majority of patients
  - The cancer cells may have more ways (kinase pathways) to receive signals than other types of cancer

Treating Triple Negative Breast Cancer

Local Therapies (Surgery and Radiation)

Dr. Winer:
Let's discuss **local therapy** (treatment at the site of the cancer) for a few minutes before we talk about systemic therapy (treating the entire body) for women who have triple negative breast cancer. Are there any differences in the surgical approach to triple negative breast cancer vs other types? In other words, are your decisions about conservative surgery (surgery that concentrates on removal of the cancer only) vs **mastectomy** (surgery that removes part or all of the breast tissues), screening of the other breast, etc, different in a woman with triple negative breast cancer?

Dr. Newman:
That's a great question. In general, a biologically aggressive cancer is going to be biologically aggressive in all parts of the body and is more likely to spread to distant organs. When an aggressive cancer is treated with lumpectomy, it is more likely to recur in the breast itself. So from that perspective, it's reasonable to be concerned about breast conservation in any woman with a triple negative tumor.

On the other hand, most of the studies looking at local recurrence following breast conservation surgery for triple negative breast cancer compared with the non-triple negatives show equal local control rates. Most research shows that women with triple negative breast cancers can be safely treated with breast-conserving surgery, as long as the patient is eligible for lumpectomy based on standard clinical criteria.

Dr. Sledge:
The one local control issue that comes up in my clinic is how to best approach those patients who have BRCA1 mutations? Can you provide some insights about the timing of surgery and the extent of surgery?

Dr. Newman:
That's a very good question. Women with documented hereditary susceptibility or who appear to be at high risk for hereditary susceptibility will be more motivated to consider bilateral mastectomy when they are diagnosed with breast cancer. It becomes a personal decision. When women with documented BRCA mutations are treated with breast conservation surgery for a known cancer, they have equal survival rates compared with the non-BRCA mutation carriers, but the in-breast risk is greater because they have about a 4 to 5 times higher risk of developing a new primary cancer in the breast.

Dr. Winer:
Sometimes it makes sense to defer the decision about bilateral mastectomy because radiation is going to be given either way.

Summary: Local Treatment of the Breast

Breast-conserving surgery (lumpectomy) can be considered

- Data suggest that lumpectomy is equally effective for women with triple negative breast cancer as for women with other types of breast cancer
- Consider use of neoadjuvant treatment (chemotherapy started prior to surgery)
  - A marker should be inserted into the location of the cancer in case the tumor becomes so small during the treatment that an x-ray is needed to locate it later for surgery

Patients with BRCA mutations

- **Bilateral mastectomy** is an option to prevent recurrence of cancer in breast tissue
- Breast-conserving surgery (lumpectomy) is also an option
  - Survival rates are equal to those of women who do not have a BRCA mutation
  - Risk for cancer developing in the breast again is 4 to 5 times higher than for women without hereditary mutations

From:

Solin LJ. *Clin Br Cancer.* 2009;9:96-100.
Freedman GM, et al. *Cancer.* 2009;115:946-951.
Haffty BG, et al. *J Clin Oncol.* 2006;24:5652-5657.
Heemskerk-Gerritsen BAM, et al. *Ann Surg Oncol.* 2007;14:3335-3344.
Kell MR, et al. *BMJ.* 2007;334:437-438.

Systemic Therapy (Medications)

Dr. Winer:
How do you approach **adjuvant systemic therapy** (medications that affect the whole body that are given after surgery) decisions in women with triple negative breast cancer, realizing that you don't have the option of using hormonal therapies or anti-HER2 therapy?

Dr. Sledge:
Several different types of standard chemotherapies are used around the world: anthracycline-based chemotherapies such as AC [doxorubicin, cyclophosphamide] followed by T [docetaxel], or TAC [docetaxel, doxorubicin, cyclophosphamide], and nonanthracycline-based regimens such as TC [docetaxel, cyclophosphamide].

Summary: Systemic Therapies for Triple Negative Breast Cancer

- Anthracycline-based regimens (course of treatment)
  - AC [doxorubicin, cyclophosphamide] followed by T [docetaxel]
  - TAC [docetaxel, doxorubicin, cyclophosphamide]
- Nonanthracycline regimens
  - TC [docetaxel, cyclophosphamide]

From:

Jones SE, et al. *J Clin Oncol.* 2006;24:5381-5387.
Heemskerk-Gerritsen BAM, et al. *Ann Surg Oncol.* 2007;14:3335-3344.
Kell MR, et al. *BMJ*. 2007;334:437-438.

One of the big questions, though, for these patients with triple negative breast cancer is the "how low do you go" question. In the past, we said we would only give chemotherapy to patients whose tumors were greater than 1 centimeter in size, but that standard may not apply to this population of patients with triple negative breast cancer. There are certainly some data that suggest that relatively smaller triple negative breast cancers still put you at significant risk for eventual distant recurrence of disease. Therefore, we probably need to think about decreasing [tumor size] boundaries for postsurgical chemotherapy in that subgroup.

Dr. Winer:
What about use of the "platinum" agents, such as cisplatin or carboplatin after surgery to prevent recurrence? What do we know about that?

Dr. Sledge:
There are fascinating data, particularly for patients with BRCA1 mutations, suggesting that platinum-based therapy might be quite an excellent approach in the preoperative setting.

Having said that, we are still far from being able to consider that a standard-of-care option.

Dr. Winer:
Sometimes disease recurs despite optimal local therapy and **adjuvant systemic therapy** for triple negative breast cancer. Are there particular sites of recurrences that are more common for those with triple negative disease or different from sites of recurrence in other patients?

Dr. Sledge:
One thing we know about estrogen-receptor-negative tumors in general is that they have a greater tendency to spread to the internal organs and a relatively lesser tendency to spread to the bone compared with estrogen receptor-positive tumors. In particular, we've recently learned that there is a significantly increased rate of **central nervous system** (brain and spinal cord) metastasis for these patients.

Summary: Recurrence Patterns of Triple Negative Breast Cancer

- Metastases more likely in
  - Internal organs
  - Brain and spinal cord
  - Lungs
- Metastases less likely in
  - Bone

From:

Anders CK, Carey L. *Clin Breast Cancer.* 2009;9(suppl2):S73-S81.
Gadiyaram V, et al. *Cancer Res.* 2009;69(suppl):Abstract 6159.
Dent R, et al. *Breast Cancer Res Treat.* 2008;115:423-428.

Dr. Winer:
When a woman who has triple negative breast cancer develops metastatic disease, what we are left with, at least at the moment, is standard chemotherapy.

Are there any particular agents that you want to comment about?

Summary: Treatment for Metastatic Triple Negative Breast Cancer

Standard chemotherapy

Treatments under study

- Platinum therapy
  - Cisplatin
  - Carboplatin
- Poly-ADP ribose polymerase (PARP) inhibitors
  - Olaparib
    - Used as a single agent
    - Benefits patients with BRCA mutations
  - Iniparib (BSI 201)
    - Used in combination with carboplatin/gemcitabine
    - Benefits patients with triple negative breast cancer (?)
- Less promising study results
  - Angiogenesis inhibitors
    - Bevacizumab + paclitaxel
  - Tyrosine kinase inhibitors
    - Sorafenib, sunitinib
      - » "Dirty" agents (activity on multiple targets)

From:

Miller K, et al. *N Engl J Med.* 2007;357:2666-2676.
Moreno-Aspitia A, et al. *J Clin Oncol*. 2008;27:11-15.
Crown J, et al. *J Clin Oncol*. 2010;28(suppl):18s. Abstract LBA 101.
Tutt A, et al. *Lancet.* 2010;376:235-244.
Gelmon A, et al. *J Clin Oncol.* 2010;28:15s. Abstract 3002.
O'Shaughnessy J, et al. *N Engl J Med.* 2011 Jan 5. [Epub ahead of print]

Dr. Ford:
There is a hint that these tumors have an underlying problem dealing with and repairing DNA damage. So, the very feature that drives these tumors to become ugly in the first place may be their Achilles' heel. It certainly seems that the platinum class and other DNA cross-linking agents may have a particular role in exploiting that genomic instability.

Dr. Winer:
What about new targets and new therapies? First on the list might be the angiogenesis inhibitors because they have been around the longest.

Angiogenesis is a process in which blood vessels multiply and grow. Just like in other tissues of the body, blood vessels bring oxygen and nutrients to tumors. Angiogenesis inhibitors are drugs that prevent the growth of these blood vessels, "starving" the cancer so it cannot grow and spread.

Dr. Sledge:
From the initial trial of bevacizumab in the front-line metastatic setting (Eastern Cooperative Oncology Group E2100 trial), we know that adding bevacizumab to paclitaxel significantly increases progression-free survival in the general population of patients with metastatic breast cancer, but also specifically in those with triple negative breast cancer. Unfortunately, in that trial and in several subsequent randomized phase 3 trials, the improvement in progression-free survival has not yet translated to an improvement in overall survival. I think we would have to say that improving progression-free survival may be important from the perspective of improving symptoms, but it certainly doesn't get us closer to our ultimate goal of having our patients live much longer lives.

Dr. Winer:
What about the other angiogenesis inhibitors?

Dr. Sledge:
Other agents, including the receptor **tyrosine kinase inhibitors** such as sorafenib and sunitinib, have been tried. Sunitinib has failed in multiple phase 3 trials so it is not going to be developed any further in metastatic breast cancer. The jury is still out on sorafenib because the trials are not as far along but certainly, the vascular endothelial growth factor (ie, VEGF) story has not been a very promising one.

***Tyrosine kinase inhibitors** are drugs that block chemical messengers called tyrosine kinases, which are enzymes that enable signaling within cells. Blocking these signals stops the cells from growing and multiplying. Some tyrosine kinase inhibitors work to block one kind of signal. Others such as sorafenib and sunitinib block multiple signals. Sorafenib and sunitinib are also angiogenesis inhibitors because they block signals needed for blood vessel development and cell growth and division.*

Dr. Winer:
We should now talk about **PARP inhibitors**, which have been a focus of much attention over the past few years. What is PARP inhibition and how might it work, both in patients who have BRCA1 and BRCA2 mutations and in those with triple negative breast cancer?

Dr. Ford:
PARP stands for **"poly (adenosine diphosphate ribose) polymerase."** PARP is a whole family of enzymes, but the relevant one is called PARP1, which is a DNA repair gene. This may be relevant because triple negative breast cancers may have defects in DNA repair.

The PARP inhibitors were developed a number of years ago, originally as radiation sensitizers or sensitizers to DNA-damaging drugs. Fascinating basic science and clinical work have shown that the PARP inhibitors have excellent clinical activity for BRCA1- and BRCA2-associated tumors. There are many ongoing trials,

some of which combine PARP inhibitors with other DNA-damaging agents and some use PARP inhibitors as single agents, so it gets hard to compare them. Certainly, some subgroups of triple negative cancers that don't have a BRCA1 or BRCA2 mutation seem to share this underlying DNA repair problem and probably share susceptibility to those agents. Whether PARP inhibitors will work as well in those women who have non-BRCA-related triple negative breast cancer as in those with BRCA mutations is not known yet.

Dr. Winer:
We probably know the most about olaparib and about iniparib. Olaparib has been used mostly as a single agent, and its benefits have largely been confined to people who have BRCA1 or BRCA2 mutations, at least in breast cancer.

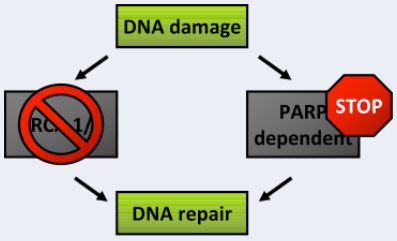
Dr. Ford:
That's right. Olaparib is quite active in ovarian cancer, but in breast cancer, its activity was not as pronounced in non-BRCA-related triple negative disease as in BRCA1-mutant tumors.

Iniparib, in contrast, was developed for use in combination with chemotherapy. There are few data on its use as a single agent in breast cancer, but in combination with carboplatin and gemcitabine it has shown interesting activity, initially in metastatic triple negative breast cancer and now in earlier-stage triple negative breast cancer.

Dr. Winer:
Can you say a few words about this concept of "synthetic lethality"?

Dr. Ford:
Synthetic lethality is a confusing term that comes from old classical genetics but refers to the notion of targeting redundant (repeated) or backup pathways. If one gene – gene A – is knocked out, it really doesn't have any effect, and if gene B is knocked out, it doesn't really have any effect, but if they both get knocked out, the cancer cell will not be able to repair damage that is inflicted by chemotherapy, for instance, and it dies.

Synthetic Lethality



Graphic courtesy of Harold Burstein, MD, PhD

What is fascinating is that concept seems to extend to at least some triple negative breast cancers that don't have an underlying BRCA1 or BRCA2 mutation. We don't really know what's underlying them, but it is likely that the pathway is compromised somehow and that allows you to target those cells.

Dr. Winer:
What do we know so far about iniparib in terms of sporadic [non-BRCA-related] triple negative breast cancer?

Dr. Sledge:
In a decently sized randomized phase 2 trial that was presented by Dr. Joyce O'Shaughnessy at the 2009 annual American Society of Clinical Oncology meeting, the addition of iniparib to the carboplatin/gemcitabine combination significantly improved response rates, significantly improved progression-free survival, and appeared to significantly improve overall survival. It has led to a much larger phase 3 trial that is closed to new patients and will be analyzed in the near future.

Dr. Winer:
Another question is whether PARP inhibition will work in combination with chemotherapy and in other types of breast cancer and even in other diseases.

What about other targets such as **EGFR [epidermal growth factor receptor]** in triple negative breast cancer? EGFR is expressed in 50% of triple negative breast cancers. A few trials have looked at cetuximab in patients with triple negative breast cancer. Where do those stand?

Like HER2, epidermal growth factor receptor, EGFR, refers to proteins that encourage the growth of cells. Researchers are studying cetuximab, a drug that blocks signals from reaching EGFR, to determine whether it will stop the growth of cells in triple negative breast cancer.

Dr. Sledge:
By and large, the single-agent trials of EGFR inhibition have been disappointing, with response rates under 10%. At the 2010 San Antonio Breast Cancer Symposium, there was a report from a group in Spain that suggested an improvement in response rate in patients with triple negative breast cancer who received cetuximab in addition to chemotherapy. It's a modest improvement, and we still don't know which patients with triple negative disease might benefit from EGFR inhibition or even whether these agents work at all in this population.

Dr. Winer:
We don't want to treat everybody with an agent that's moderately toxic and moderately expensive if only a small number of patients will benefit.

The last target for us to talk about is alterations in the **PI3 kinase pathway**. Although PI3 kinase mutations are quite uncommon in triple negative breast cancer, loss of **PTEN**, which activates that pathway, seems to be quite common.

Summary: Potential New Targets

EGFR

- Expressed in 50% of triple negative breast cancers
  - Single-agent trials with **EGFR inhibitor** (cetuximab) have been disappointing
  - EGFR inhibitor (cetuximab) + cisplatin
    - Improved response rate in patients with triple negative disease

Phosphatidylinositol 3-kinase (PI3 kinase)

- Studies are classifying subgroups within triple negative breast cancer on the basis of gene expression
- Potential for identifying subgroups that may be sensitive to PI3 kinase inhibitors

From:

Nielsen TO, et al. *Clin Cancer Res.* 2004;10:5367-5374.
Sanchez-Munoz A, et al. *BMC Cancer.* 2010;10:136.
Corkery B, et al. *Ann Oncol.* 2009;20:862-867.
Baselga J, et al. *Cancer Res.* 2010;70(suppl):95s. Poster PD01-01.
Lehmann BD, et al. *Cancer Res.* 2010;70(suppl):97s. Poster PD01-07.

***Phosphatidylinositol 3-kinase (PI3 kinase)** is a family of enzymes that, like tyrosine kinase, are involved with signaling that prompts cells to grow and multiply. **Phosphatase and tensin homolog (PTEN)** is a gene that provides instructions for making a protein that works to kill cells that are growing and dividing too quickly or in an uncontrolled way. Changes to/loss of PTEN activates the PI3 kinase pathway and enables cancer cells to grow and multiply. This problem has been identified in triple negative breast cancer.*

Dr. Ford:
There were some interesting data at the San Antonio Breast Cancer Symposium 2010 meeting showing that 6 or 7 subgroups could be distinguished within the triple negative subtype on the basis of gene expression. In animal studies, they demonstrated that some of those groups (not all of them) were sensitive to different agents, including PI3 kinase inhibitors.

Dr. Newman:
I had a medical oncology question.
How important is it to obtain a biopsy from a metastatic site? Can marker expression change?

***A marker** is a substance or physiologic trait that indicates the presence of a medical condition such as cancer. Here, Dr. Winer and Dr. Sledge discuss potential changes in tumor receptor status (marker) between the original breast cancer diagnosis and the occurrence of metastatic disease. Changes in tumor markers may be important for treatment decisions.*

Dr. Sledge:
Like many of my colleagues, I repeat the biopsy at least at the time of the initial diagnosis of metastatic disease. If we look at the changes, though, most go from estrogen receptor positivity to estrogen receptor negativity, with occasional changes of HER2 negativity to HER2 positivity. A question that's unanswered yet is how much of this is just simply the result of testing errors and blips. I don't think we know the answer to that. There was a presentation at the 2010 San Antonio Breast Cancer Symposium that suggested this is more common than we thought. It is certainly reasonable to repeat the biopsy at least once from a metastatic site to see whether the biology of the tumor has changed.

Dr. Winer:
Most cancers that are triple negative at diagnosis are still triple negative when they are rebiopsied. Nevertheless, I tend to rebiopsy virtually everyone at some point.

Summary: Changes in Marker Expression Between Primary (First) and Metastatic Breast Cancer

Repeat biopsy in metastatic setting to see whether the biology of the tumor has changed

- Test for differences between primary and metastatic tumors
  - Change of estrogen- or HER2-receptor status from negative to positive occasionally seen
  - Treatment decision may change if tumor receptors change

From:
Nakamura R, et al. *Cancer Res.* 2010;70(suppl):296s. Poster P3-14-13.

Dr. Winer:
Dr. Newman, do you have any insights into how difficult this is for people and the anxieties that they face about having this particular subtype of breast cancer, perhaps knowing that there just aren't as many treatment options?

Dr. Newman:
That is a very important point. It's appropriate to make sure that we are very aggressive with support services for these patients because the label "triple negative breast cancer" is receiving a lot of media attention and a lot of women are scared that it's an automatic death sentence. Yet, there are treatments for these cancers, and for women with a predisposition for triple negative breast cancers, early detection and treatment are crucial.

Additional Resources

Sharing a discussion among experts on triple negative breast cancer, such as this one, is one way for you to learn more about the types of questions that physicians have about the disease and how researchers are trying to address them. However, you may still have questions.

Following is a list of some available resources to help you further understand triple negative breast cancer and its treatment:

The Triple Negative Breast Cancer Foundation

PO Box 204
Norwood, NJ 07648
(646) 942-0242

TNBC Helpline
Phone (toll free): 1-877-TNBC(8622)
E-mail: TNBCHelpline@cancercare.org

Website: http://www.tnbcfoundation.org

Facebook: http://www.facebook.com/pages/Triple-Negative-Breast-Cancer-Foundation/152736808090947

Twitter: http://twitter.com/tnbcfoundation

BreastCancer.Org

7 East Lancaster Avenue
3rd Floor
Ardmore, PA 19003

News, informational booklets, online discussion boards, blog, chat rooms, and ask-the-expert conferences.

Website: http://www.breastcancer.org/symptoms/diagnosis/trip_neg

Facebook: http://www.facebook.com/pages/Breastcancerorg/40868540984

Twitter: http://twitter.com/Breastcancerorg

National Cancer Institute

NCI Office of Communications and Education
Public Inquiries Office
6116 Executive Boulevard
Suite 300
Bethesda, MD 20892-8322
Phone: 1-800-4-CANCER (1-800-422-6237)

Online disease information and links to clinical trials: http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/page8#Section_Trial-Search_743_sid_8

Facebook: http://www.facebook.com/cancer.gov

Twitter: http://twitter.com/@ncibulletin

American Cancer Society

250 Williams St., NW
Suite #6000
Atlanta, GA 30303
Phone: 1-800-227-2345

Website: www.cancer.org

Facebook: http://www.facebook.com/AmericanCancer-Society

Twitter: http://twitter.com/americancancer

Definitions

Adjuvant systemic therapy: treatment administered after surgery by infusion or by mouth to reduce the risk for disease recurrence

Angiogenesis inhibitors: drugs that prevent the growth of blood vessels that feed a tumor, "starving" the cancer so it cannot grow and spread

Ashkenazi panel: a test for the 3 BRCA mutations specifically known to occur in people of Ashkenazi heritage

Bilateral mastectomy: surgery that removes part or all of both breasts

BRCA1/BRCA2: genes that normally work to prevent cancer from developing

Breast-conserving surgery (lumpectomy): surgery that concentrates on removal of the cancer only

Central nervous system: brain and spinal cord

DCIS: ductal carcinoma in situ, an early form of breast cancer that develops in the milk duct but has not invaded the breast tissue

Disease stage: how much the cancer has spread

EGFR (epidermal growth factor receptor): proteins that encourage the growth of cells

HER2 (human epidermal growth factor receptor): receives signals that stimulate the growth of breast cancer cells. The more HER2 receptors the cancer cells have, the more likely the breast cancer is to grow.

Histopathology: what cells look like under a microscope

Grade: how much the cancer has progressed

Local therapy: treatment given at the site of the cancer (eg, surgery, radiation)

Marker: a substance or physiologic trait that indicates the presence of a medical condition such as cancer

Mastectomy: surgery that removes part or all of the breast tissues

Mutation: a change in the gene that can prevent its normal function

Mutational load: the burden/problems created by growing numbers of genes that do not function properly

Phosphatidylinositol 3-kinase (PI3 kinase): a family of enzymes involved with signaling that prompts cells to grow and multiply.

Phosphatase and tensin homolog (PTEN): a gene that provides instructions for making a protein that works to kill cells that are growing and dividing too quickly or in an uncontrolled way.

PARP [poly(adenosine diphosphate ribose) polymerase]: a family of enzymes; the relevant one is called PARP1, which is a DNA repair gene.

Radiologic features: what the tumor looks like on a mammogram, MRI, or ultrasound image

Receptors: proteins on the surface of cancer cells that receive signals and cause the cells to grow

Sporadic cancer: not hereditary

Synthetic lethality: refers to the notion of targeting redundant (repeated) or backup pathways for cellular repair

Triple negative breast cancer: tumors that test negative for the 3 key breast cancer receptors–estrogen, progesterone, and HER2

Tyrosine kinase inhibitors: drugs that block chemical messengers called tyrosine kinases, which are enzymes that enable signaling within cells. Blocking these signals stops the cells from growing and multiplying

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