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BIG TAKEAWAY FROM ASCO: 70 PERCENT OF WOMEN WITH EARLY BREAST CANCER DON'T BENEFIT FROM ADJUVANT CHEMOTHERAPY

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THE CLINICAL CANCER LETTER

BIG TAKEAWAY FROM ASCO:
70 PERCENT OF WOMEN WITH EARLY BREAST CANCER DON'T BENEFIT FROM ADJUVANT CHEMOTHERAPY

By Paul Goldberg

An NCI-sponsored trial showed that up to 70 percent of women with hormone receptor-positive, HER2-negative, axillary lymph node-negative breast cancer would not benefit from chemotherapy.

The trial—called TAILORx, or the Trial Assigning Individualized Options for Treatment (Rx)—was presented at a plenary session at the annual meeting of the American Society of Clinical Oncology June 3.

A paper stemming from the study was simultaneously published in the *New England Journal of Medicine*.

About half of breast cancer patients diagnosed worldwide each year have hormone-receptor positive, HER2-negative, node-negative disease. TAILORx found that for the vast majority of women with this form of breast cancer, adjuvant chemotherapy and hormone therapy is non-inferior to hormone therapy alone.

TAILORx was designed and led by the ECOG-ACRIN Cancer Research Group. The trial, which began in 2006, is the largest ever conducted in adjuvant therapy for breast cancer. It is also one of the first large-scale trials to examine a methodology for personalized cancer treatment.

Altogether, the phase III trial enrolled 10,273 women and randomized 6,711 of them. The trial was conducted at 1,182 sites in the United States, Australia, Canada, Ireland, New Zealand, and Peru.

Joseph Sparano

"In terms of the big picture and the impact on care, application of this test in clinical practice in this population will be estimated to spare chemotherapy in about 70 percent, and to select chemotherapy in about 30 percent, on average," said Joseph Sparano, lead author of the NEJM paper, who presented the results at ASCO. Sparano is the associate director for clinical research at the Albert Einstein Cancer Center and Montefiore Health System and vice chair of the ECOG-ACRIN Cancer Research Group.

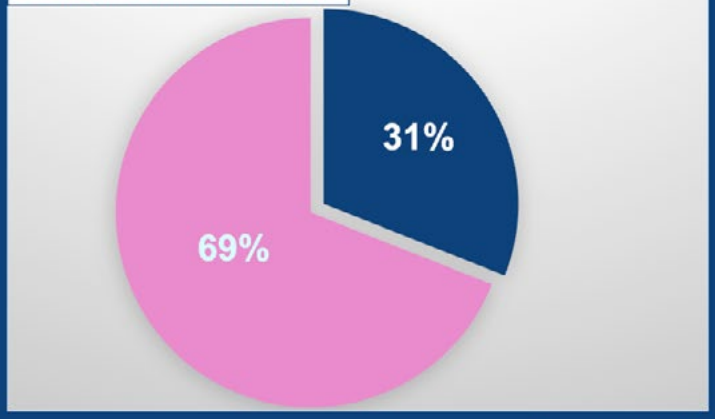
NCI doesn't regularly tabulate the cost of individual trials, but a back-of-the-envelope calculation by Jeffrey Abrams, associate director of NCI's Cancer Therapy Evaluation Program, suggests that over 12 years, the institute spent $35 million to $40 million on the trial. An additional $5 million came from the sale of the Breast Cancer Research Stamp.

"It speaks to the fact that we really do have a national network that can con-

TAILORx: Impact on Care

RS Spares Chemo in about 70%
- > 50 yrs with RS 11-25 (45%)
- Any age with RS 0-10 (16%)
- ≤50 yrs with RS 11-15 (8%)

RS Selects Chemo in about 30%
- All with RS 26-100 (17%)
- < 50 with RS 16-25 (14%)



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TAILORx Volunteers
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PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Joseph A. Sparano, MD

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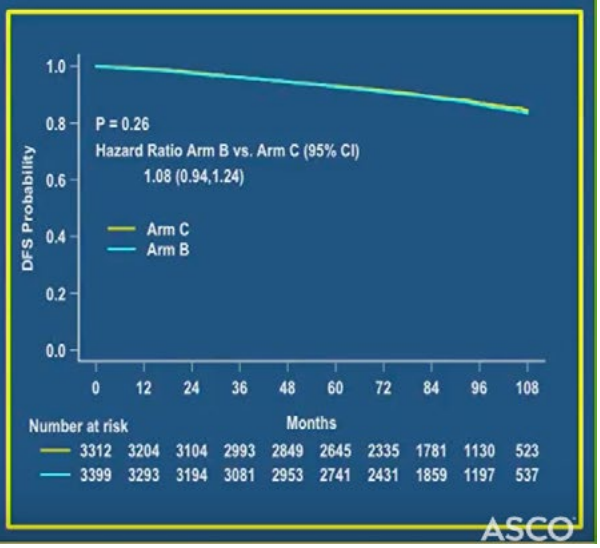
TAILORx: Top-Line Results

- **Primary endpoint – ET non-inferior to ET + Chemo**
  - Hazard ratio 1.08 (95% CI 0.94, 1.24), p=0.26
  - 9 year IDFS rates 83.3% vs. 84.3%
- **Other endpoints in RS 11 – 25 arms - similar outcomes**
  - Distant recurrence rate (5%)and overall survival rates similar at 9 years irrespective of chemo use
- **Other arms: RS 0-10 and RS 26-100**
  - Low RS 0-10: 3% distant recurrence rate with ET alone
  - High RS 26-100: 13% distant recurrence despite chemo
- **Exploratory analysis in RS 11-25 group – determine whether any subgroups derived some chemo benefit**
  - ≤ 50 years & RS 16-25: some chemo benefit – 2% fewer distant recurrences for RS 16-20 & 7% fewer for RS 21-25

Primary Endpoint – IDFS
RS 11 - 25
Arm B-ET alone; Arm C –ET + Chemo
N=6711 Randomized



ASCO

duct studies like this," Abrams said to The Cancer Letter. "This is the type of study that a pharma company would not do because it's not intended to bring a new treatment into medicine; it's really to decide how best to treat patients, and actually remove some treatments from patients.

"It shows that the government still has a role to play for this kind of trial."

A conversation with Abrams appears on page 13.

Harold Burstein

"I think [TAILORx] is important for several reasons," Harold Burstein, associate professor at Harvard Medical School and staff physician at Brigham and Women's Hospital, said at a press conference at ASCO. "First, the original data for use of the Oncotype DX recurrence score were based on chemotherapy regimens that were 25 years old now. So, the question has been, if we use modern chemotherapy, would the results be different?

"Secondly, we've improved our endocrine treatments, our anti-estrogen approaches, which also may have affected these results.

"Third, it's important to have prospective validation of the data, and finally, there was a gray zone, an intermediate zone, where it was unclear what the magnitude of benefit for chemotherapy might be, and this created practical decision-making challenges for patients and for clinicians.

"For those of you who have ever been a clinician in a consultation room, or a patient in a consultation room, you know there is a huge difference between saying, 'Well, you might benefit a little bit,' and saying, 'There is no benefit for you. 'And with the data provided here, from this massive NCI-sponsored trial, show that the vast majority of women who have this test performed on their tumor can be told that they don't need chemotherapy, and that can be said with tremendous confidence and reassurance.'

Experts' commentary about TAILORx appears on page 8.

In 2000, an NIH consensus conference recommended wider use of adjuvant chemotherapy for women with localized breast cancer. At the time, it was clear that a minority of women stood to benefit from adjuvant chemotherapy, but no technology existed to identify the women who stood to benefit.

Nearly two decades later, the hottest controversies at that consensus conference now look like a side issue—the role of paclitaxel in adjuvant therapy. (The Cancer Letter, Nov. 10, 2000).

TAILORx used a molecular test, the Oncotype DX Breast Recurrence Score, to assess the expression of 21 genes associated with breast cancer recurrence.

With these results, the use of Oncotype DX, which costs around $4,000, becomes even more hardwired into treatment decisions in breast cancer. Indeed, when the stock market opened on Monday, June 4, the price of a share of Genomic Health jumped from $39.7 to $43.9. It reached the high of $51 on June 6, and is now hovering around $49.

Oncotype DX doesn't have FDA clearance, while a competing product, Mammaprint, has FDA 510(k) clearance. The Genomic Health central laboratory has the US Clinical Laboratory approval to offer Oncotype DX as a homebrew.

In TAILORx, researchers used the Oncotype DX score to assign women with early-stage, HR-positive, HER2-negative, axillary lymph node-negative breast cancer to adjuvant treatment.

Only women with Oncotype DX results of 11 to 25 were randomized to receive endocrine therapy with or without chemotherapy.

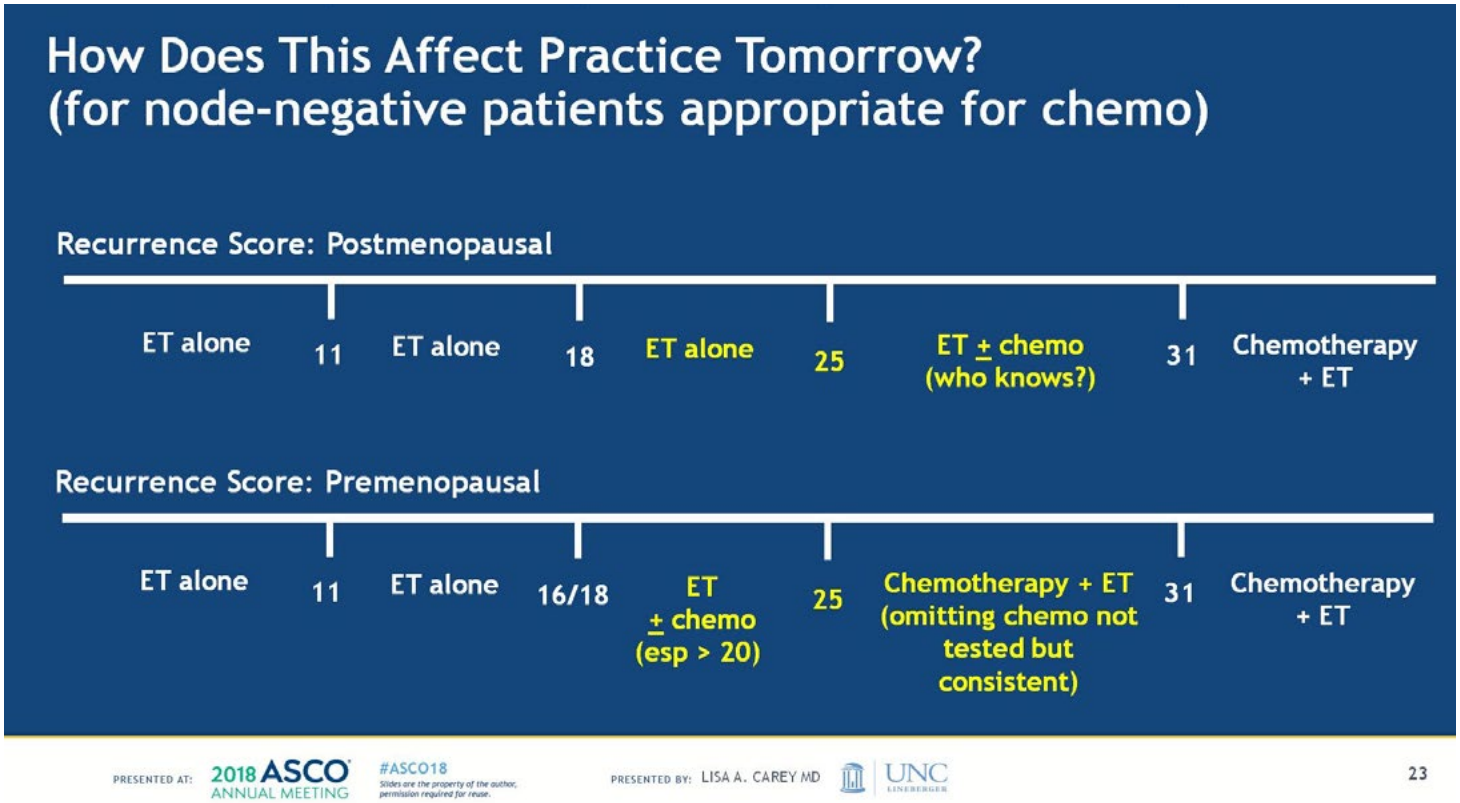
Women with the scores of 0 to 10 were assigned to endocrine therapy alone, based on the prior results from the NSABP B-20 study, which showed no benefit of chemo in this low-risk group.

Women with the score of 26 to 100 were assigned to chemotherapy and endocrine therapy, also based on NSABP B-20 study, which showed an absolute benefit of chemotherapy greater than 20 percent.

The primary endpoint was disease-free survival, based on recurrence of cancer in the breast, regional lymph nodes or distant organs, a second primary cancer in the opposite breast or another organ, or death from any cause.

At a median follow-up of 7.5 years, the study met its primary pre-specified endpoint indicating that hormone therapy alone was not less effective than chemotherapy plus hormone therapy in women with a Breast Recurrence Score of 11-25.

Nine-year rates were similar in the two treatment arms for disease-free survival (83.3% vs. 84.3%), distant recurrence (94.5% vs. 95.0%), and overall survival (93.9% vs. 93.8%), indicating



no benefit from adding chemotherapy to hormone therapy.

In a post-hoc analysis, the researchers identified the group that seemed to have some benefit from chemotherapy—women 50 years or younger who had a Breast Recurrence Score of 16-25.

"A very important finding was that in an exploratory analysis in a randomized group, which we conducted to really nail down and determine that there is no subgroup that derived some benefit from chemotherapy, we found an interaction between age and recurrence score," Sparano said at a press conference at ASCO. "Younger women—50 or younger—who had the recurrence score of 16 to 25 had some chemo benefit, and there were 2 percent fewer recurrences for the recurrence score of 16 to 20, and 6 to 7 percent for those with a recurrence score of 21 to 25.

"And this is information that could drive some women who have the recurrence score in this range to accept chemotherapy."

The researchers found that women with a recurrence score of 10 or less had very low recurrence rates with hormone therapy alone, irrespective of age or other clinical factors. In addition, those with a recurrence score of 26 or higher had a distant recurrence rate of 13% despite chemotherapy and hormone therapy, indicating the need to develop more effective therapies for this group.

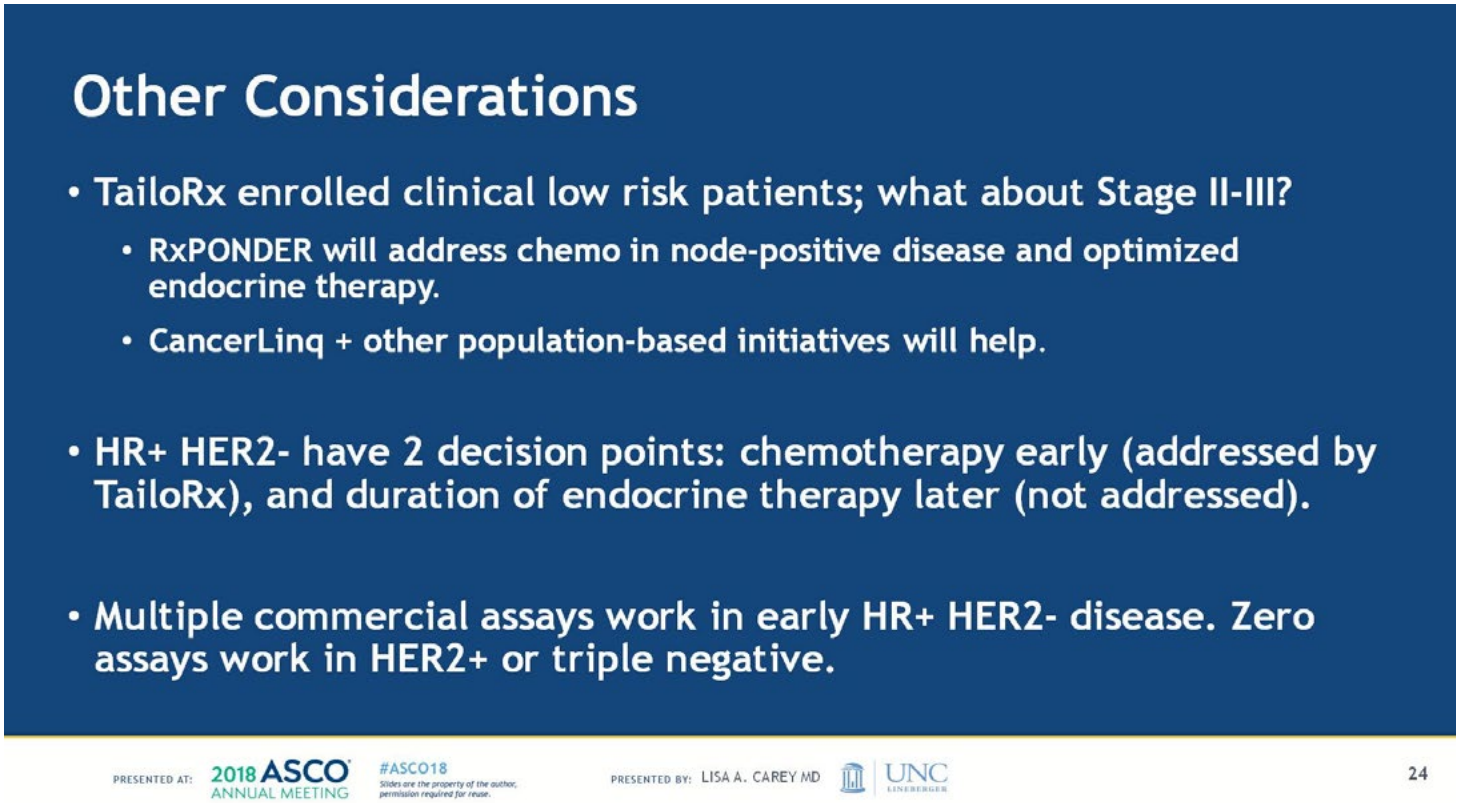
According to the authors, the findings suggest that chemotherapy may be spared in:

- All women older than 50 years with hormone-receptor positive, HER2-negative, node-negative breast cancer and a Recurrence Score of 0 to 25 (about 85% of women with breast cancer in this age group)
- All women 50 years or younger with hormone-receptor positive, HER2-negative, node-negative breast cancer and a Recurrence Score of 0 to 15 (about 40% of women with breast cancer in this age group).

The researchers also found that women with a score of 0–10 had very low recurrence rates with hormone therapy alone at nine years (3 percent).

This confirms similar findings from earlier studies. In addition, they found that women with a score of 26–100 had a distant recurrence rate of 13 percent despite receiving both chemotherapy and hormone therapy. This finding points to the need to develop more effective therapies for women at high risk of recurrence.

"This is not so much about de-escalation, which is a phrase that many in the media had picked up on," Burstein said at a press conference at ASCO. "The



goal of this study is not just to use less treatment. The goal is to tailor treatment. They chose the title very aptly, with the idea that some women are going to need more of one kind of therapy and less of another and others are going to get a different treatment, based on the biology of their tumor.

"Even in the highest risk group of patients here, the ones that got chemotherapy and hormone therapy because their Oncotype scores were in the high range, the 10-year disease-free survival was 87 percent. We have made extraordinary progress in the way we are managing breast cancer. In the low-risk group, the recurrence rate is less than 5 percent.

"Women with breast cancer who are getting modern therapy are doing extraordinarily well, and this test shows us how to tailor that management so they get exactly the right amount of treatment—not too much and not too little."

Lisa Carey

Lisa Carey, the discussant at the plenary session focused in part on the subgroup analysis that pointed to a potential benefit for a narrow group of patients.

"A couple things that we have to note: the first is this is an exploratory analysis. It's also an unplanned analysis," said Carey, the Richardson and Marilyn Jacobs Prior Distinguished Professor in breast cancer research and the chief of the division of hematology oncology at the University of North Carolina at Chapel Hill. "So, it's an exploratory unplanned analysis of a very large study. It is, however, biologically plausible. We do know that, for example, chemotherapy has a substantial impact on ovarian function.

"And it is entirely possible that this is an impact of chemotherapy on ovarian function. We now know that ovarian suppression does improve outcomes in this setting. And so, it's possible that that's what we're measuring here. It's also possible there are other features of premenopausal disease that we have not taken into account."

What experts say:

Richard Schilsky
Chief medical officer, American Society of Clinical Oncology

We talk a lot at these meetings about diagnostic tests and whether they are well validated or not, and the series of studies over many years now, culminating in TAILORx, all performed using the Oncotype DX test is a paradigm for how diagnostic test development should be done, going from the retrospective analyses of completed clinical trials all the way to a large prospective clinical trial that shows such a definitive and important role for this particular test.

But I am not talking so much about the test itself as about the process, which I think is important to keep in mind.

TAILORx is a triumph for the publicly-funded cancer clinical trials system in the U.S., and once again demonstrates the crucial role played by the National Clinical Trials Network in answering clinically important questions that can change practice overnight.

The study also demonstrates the importance of public-private partnerships in advancing research and ensuring access to care. In my mind, the clinical development of Oncotype DX over the past two decades and culminating in TAILORx, provides a prime example of how molecular diagnostic tests should be developed and validated to provide high level evidence of their clinical utility.

As is always the case with research, there are still questions to be answered, and an important one, in my mind, is whether the 21 gene recurrence score can be used to identify a subset of women with hormone receptor positive, HER2 negative, node positive breast cancer who can also safely avoid adjuvant chemotherapy. This might require another study on the scale of TAILORx, although since the event rates are likely to be higher in this higher risk population, I would hope that such a study could be completed with fewer patients and shorter follow-up.

This study was initiated by ECOG, and I would be remiss if I didn't acknowledge the key role of my good friend and colleague, Dr. Bob Comis, who was the group chair of ECOG when the study was conceived. He was the driving force in bringing it to fruition, and who, sadly, passed away last year. This is such an important part of Bob's legacy.

Joanne Mortimer
Director, Womens Cancers Program; vice chair, medical oncology; professor, Division of Medical Oncology & Experimental Therapeutics; associate director for education and training; Baum Family Professor of Women's Cancers; City of Hope Comprehensive Cancer Center

It is comforting that chemotherapy did not benefit postmenopausal women with recurrence scores of 11-25. How then can we explain the small benefit of chemotherapy to premenopausal women in the subset analysis? The benefit from chemotherapy in this group is smaller than we generally see from chemotherapy and raises the suspicion that the "benefit" observed with the addition of chemotherapy may be due to ovarian suppression by the chemotherapy. It may be that premenopausal women with higher recurrence scores should receive ovarian suppression in addition to tamoxifen rather than tamoxifen with chemotherapy.

Fran Visco
President, The National Breast Cancer Coalition

I very much hope this is sufficient evidence for the medical oncology community to walk away from chemotherapy for the vast majority of women with ER-positive early breast cancer.

The data have shown for many years that toxic chemo in this population is not effective, at all ages, and particularly in women over 50. But all these women face the significant harms that come along with chemo.

I often wondered why these women continued to be subjected to this treatment and what would convince doctors to stop.

We need criteria to take away less effective and harmful drugs when the data warrant and to make certain we add these toxicities only when the highest level of evidence tells us it will save lives. That would be a paradigm shift.

I remember us, NBCC, being involved from the very beginning, giving input on the protocol, doing outreach for the trial. Carolina Hinestrosa was part of the steering committee and Musa Mayer was on the DSMB. I recall many in the oncology community saying that women would never enroll in a trial like this, and forgo chemo.

At NBCC, we knew women had the courage and vision to join the trial. We never doubted that.

Eric Winer
Chief clinical strategy officer, chief, of the Division of Women's Cancers, senior vice president for medical affairs, chief of the Division of Breast Oncology Center, Susan F. Smith Center for Women's Cancers, Thompson Chair in Breast Cancer Research, institute physician at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School

Overall, the study will not have a dramatic impact on our practice at Dana-Farber, because we have tended to give less chemotherapy to patients with node-negative ER+ breast cancer.

We did not expect to see a significant overall benefit of chemotherapy in the trial. But it will make us even more comfortable omitting chemotherapy in virtually all women who are over 50 and have a node negative cancer under 5 cm with an Oncotype of 25 or less.

In women 50 and under with an Oncotype of 21-25, we will have long conversations and weigh the pros and cons of chemotherapy.

Almost certainly, some of the benefits of chemotherapy in women 50 and younger arise from the impact of chemotherapy on ovarian function, and we have far less toxic ways of suppressing ovarian function.

With this in mind, I doubt that we will recommend chemotherapy to all patients under 50 with RS of 21-25, but we will discuss it. There is no question that the study is good news for women with node-negative, ER+ breast cancer.

Otis Brawley
Chief medical and scientific officer, American Cancer Society

"The TAILORx result is far more than a success in that it will save thousands of women from unnecessary treatment.

It is an example of how cancer medicine is evolving. For more than 150 years, cancer was diagnosed with a biopsy and a microscope. Today, the diagnosis of breast cancer involves a biopsy, a microscope and genomic testing.

We have moved from a mid-19th century definition of cancer to a 21st century definition of cancer.

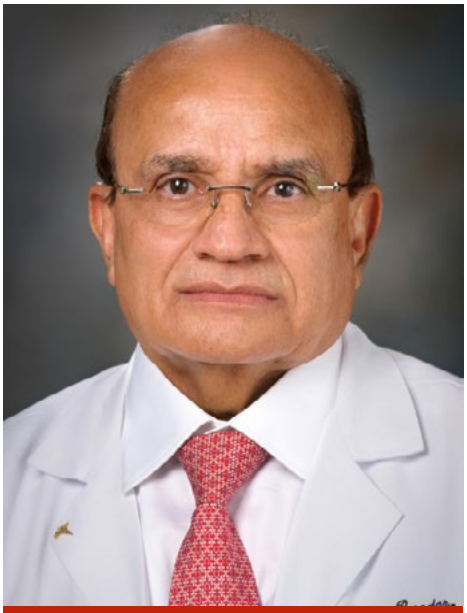
Breast cancer was once one disease. Today, it is a number of diseases, each defined by genomic analysis. Each with a different prognosis and deserving treatment of varying aggressiveness.

With the discovery of the estrogen receptor and HER2/neu, breast cancer was one of the first cancers to so clearly become multiple diseases.

Cancer, in general, is trending toward more personalized medicine and many organ-specific cancers are moving towards being considered a series of different cancers.

For example, the numerous genetic mutations associated with non-small cell lung cancer almost make it a series of orphan diseases.

Progress comes with a cost. This will complicate efforts to develop some treatments and increase the complexity of clinical trials.



Aman Buzdar
Vice president, clinical research, professor of medicine, MD Anderson Cancer Center

The results of this study were surprising; as addition of chemotherapy resulted in no improvement in disease free survival in this intermediate risk subgroup.

However, it is consistent with what we understand about endocrine therapy today. In earlier retrospective studies, the endocrine therapy consisted of tamoxifen therapy as an adjuvant.

Over the years, adjuvant endocrine therapy has evolved from tamoxifen to aromatase inhibitors, aromatase inhibitors are superior than tamoxifen in the adjuvant setting.

Thus, it is not surprising that any small benefit of chemotherapy in this intermediate risk group would not be detected with improved adjuvant endocrine therapy. Adjuvant chemotherapy in a subgroup with no gains in disease-free survival will only add side effects, like treatment-related leukemias and/or rare fatal infectious complications.

The physicians have the responsibility to inform patients about the results of this well designed study. As a number of women may still want to accept additional risks to reduce their risk of recurrence and want to take systemic chemotherapy.

Susan Love
Chief visionary, Dr. Susan Love Research Foundation

For too long in breast cancer the model has one of addition!

The TAILORx study is a powerful example that more is not better in treating breast cancer. This is important in terms of the cost of care both financially as well as in long term collateral damage from treatment.

Daniel Hayes
Stuart B. Padnos Professor of Breast Cancer Research, University of Michigan Rogel Cancer Center

Great to see this come to completion. We've been working on this trial since 2003. Joe Sparano has done a great job running it, and his presentation was, in my opinion, exciting, but very thoughtful. Kudos to him.

One "side" conclusion, raised by Lisa Carey, is that patients diagnosed in the 2000's with ER positive breast cancer are doing better than those diagnosed (and put on trials) in the 1970-'80s, from which we drew our assumptions to power TAILORx.

Breast cancer research and treatment has been special in two ways, in my opinion:

- The biology (ER, HER2) has made it amenable to targeted, and effective, therapies for decades, and furthermore it has just been more chemosensitive than the other common solid tumors

- The approach taken by our surgical forefathers--we all owe Drs. Fisher, Bonadonna, Danforth, Crile, and others, coupled with their radiation oncology partners, for courageously challenging Halstedian dogma and "de-escalating" surgical approaches. Almost unheard of in the other diseases.

We (medical oncologists) justifiably spent the first 40 years of the field (1960-2000 or so) "escalating"–because we had to.

The reduction in breast cancer mortality over the last 30 years (by as much as 1/3-1/2) is a gratifying result. But, now we take a page from their book and see de-escalation with no detriment in this reduction in mortality–terrific.

Taken together, the advances in biologically-based therapies and now personalized delivery of chemotherapy will continue to improve both the length, and quality, of our patients' lives.

We now look forward to:

- Results from the RxPonder trial – can we further reduce therapy that is either not needed or won't work? Can we expand the percentage of patients whom we will no longer over-treat while simultaneously getting the "right drugs to the right patients at the right time, dose and schedule?"

- New therapies that continue to take advantage of the cancer biology – PARP inhibitors, etc.

Steven Shak
Chief scientific officer and chief medical officer, Genomic Health

TAILORx, as well as the completed NSABP B-20 Oncotype DX study, are unparalleled in their design to define who does, and who does not, benefit from chemotherapy. The long-term TAILORx results provide the highest level of evidence for Oncotype DX, allowing physicians to now tell every patient, with precision, what their magnitude of chemotherapy benefit will be.

Q & A

Abrams spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Abrams: Only about 20-30 percent of the group might benefit from chemotherapy

Jeff Abrams
Acting Director for Clinical Research, NCI, Associate Director of Cancer Therapy Evaluation Program and Division of Cancer Treatment and Diagnosis

"It speaks to the fact that we really do have a national network that can conduct studies like this."

The practice-changing TAILORx trial was brought to you by publicly funded cancer clinical trials system, pointing to its continuing relevance, said Jeff Abrams, NCI acting director for clinical research and associate director of the Cancer Therapy Evaluation Program.

Genomic Health, the company that developed the test, used specimens from NSABP to test the Oncotype DX recurrence scores, "These samples from the NSABP trials were very important in the development of Oncotype Dx, although Genomic Health also used samples from other studies to help confirm the results they achieved with the NSABP samples," Abrams said.

"It is important to cite the people who made this study possible. First, and foremost, the over 10,000 volunteers who participated in this study. We owe them immense gratitude," Abrams said. "ECOG- ACRIN ably led this study on behalf of all the adult Group including the Alliance, NRG, and SWOG, plus the Canadian Clinical Trials Group. Without participation by all, we would not have been able to complete such a large study.

"It speaks to the fact that we really do have a national network that can conduct studies like this."

Abrams spoke with Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: Can we do a little history? It all begins with the 2000 NIH consensus conference on adjuvant breast cancer; right?

Jeff Abrams: Well, the NIH Consensus Conference took place in 2000, and it was based on some NSABP trials and other trials that showed a small survival benefit for women who had node-negative, hormone-receptor positive breast cancer with no underarm lymph nodes who got hormonal therapy plus chemotherapy compared to hormone therapy alone. And, based on these findings, the recommendation was that chemo should be considered in all these women, even though the benefit from chemo was small. We knew we were probably overtreating many of the women to help a few, but we were not able to select who would benefit.

I guess, there was no way to stratify risk; right?

JA: There were some ways to select the patients based on tumor size. If the tumor was very small, then the patients didn't get chemotherapy. Basically, if the tumor was a centimeter or more, and they had positive receptors, then chemo was indicated, even though the survival benefit was small overall.

The question became: can we figure out who are the patients who really need the chemo based upon a high risk of recurrence? And who are the patients who are getting only the side effects of chemo, as their risk is low and chemo isn't likely to help?

What about the technology? That wasn't available until much later.

JA: It's an interesting story. Steve Shak had worked for Genentech, where he had helped in the development of Herceptin back in the 1990's, and that's when I first met him.

He had moved to a new company that was just starting up, Genomic Health, and because we had known each other, he came to visit me at NCI, and asked if I knew of any possible patient samples which could help them confirm the genetic test they were developing. Their 21-gene recurrence test, called Oncotype DX, was being developed to determine the risk of recurrence in patients being considered for adjuvant chemotherapy.

NCI had supported two large NSABP studies, the B14 study with tamoxifen, and the B20 study which used tamoxifen and chemotherapy. They were the perfect studies to test their Oncotype DX test on.

Steve Shak met up with Soon Paik, who was the pathologist at NSABP, who had access to all these samples, and Steve worked very closely with Soon Paik to test this recurrence score, doing their particular genetic test, on all these samples from the two studies.

These samples from the NSABP trials were very important in the development of Oncotype Dx, although Genomic Health also used samples from other studies to help confirm the results they achieved with the NSABP samples.

It goes back to the question of how useful are cooperative groups. Coke versus Pepsi, all this criticism. We wouldn't be here if not for those annotated samples.

JA: Exactly. And, it was a great thing that the Groups had those samples stored, on a high percentage of the patients, which made this retrospective analysis more believable.

And then, you go onto a prospective study. But, before we get to that, as I look at the results, I'm seeing the Genomic Health test, now, being hardwired into the system. Can any other test be used?

JA: There are other genetic tests on the market. This study began in 2006. It accrued patients from 2006 to 2010. And then we had to wait for the outcome results, to follow all these patients for another eight years before we had sufficient follow-up to be certain that we could omit chemotherapy in some patients. And, it is now very reassuring to the have nine-year follow-up.

In this particular disease, if we only had five-year follow up, I think a lot of people would be saying, "Oh, you have to wait longer to see if the chemotherapy didn't have an effect over more time." But now that we have nine-year results, I think we feel very secure in the recommendation to omit chemo.

But, the Genomic Health test is really the only one to use?

JA: There are other tests on the market that can select patients at risk of recurrence.

Right, that's why I was asking.

JA: MammaPrint, from Agendia, was tested in a major international study called MINDACT. The study was conducted by BIG, the Breast International Group, primarily outside the U.S.. And that study actually reported out, two years ago at ASCO. The way that test works is it puts patients into two baskets: low-risk, and high-risk. So, it doesn't have this recurrence score idea, but rather puts patients into the two categories.

And, then, there's yet another test called Prosigna, by NanoString. And it also tries to predict risk. So all these tests try to predict recurrence in the same group of node negative, hormone receptor positive patients taking hormonal therapy.

What about the cost of this trial? How much did it cost?

JA: NCI doesn't fund its trials on a trial-by-trial basis. We give grants to our trial Groups, and they do a number of trials with the funds, but a rough calculation is possible. We estimate the trial cost about $35 to $40 million over the years.

That money was to reimburse the sites around the country for their work. There were a lot of sites who participated in this trial. Then, the funds also go to pay the operations and statistical costs of ECOG-ACRIN, and then there were costs for the Oncotype Dx test. We were fortunate at NCI to receive Breast Cancer Stamp Act funds to help pay for the test, as well as Genomic Health donated some in-kind cost reductions for the tests.

How much did the Breast Cancer Stamp provide?

JA: About $5 million.

So, that's another five, so could be around $45-ish million at the most.

JA: Yes, that is a reasonable estimate.

Can a trial like this be done today? Because you're talking about randomizing over 6,000 women.

JA: I think it could be, if we had an important question to ask. However, we've gotten much better at picking out molecular subsets. Due to the advances in diagnostics, most of our trials nowadays are much smaller, focusing on the subset we think will benefit most from the treatment. So, we aren't doing nearly as many very large trials as we used to.

So, you don't think it would be necessary? You might be able to zero in on a specific set of patients.

JA: I think there may still be some large trials. For instance, we're doing a trial called BWEL in breast cancer, which is still pretty large. Not 6,000, but several thousand patients, and that's a trial looking at exercise and weight loss in women who've had breast cancer to see how these factors can change outcomes. So, when you don't have something that's targeting a specific molecular effect, you have to do a larger trial, but for our treatment trials, where we're using drugs, we try in most cases to limit the trial to include only those patients likely to benefit. Such trials are usually under a thousand, even under 500, patients nowadays.

What are the questions that are left unanswered right now about this trial?

JA: If your score is above 25, I think the study provides evidence that one should discuss chemotherapy with these women. The study showed that women who received hormones plus chemotherapy in this group had a higher recurrence rate than the women with scores under 25. Based on the earlier studies that indicate a benefit for adding chemotherapy to hormones, the data from this study suggest that any woman with a recurrence score above 25 should at least consider chemo with their oncologist.

The area of uncertainty in this trial is for women 50 and younger who have a recurrence score between 16 and 25. The data indicate that for women with a recurrence score of 11 to 15, chemotherapy isn't going to improve their outcome, so no need to get it.

But, from 16 to 25, the data show some benefit for chemotherapy in women under 50 years old. From 16-20, the benefit is still small but becomes more obvious from 21-25.

So, I think RS 16 to 20, it's worth a discussion, and each patient and their doctor will have to decide; from 21 to 25 in the younger women, the benefit appears more clear and these women should be considered to be more similar to other women with scores above 25.

Now, there is one other very interesting point in these younger women, and that may be that what chemotherapy actually does in these younger women: it may be that chemotherapy primarily works to suppress their ovarian function, put them into menopause. Thus, it may not be the typical cytotoxic effect of chemotherapy on the tumor that is occurring but rather the chemotherapy is suppressing estrogen production by the ovaries. We've learned from other studies that ovarian suppression combined with hormonal therapy is necessary to get the best effect in younger women.

So, what remains unclear from this study is: do they need chemotherapy or could they do just as well with other non-chemo drugs that suppress ovarian function?

Are you planning to address this question?

JA: Well, we do know from an international study that our Groups helped to conduct called SOF that, in younger women, if you suppress the ovaries with a drug, plus give an aromatase inhibitor to those women, their outcome is better than women who just receive hormonal therapy with tamoxifen.

So, we know that, in younger women before menopause, ovarian suppression is critical. What remains uncertain is: is chemotherapy doing anything beyond just ovarian suppression? How to answer that question would require further study.

What about the improvement in hormonal treatments and the chemotherapies used over this time, or what's available now versus what was available when the trial was started? Is that a factor?

JA: It is a factor, although it's interesting. Back in the 1990s, a lot of women got an anthracycline-containing regimen which has cardiac toxicity concerns long-term. But in this study already, the field had begun to change, and the majority of women in this study did not get an anthracycline, so that's consistent with modern chemotherapy.

It was mostly a taxane and cyclophosphamide that was used in this study. As far as the hormonal therapy, most of the women in this study got aromatase inhibitors, not tamoxifen, except if you were under 50, where aromatase inhibitors don't work so you have to get tamoxifen.

So, I think even though it started a long time ago, the therapy used in this study is consistent with the type of treatments women are getting now.

If you were to look back and think of the overtreatment size—this is 20/20 hindsight of course—but how would you estimate that?

JA: With 260,000 women a year being diagnosed with invasive breast cancer, about half are in this node-negative, hormone-receptive-positive group. So, that's 130,000 women. Back in 2000 at that consensus conference, we were suggesting that chemotherapy be considered in most of them.

Now, it's sort of totally reversed.

Using Oncotype or similar tests, chemotherapy is now considered for only 20-30 percent of patients.

This test and others have really turned our recommendation around and chemotherapy is really reserved for those with the high recurrence scores at any age or for those women that I just talked about who are under 50 and have the score in the 16 to 25 range.

We estimate that's only about 20-30% of the group that might benefit from chemotherapy so 70 percent or more can be spared chemo.

What's the take-home from all of this? Is there anything we have learned that surprises you here?

JA: As we learned over many years. cancer is, at base, a genetic disease, and if you can understand the genes, it really goes a long way to helping you decide what's the appropriate treatment. With all the targeted therapies today, oncology has really changed; we are now targeting the therapy to the genetic changes.

That was the theme behind the MATCH study that NCI and ECOG-ACRIN are conducting. This approach has helped women with breast cancer too, dating back to the discovery of of Herceptin for the HER2+ breast tumors, and more recently the advent of the CDK4/6 inhibitors that improve outcomes for women with hormone sensitive metastatic disease.

It's all based on truly understanding the underlying genetics of the tumor.

It's not where we all were in 2000, which isn't a long time ago, really.

JA: Now we have next generation DNA sequencing technology that can be applied broadly which has resulted in a major change in how we approach patients with cancer. Fortunately, recent approval of this testing for advanced cancer by Medicare should help make this technology more affordable for all patients with cancer.

Is there anything we've missed?

JA: It is important to cite the people who made this study possible. First and foremost, the over 10,000 volunteers who participated in this study. We owe them immense gratitude. ECOG-ACRIN ably led this study on behalf of all the adult Group including the Alliance, NRG, and SWOG plus the Canadian Clinical Trials Group. Without participation by all, we would not have been able to complete such a large study.

It speaks to the fact that we really do have a national network that can conduct studies like this.

This is the type of study that a pharma company would not do because it's not intended to bring a new treatment into medicine; it's really intended to decide how best to treat patients, and actually ended up omitting chemotherapy for many women.

It shows that the government still has a role to play for this kind of important trial.

Actually, to go down that path, if you were to take the number of women who should not be treated, which is roughly around 100,000 a year, right, and multiply out the cost of chemotherapy and not even looking... think of how many billions of dollars could be saved.

JA: I think there are going to be health economists who will do these calculations more accurately, but the one thing that is obvious is the test itself, and the other tests that I mentioned to you, all run around $4,000, whereas a course of chemotherapy can vary from as low as $25,000 if there's no complications, and up to $100,000 or more if you have to use a lot of supportive care or hospitalization. So, when you look at the $4,000 versus $25,000 or more, there's a major difference there.

Right, and when you multiply it all out by the number of women who are not going to get that $25,000 to $100,000 expense, in addition to morbidity and side effects from chemotherapy, you're talking, really, many, many, many, many, many billions of dollars saved every year for the system.

JA: Firstly, it's a great outcome for women who don't have to undergo the toxicity. But second, it's a good outcome for the healthcare system.

Part of the savings that we just discussed in terms of the difference between the cost of chemo and the cost of the test have already been realized. Over the the intervening years while we were waiting for the results from TAILORx, the Oncotype Dx was on the market and was already being used by physicians to help them decide whether or not to recommend chemo.

A large part of the savings from a recurrence score of zero to 18 has already been realized because many oncologists and patients were already acting on the information. What is likely is that we will see further savings, because there was a zone of uncertainty between 18 and 31, where people were still debating, based on the older, retrospective results, whether they should or shouldn't give chemotherapy.

And, with the new results from TAILORx, there'll be more certainty that from 18 to 25 women can be spared, and only above 25 should chemotherapy be considered.

Thank you so much.

Sharpless: NCI adds $10 million for NCTN and NCORP trials

By Matthew Bin Han Ong

NCI is providing an additional $10 million to support trials run with the National Clinical Trials Network and the NCI Community Oncology Research Program, Norman "Ned" Sharpless said in his first appearance as NCI director at the annual meeting of the American Society of Clinical Oncology in Chicago.

"NCI's major efforts with regards to large clinical trials are largely supported through our clinical trials networks like the National Clinical Trials Network," Sharpless said in his June 2 talk at ASCO. "One of the major challenges for these networks over the past few years, however, has been a rapid increase in the per-patient costs for patients on trials.

"NCI appreciates the problems that these skyrocketing costs have caused for NCTN trials, and today I am announcing that we are going to help. The majority of this funding will be used to augment per patient reimbursement rates at 180 sites that treat adult or pediatric cancers."

Listing his four areas of priority for NCI—investing in basic science, growing the workforce, leveraging Big Data, and modernizing clinical trials—Sharpless said that the overarching worry of oncologists today is the management of patient's expectations.

"I think we have become scared to tell our patients that we hope to 'cure' them, and it may be time to re-examine how we communicate our efforts in this area," Sharpless said. "I especially know why the notion of 'cure' makes so many of us uncomfortable. Curing cancer, making it go away and never come back, is really hard, much harder than initially conceived, and the word 'cure' should not be thrown around lightly with vulnerable patients present.

"It is also worth making two points. First, we are curing patients now, and more people than ever, even some people with really bad cancers, at very advanced stages. I never thought I'd see some of the results that we are now seeing in metastatic lung cancer and melanoma.

"Second, even if the idea of curing cancer makes us uncomfortable, it is what are patients, and our funders, expect. They don't just want extended progression-free survival or enhanced quality of life, or reduced costs, or whatever other surrogate marker we might pick.

"They expect us to deliver."

The text of Sharpless's remarks follow:

Thank you for that kind introduction and thanks for your terrific leadership of ASCO at this important juncture in cancer research. Thank you to the American Society of Clinical Oncology and it's nearly 45,000 members: your commitment to cancer research and care has led to meaningful progress for our patients.

A few weeks ago, I appeared before the Senate Appropriations subcommittee that funds the NIH. The chair of that subcommittee, Sen. Roy Blunt [R-MO], asked me about the future of cancer research. I explained that this is a time of great hope and optimism. We have seen real therapeutic progress with kinase inhibitors, immunotherapy and precision medicine and the ASCO community is a huge part of these advances. As I told Senator Blunt, the day the ASCO Abstracts are finally released online is like Christmas morning to me.

I have to confess, I originally joined the American Society of Clinical Oncology in 1998 in response to one of the most primal of human emotions: abject fear. Let me explain. You see, back then, I was an oncology fellow at the Dana-Farber/Partners Cancer Care. I was barely done with residency, and I was called upon to provide care for some sick and often desperate patients. In some cases, they had made grueling trips to Boston, traveling hours to see a cutting-edge specialist at Harvard, and often the first doctor they ended up seeing was me.

As a new cancer doctor, I did not feel up to the task. I suffered from that "imposter syndrome" that most young doctors feel. Medical residency had not prepared me for this. I felt afraid: of making a mistake, of missing something important, and of letting these people down.

So, I joined ASCO, probably for the same reason as many of you from a desire to become better educated about cancer, so I could take better care of my patients. Then, as now, ASCO provided educational materials for oncologists, and the most important of which, to me was the Journal of Clinical Oncology. As an oncologist-in-training, I felt that if I read every issue of the JCO as it came out, I would be sufficiently knowledgeable about cancer to be able to help my patients.

Back in that pre-internet era, we used to pass around and carry with us these Xeroxed copies of articles. We employed these as a totem to ward off our clinical insecurities. If we were battling cancer, JCO was provisioning the armor.

I recall carrying around a raggedy-eared copy of a 1990s Art Skarin paper from the JCO, that I would quickly scan before seeing a new patient with lung cancer. I recall learning how to use tamoxifen to treat ER+ breast cancer from Hy Muss, also via his writing in the JCO, many years before I actually met Dr. Muss [director of the Geriatric Oncology Program at UNC Lineberger Comprehensive Cancer Center].

Reading the JCO would help me and my peers march into the exam room of a new patient suffering from a cancer we had not treated before. In those rooms waited for us some extreme challenges, and I can still picture their faces: the mother of four with metastatic breast cancer; the incarcerated young sarcoma patient who left prison once a week so I could give him chemo; the guy with a metastatic islet cell tumor whose main symptom was that he kept passing out at work from severe hypoglycemia; the young HIV+ artist with lymphoma, whose tumor we cured, but whose outcome was still terrible because of his failing immunity.

These patients were suffering and wanted help. They needed a really, really good oncologist—someone who was educated and thoughtful. So, I joined ASCO in 1998 so that I could become that, a really good oncologist, whose education in large part developed from reading the JCO.

Besides the JCO, another of ASCO's most important tools is happening right here and now: the ASCO Annual Meeting, which is one of the most important events for cancer doctors, patients and other caregivers around the world.

"The potential for breakthroughs has never been greater"

I am happy to share the news, as you may have seen is last week's Annual Report to the Nation on the Status of Cancer, that we continue to see a steady decline in cancer mortality. In 1991, the cancer mortality rate was 215 deaths per 100,000 people in the U.S. In 2015, that number was down to 159. There is reason to believe that the number is even lower now, and will continue to decline. This represents decreases in cancer death for men, women and children, and for all major ethnic groups.

More good news, is the strong, bipartisan support we're receiving from Congress. For the fourth year in a row, we have seen budget increases for the NIH and NCI. The fiscal year 2018 Omnibus spending bill passed in March provides a $275 million increase to the NCI budget as well as continued full funding for the Cancer Moonshot. So, with new discoveries, successful treatment approaches, continued research progress and additional funding, as a community, oncologists can feel a lot of optimism: the potential for breakthroughs has never been greater than it is right now.

That's the good news, and it is good news, but no doubt we still face significant challenges. These are well known to this audience: little progress in certain cancer types such as pancreatic adenocarcinoma and glioblastoma.

There are still too many children dying of cancer. We have to admit that it is not sufficient to make progress in just the common cancers or the best understood cancers or the easiest to treat cancers. NCI is charged with making progress in ALL types of cancer, to benefit all patients. Even when we can cure kids and adults of cancer, too often this comes with the cost of significant and lifelong toxicities from the cure.

One side effect of curative therapy whose true consequences we are just starting to fully appreciate is financial toxicity, which can be devastating for cancer survivors. I would argue these areas of continued slow progress in turn reflect an incomplete understanding of cancer biology, and challenges to the ways we do cancer research.

I think it is NCI's job to take these challenges head-on. When I started in this new role last October, I decided to take six months to go on a listening and learning tour. During which time, I spoke to many patients, advocates, clinicians and scientists about what NCI does well and areas that needs improvement.

NCI's key focus areas

That effort helped me identify four key focus areas on which I wanted to focus as leader of the NCI. These are not new areas for NCI. However, they are areas where I think the scale and reach of NCI plays an especially important role and NCI's resources and convening power and leadership can act as a catalyst.

They are Basic Science, Workforce, Big Data, and Clinical Trials. You can read more about each of these areas on my blog on cancer.gov, but I will share some highlights that I think will be of greatest interest to ASCO attendees.

I don't think the basic science work of cancer is done. NCI continues to strongly support investigator-driven basic research and always will while I am director. We have a much better understanding of cancer now than at any time in human history, but we must also admit that we need more fundamental research in this area. I believe a top-down approach is not the way to go here. Focus has to be on investigator-initiated discovery. NCI has some role to identify topics for specific focus and once we have done that, we have to sit back and let the proverbial magic happen.

One of the best ways to support investigator-initiated science is through the funding of the Research Project Grants. This pool funds the vast majority of investigator-initiated awards: the R01's and the even larger program project grants, such as P01's. Toward that end, this year I have dedicated an additional $127 million into investigator-initiated science. This is the largest increase to the RPG pool since 2003 and is possible thanks to significant increases in our congressionally appropriated budget over the past few years. While this is not solely for basic science, this is the most straightforward way to assure we continue to fund investigator-initiated basic science. Discoveries in basic science propel progress for patients.

> "In 1991, the cancer mortality rate was 215 deaths per 100,000 people in the U.S. In 2015, that number was down to 159. There is reason to believe that the number is even lower now, and will continue to decline."

One of our most important jobs at NCI, perhaps the most important job of NCI, is to ensure a talented and innovative research workforce for the decades ahead. We must continue to press for a diverse workforce regarding background, interest areas, ethnicity and gender. We must broaden our notions of who we consider to be our colleagues. For example, I predict we will be working more closely with an increasing diversity of experts: immunobiologists, computer engineers, healthcare economists, geriatricians, data scientists, and yes, community oncologists.

We are doing many things in this area, but one in particular is intended to address the plight of the Early Stage Investigator. Again, thanks to the support of Congress, this year NCI is able to set aside dedicated funding ESIs to increase their chances of getting a first major grant (an R01) from NCI. This extra funding will increase the number of first R01's to ESIs by at least 25 percent.

NCI will also be looking at many strategies to encourage development of the right skill sets for the future of cancer research, through dedicated funding of training grants and professional development opportunities.

Big Data is another area where we've seen a transformation that creates great opportunities for cancer research and care, but also new challenges. Embracing the potential of big data will add speed and dimension to our work across the cancer enterprise. Consider that more than 90 percent of all digital

data created to date across all fields was produced in the last two years.

You hear a lot about data sharing and that is important, but we must also move beyond passive data sharing to intentional data aggregation in order to fully leverage the power of data. Establishing linkages and inter-operability of diverse, complex data sets to understand cancer care and provide real world evidence. For example, linking genomic data with pathology data with radiology data with clinical data mined by machine learning from EHRs in a large number of patients, while assuring data privacy and security. The power of that is incredible. This will benefit the entire research community, including all of you. Research questions that are almost intractable by traditional means can be addressed by large, annotated multimodal datasets.

So, how are we going to harness Big Data? This is a place where we need to pay attention to the workforce, attracting young data scientists into cancer research. We will focus on the linkage of many large datasets maintained by NCI to provide interoperability. There are several interesting efforts in this area to talk about. For example, we are going to link the enormous data set of the cancer genome atlas, where possible, to the clinical data for those patients.

NCI's SEER program is one of the biggest of NCI's big data initiatives, and is taking some innovative steps worth noting. The NCI-supported Surveillance, Epidemiology, and End Results Program was created by federal law in 1971 as part of the National Cancer Act. It has collected statistics on cancer deaths and outcomes for 45 years to support research on the diagnosis, treatment and outcomes of cancer since 1973. It consists of 16 population-based registries covering 33 percent of the US population. These registries collect information on all cancer cases for residents of the state or region. They represent racial and ethnic minorities and various geographic subgroups.

SEER is one of the most important things NCI does to support population sciences research. The SEER contracts were just re-competed and we are actively exploring approaches to innovatively augment this rich dataset's capabilities through many sorts of novel data linkages.

Beyond SEER, we are also working on data initiatives with federal partners like the Department of Energy, which gives NCI access to cutting-edge exascale computing, as well as working with the FDA and CMS, which have interesting large datasets of potential value to cancer researchers. These data efforts are supported by a developing a NCI Cancer Data Ecosystem, which is being significantly amplified with new targeted funding from the Cancer Moonshot. This includes highly successful cloud resources for storage and computing, as well as robust efforts for NCI to set standards for data sharing and interoperability.

We have to do these things because the costs of not harnessing Big Data are too great. By doing this, we can learn from every patient.

“Every one of today's standard-of-care therapies is available because of a past successful clinical trial, but translating today's discoveries into routine, effective treatments isn't a matter of doing more of the same.”

Funding clinical trials

Every one of today's standard-of-care therapies is available because of a past successful clinical trial, but translating today's discoveries into routine, effective treatments isn't a matter of doing more of the same.

There are several problems that we have to face: decreased accrual and poor accrual of underrepresented populations; increasing per patient costs; spiraling times to open and to the completion of clinical trials. These problems are bad for clinical researchers, and even worse for patients.

As a major funder of clinical trials, NCI can improve these problems. We have to get rid of unnecessary exclusion criteria and confusing consent forms. We need to encourage and expand the use of central IRBs. We need trials with innovative, adaptive designs, to identify inactive agents quickly and thereby prioritize good drugs for further testing. We need trials that are based on a modern understanding of cancer.

The fact of cancer's tremendous heterogeneity means that traditional clinical trials models are becoming less useful. Largely gone are the days when the cardiology paradigm of clinical trials reigned—when we enrolled enormous numbers of patients into large phase III trials with slightly different treatment protocols, where very modest improvements upon a largely ineffective regimen was considered success.

One emerging approach about which I am excited is demonstrated by the NCI-MATCH trial. NCI-MATCH is an example of innovative trial design. This precision oncology trial allocated patients to one of approximately 30 arms of therapy based on somatic genetic testing.

Some of the first efficacy results from MATCH are being presented here at ASCO, so I won't go into detail, but I would like to highlight the importance of this trial as an example of new ways to conduct clinical research. This map shows what to me is one of the most important facts of MATCH: coordinated with ECOG-ACRIN it has enrolled more than 6,000 patients to cutting-edge therapeutic trials at 1,100 sites across the country. It has been the fastest accruing trial in NCI's history. This shows us that even highly complex precision medicine trials can be conducted in the ethnically diverse communities where real-world patients live. If we have well-designed efforts like MATCH, the patients will come.

We are also employing this same approach through the Pediatric MATCH Trial. Working with the Children's Oncology Group, NCI has brought Pediatric MATCH to 200 sites across the country with eight arms currently open. These efforts are important, and will become even more so as more and more drugs are approved based on driver mutation rather than on tissue-of-origin.

Mark my words—trials like MATCH and Pediatric MATCH are already changing how we make progress in oncology.

Lastly, while novel trial designs like that of MATCH are generating much excitement; larger, traditionally structured trials to define standards of care remain critical for progress in cancer research, and NCI will continue its robust support for these efforts. For example, at this meeting, results from the TAILORx trial will be reported. This clinical trial in 6,700 women with breast cancer has examined the use of anti-hormonal versus cytotoxic therapy for women with ER+ breast cancer based on results of an RNA-based genetic risk score. The results of this trial will have implications for thousands of women with breast cancer over the next few years.

NCI's major efforts with regards to large clinical trials are largely supported through our clinical trials networks like the National Clinical Trials Network. One of the major challenges for these networks over the past few years, however, has been a rapid increase in the per-patient costs for patients on trials. NCI appreciates the problems that these skyrocketing costs have caused for NCTN trials, and today I am announcing that we are going to help.

I am announcing that, this year, we will be providing an additional $10 million to support trials run within the NCTN and NCORP. The majority of this funding will be used to augment per patient reimbursement rates at 180 sites that treat adult or pediatric cancers.

Patients expect "cures"

I'm sure we will hear about rapid progress in clinical oncology research at this meeting. What we are doing together is shaping the future of cancer research and changing lives. Before I conclude, and we dive into all that is ASCO—the posters, the sessions and the networking—I'd like to talk about something that's been on my mind.

An almost overarching worry of the cancer doctor today has become the management of expectations: we don't want to overpromise and give people—especially patients—false hope, but I am worried we have been losing the point: I think we have become scared to tell our patients that we hope to "cure" them, and it may be time to re-examine how we communicate our efforts in this area.

As an oncologist, I used to cringe at the notion of "curing cancer," when talking to a patient. What if I told them they were cured, but then the cancer actually came back? I especially know why the notion of "cure" makes so many of us uncomfortable. Curing cancer, making it go away and never come back, is really hard, much harder than initially conceived, and the word "cure" should not be thrown around lightly with vulnerable patients present.

It is also worth making two points. First, we are curing patients now, and more people than ever, even some people with really bad cancers, at very advanced stages. I never thought I'd see some of the results that we are now seeing in metastatic lung cancer and melanoma. Second, even if the idea of curing cancer makes us uncomfortable, it is what are patients, and our funders, expect. They don't just want extended progression-free survival or enhanced quality of life, or reduced costs, or whatever other surrogate marker we might pick.

They expect us to deliver.

This was the subtext behind Sen. Blunt's question to me when I recently testified. Our patients and their representatives want to know that we are making progress to prevent and to cure this set of formidable diseases.

After being a member of ASCO for 20 years, I'm happy to say that those early fears of walking into a new patient's room and having absolutely no options are going away if not already gone.

Almost every day we learn of new discoveries, advances and approaches that show promise. We have options. We have treatments. And sometimes, we now do have a cure. Now, there is enormous optimism in our field. There is reason for this optimism.

Thank you.

IN BRIEF

J&J Innovation and Boston University form lung cancer research alliance

Johnson & Johnson Innovation announced a five-year alliance with Boston University to accelerate lung cancer research.

As part of the alliance, a Johnson & Johnson Innovation Lung Cancer Center at Boston University will be established, allowing collaboration between Boston University investigators and members of the Lung Cancer Initiative within Johnson & Johnson to develop solutions that prevent, intercept and cure lung cancer.

Avrum Spira, professor of medicine, pathology and bioinformatics at Boston University has joined Johnson & Johnson Innovation as Global Head, Lung Cancer Initiative, Johnson & Johnson, and will direct the new center.

The alliance seeks to build upon collaborative programs related to three extensive lung cancer research studies. Two studies, which involve cohorts of military personnel, seek to enable the development, integration and validation of molecular and imaging-based biomarkers to improve lung cancer detection.

In the third study, known as the pre-cancer genome atlas, investigators are defining the determinants of premalignant disease progression to enable the development of molecularly targeted interception strategies.

It is also envisioned that pilot programs developed by teams from across the Boston University ecosystem will be selected and advanced with close collaboration from Johnson & Johnson Innovation.

Through this academic-industry alliance, programs focused on the prevention, interception and curing of lung cancer will be supported.

Kochevar to retire from Colorado Cancer Center

Mark Kochevar, associate director for administration and finance at the University of Colorado Cancer Center retired on May 31, 2018, after a career of 41 years in cancer research administration. Kochevar began his career as the assistant administrative officer for the Clinical Oncology Program in the NCI's Division of Cancer Treatment in May 1977.

FUNDING OPPORTUNITIES

Addario, Van Auken foundations announce 2018 Young Innovators Team Award

The Bonnie J. Addario Lung Cancer Foundation, in collaboration with the Van Auken Private Foundation, announced the 2018 Young Innovators Team Award to fund and support teams of young investigators conducting innovative research with a potential of delivering meaningful and measurable results in the field of lung cancer.

The 2018 Young Innovators Team Award will provide up to a total of $250,000 to teams of two or more young investigators over two to three years. The awardees must be within five years of their first faculty appointment.

The YITA Scientific Review Committee will evaluate all submissions on the following four main criteria:

- Out-of-the-box: High-risk, high-impact research that will typically not be selected for federal funding, is creative and has potential for near-term benefit to lung cancer patients
- Collaborative: Research that fosters collaboration among young researchers who have not worked together in the past, preferably across-institutions
- Translational: Research with outcomes that can be quickly moved from the lab to the clinic, or from the bench to bedside
- Multi-Disciplinary: Projects that involve multiple academic disciplines/specializations in their approach to solve a problem in the field of lung cancer

The funding mechanism is designed so that young investigators work together in cross-disciplinary teams. The teams drive the projects with guidance from mentors at their own institution. The 2018 YITA Scientific Review Committee also guides and steers their progress, and makes final decisions on continued funding.

ALCF prefers lung cancer patient-oriented research in the following topic areas (however, the 2018 YITA Scientific Review Committee will evaluate all submissions):

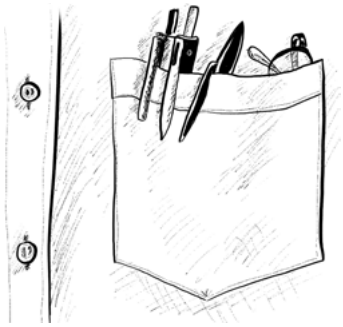
- Early detection and screening using novel, validated biomarkers
- Targeting the tumor microenvironment-combination strategies
- Biomarkers for response to immunotherapies
- Small Cell Lung Cancer: identifying and targeting specific underlying genomic abnormalities
- Causative factors in non-smokers

Key Dates

- May 31, 2018 - RFA announcement
- May 31, 2018 - Online application submission portal opens
- July 1, 2018 - Optional pre-application counseling deadline
- July 15, 2018 - Application submission deadline
- Aug. 15, 2018 - Peer review round 1October 15, 2018 - Peer review round 2: Top 3-5 applicants present to the Scientific
- Review Committee/ in-person review
- Oct. 31, 2018 - Award announcements
- Nov. 1, 2018 - Award start date
- Nov. 1, 2020 or Nov. 1, 2021 - Award end date (depending on the proposal)

For more information, visit www.lungcancerfoundation.org/yita-2018. The website also has information on the award, guidelines for submission, FAQs and the online submission portal. ALCF will accept online applications during May 31 – July 15, 2018. ALCF and the Van Auken Private Foundation provide funding for this award.

THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

Searching for Breast Cancer's "Extreme Survivors"

By Mark Burkard,
University of Wisconsin Carbone Cancer Center

I remember the day I met Margaret "Peg" Geisler, who has now been living with breast cancer for 40 years, and with metastatic disease for 36 of those years.

She had long outlived her original oncologist, pioneering breast cancer researcher Dr. Paul P. Carbone, for whom our cancer center is named. I saw her for a colleague, her third oncologist, who was out on maternity leave.

Peg's records showed she originally had breast cancer in 1978, it recurred in the 1980s, and she had a biopsy-proven pelvic metastasis that had been treated with radiation, but had never disappeared. She had received multiple medical treatments over the decades, including hormonal therapies and a few chemotherapies. The mass had grown slowly over the years and the most recent scan again showed a slight growth. What treatment did I recommend? I could select a number of possibilities, but, in the end, I recommended observation. Four years later, at age 82, her health is good. She attributes her survival to her "cantankerous" attitude,

Margaret "Peg" Geisler,

> We hope to learn what allows some people with breast cancer to survive for extreme durations of time. Is this an intrinsic feature of the cancer, perhaps driven by a specific set of genes that drive its growth?

but everyone else describes her as charming, so I suspect another cause.

How many extreme survivors with metastatic cancer are there and what makes them tick? With the help of Dr. Susan Love's Army of Women, advice from leaders at The Metastatic Breast Cancer Alliance, and support from the AVON Breast Cancer Crusade, we have launched an international study looking for extreme survivors of metastatic breast cancer.

Patients can take the web survey to see if they qualify. It is not necessary to be a long-term survivor to take the survey.

Next, men or women with metastatic breast cancer will be invited to take an hour-long survey describing their medical history, lifestyle, and diet. Patients with the longest survival will be invited later to a substudy involving genomic analyses of their tumors and germline DNA. We hope to learn whether, compared with most breast cancers:

- These cancers are genetically distinct,
- The immune system is different, or whether
- The treatment or behaviors are unique.

Others have described these extreme survivors. A classic 1962 paper—"Natural History of Untreated Breast Cancer," by HJG Bloom—describes a series of 19th century women with breast cancer who were not treated. Some of these women lived over a decade after the breast cancer was found, and in one case, for 35 years. Dr. Bloom focused on tumor grade as an explanation, but today, genomic sequencing and other tumor analyses could provide deeper knowledge. Additionally, today's information age has made it possible to reach many extreme survivors quickly through social media.

In our institutional cohort, the most common and longest extreme survivors had hormone-sensitive cancers, but we also identified extreme survivors with HER2-positive cancer metastatic cancer who lived for more than a decade, and several with indolent triple-negative breast cancer with survival of more than five years. Still, these non-hormone driven cancer cases were usually less extreme than the decade-long histories identified with estrogen-receptor-positive breast cancers.

As I spoke with colleagues, I found it important to be clear what I meant by "extreme survivors." Many colleagues were familiar with the National Cancer Institute project looking for "extraordinary responders," and expected that I was looking for the same. However, few of our extreme survivors had ever had an extraordinary response to therapy. Most had received many therapies, with evidence of slow disease progression. Thus, there was little overlap between extraordinary responders and extreme survivors.

Second, we found some confusion about how to define extraordinary survival. We used the time of initial breast cancer diagnosis to define extreme survivors with metastatic cancer, because in micrometastatic cancer, disease is present for those who receive primary surgery and develop distant metastatic recurrence many years later. For hormone-receptor positive breast cancer, we used 10 years as a cutoff and for hormone-receptor negative breast cancer, 5 years.

We hope to learn what allows some people with breast cancer to survive for extreme durations of time. Is this an intrinsic feature of the cancer, perhaps driven by a specific set of genes that drive its growth? If so, we could collect tumor samples and identify the genetic drivers of these cancers, and use this to identify future individuals likely to be extreme survivors.

However, there are clearly other possibilities and scientists, physicians, and survivor-advocates who offered disparate ideas of what could drive extreme survival. Among the ideas proposed were that specific cancer treatments were selected or rendered in a particular order to allow for extreme survival. Other ideas were that survival was prolonged by medical treatments for comorbid conditions, driven by intrinsic features of the immune system or tumor immunogenicity in these survivors, or by habits (diet, exercise, alternative medical practices). Some ideas offer the possibility of empowering individuals living with metastatic breast cancer to alter their fate. Thus, we concluded that all were worth a detailed evaluation.

After obtaining IRB approval, we reviewed charts of extreme survivors at the UW Carbone Cancer Center and identified a total of 53 individuals who qualified as extreme survivors. The four longest survivors had an original diagnosis between 1978 and 1980. These individuals had developed distant metastases in 1982, 1996, 2000, and 2007. All were alive at the time of data collection with distant and persistent metastatic disease. We enrolled 15 of the longest-term survivors with available tissue into a companion study to perform genome analyses of tumor and blood, and analyze their tissues for unusual cancer features. Thus far, we have not identified a specific cause of extreme survival, but variation between these individuals made it clear that our analysis would require a larger cohort of extreme survivors. At the same time, word got out about our project and we were contacted from other survivors across the US and beyond.

In order to expand our study, I teamed up with Dr. Gabrielle Rocque at University of Alabama Birmingham who is identifying extreme survivors using SEER-Medicare. In addition, she has developed innovative approaches to evaluate the treatment patterns of extreme survivors. We submitted a grant proposal to Avon Breast Cancer Crusade to enroll large numbers of extreme survivors across the U.S. and beyond to complete a survey, and to allow us to re-contact them for a substudy of genomic and immunologic features of the cancer.

Dr. Susan Love's Army of Women also collaborated in getting the word out. Additionally, leaders at The Metastatic Breast Cancer Alliance offered critical feedback on our survey. These and other advocates have asked us to share de-identified patient-level data to the research community to maximize the value of these data in learning about metastatic breast cancer and helping survivors.

Many physicians have extreme survivors with metastatic breast cancer in their practice. We invite these physicians to participate by notifying their patients of this project.

Participation is initiated by survivors who choose to visit our website and select 'Participate Now.' People living with metastatic breast cancer need not be long-term survivors to participate in the survey. However, we anticipate at least 1,000 long-term survivors to participate. Those who fill out the survey will allow us to gain critical information about treatment patterns, comorbid illnesses, diet, exercise, and habits.

We plan to recontact about 50 of the most extreme long-term survivors with available archived tumor samples to participate in an optional substudy of genomic analyses of tumor and saliva. If we identify common features of the long-term survivors, we hope to make this information available to physicians and survivors with metastatic breast cancer.

We hope that this information may allow others to become long-term survivors, but it may also be useful to identify who are likely long-term survivors at the outset of a breast cancer diagnosis. It may be that these individuals can be treated in a distinct way. For example, if the intrinsic features of the tumor or their immune system dictate a very indolent type of breast cancer, it may be possible to de-escalate treatment and rely primarily on endocrine and/or targeted therapies.

As with our 40-year survivors, we may identify a group for whom 'observation' is a valid approach even for metastatic breast cancer.

CLINICAL ROUNDUP

New treatment combination improves outcomes for some patients with colorectal cancer

Research from Roswell Park Comprehensive Cancer Center suggests a new treatment combination can extend survival for many patients with advanced colorectal cancer.

The study focused on the targeted drug nintedanib in combination with capecitabine, an approved standard therapy for colorectal cancer.

The phase I/II study was led by Patrick Boland, assistant professor of oncology in the department of medicine at Roswell Park. The research team sought to evaluate the recommended dose and efficacy of nintedanib, atyrosine kinase inhibitor, pluscapecitabine in patients with refractory metastatic colorectal cancer—those whose cancer progressed after they received standard chemotherapy.

The team, which includes researchers from City of Hope, reports that among 40 patients who received the new combination, progression-free survival at 4 months was 36%, compared to 25% in a historical comparison group receiving standard therapy alone—a statistically significant increase.

The authors conclude that this treatment combination was well tolerated and that its efficacy compares favorably to single-agent approaches.

Exact Sciences, Mayo Clinic identify blood-based DNA biomarkers to diagnose hepatocellular carcinoma

Researchers at Exact Sciences Corp. and Mayo Clinic announced progress toward developing a panel of novel, blood-based, DNA biomarkers that could accurately detect hepatocellular carcinoma, the most common cancer that originates in the liver.

The biomarker panel was shown to be 95 percent sensitive for detecting HCC across all stages. Sensitivity among patients with curable-stage disease was 91 percent. The panel has overall specificity of 93 percent, demonstrating its ability to discriminate between normal and diseased patients. Sensitivity and specificity are the most important statistical measures of a cancer detection test's performance.

Individuals diagnosed with cirrhosis have the greatest risk of developing HCC, and it is recommended that they undergo ultrasound and blood monitoring every six to 12 months.

John Kisiel, the gastroenterologist and assistant professor of medicine at Mayo Clinic Medical School who led the study, said the current options for monitoring at-risk patients are "sub-optimal."

"We estimate that fewer than half of at-risk patients are tested regularly, and some estimates suggest the monitoring rate is less than 20 percent in primary care settings, where most people get their care," he said.

Using DNA extracted from the blood samples of 244 people, including 95 diagnosed across all stages of HCC, 51 with cirrhosis, and 98 healthy volunteers, researchers tested the samples against 15 biomarkers to identify the combination of six biomarkers that yielded the most accurate detection of HCC.

Exact Sciences and Mayo Clinic have been collaborators since 2009. The collaboration previously yielded Cologuard, the stool-based, advanced-DNA screening test for colorectal cancer.

The study results can be found here.

Opdivo demonstrates superior RFS vs. Yervoy for patients with resected stage III or IV melanoma

Bristol-Myers Squibb Co. announced updated results from the phase III CheckMate -238 trial evaluating Opdivo (nivolumab) versus Yervoy (ipilimumab) in patients with stage IIIB/C or stage IV melanoma who are at high risk of recurrence following complete surgical resection.

In updated results from the study, Opdivo continued to demonstrate statistically longer recurrence-free survival of 62.6%, the primary endpoint of the study, versus 50.2% for Yervoy (HR: 0.66, P<0.0001) at a minimum follow-up of 24 months across key subgroups, including disease stages and BRAF mutation status.

No new safety data were generated as part of the 24-month analysis. As previously reported from the 18-month analysis, Opdivo demonstrated a significantly lower rate of adverse events leading to discontinuation (9.7% of patients in the Opdivo arm compared to 42.6% of patients in the Yervoy arm) and treatment-related grade III/IV AEs (14.4% of patients in the Opdivo arm compared to 45.9% in the Yervoy arm).

In the study, Opdivo demonstrated superior RFS versus Yervoy, regardless of disease stage, PD-L1 expression or BRAF mutation status, with RFS rates of 62.6% with Opdivo compared to 50.2% with Yervoy in the intent-to-treat patient population.

In patients with stage IIIB melanoma, RFS rates at 24 months for Opdivo were 70.8% versus 60.7% with Yervoy; for patients with stage IIIC melanoma, RFS rates were 58.0% with Opdivo versus 45.4% with Yervoy; and for patients with stage IV melanoma, RFS rates for Opdivo were 58.0% versus 44.3% with Yervoy. In patients with BRAF mutant melanoma, RFS rates for Opdivo were 61.9% versus 51.7% with Yervoy; in patients with BRAF wild-type melanoma, Opdivo demonstrated a RFS of 63.5% versus 46.2% with Yervoy.

CheckMate -238 is an ongoing phase III, randomized double-blind study of Opdivo versus Yervoy in patients who have undergone complete resection of stage IIIB/C or stage IV melanoma. The trial randomized 906 patients 1:1 to receive either Opdivo 3 mg/kg every two weeks (n=453) or Yervoy 10 mg/kg (n=453) every three weeks for four doses and then every 12 weeks starting at week 24.

Patients were treated until disease recurrence, unacceptable toxicity or withdrawal of consent for up to one year. The primary endpoint is RFS, defined as the time between randomization and the date of first recurrence, new primary melanoma or death. After meeting the primary endpoint, the trial will continue to evaluate for overall survival, a secondary endpoint.

Opdivo plus Yervoy provide QOL improvements in RCC

Bristol-Myers Squibb Co. announced patient-reported outcomes data from the phase III CheckMate -214 trial in intermediate- and poor-risk patients with advanced renal cell carcinoma treated with the immuno-oncology combination Opdivo (nivolumab) plus low-dose (1mg/kg) Yervoy (ipilimumab) vs. sunitinib over a two-year follow-up period.

Patients in the study treated with Opdivo plus low-dose Yervoy reported significant benefits in disease-related symptoms and improvements to their cancer-related quality of life and well-being. These benefits occurred early during Opdivo plus low-dose (1mg/kg) Yervoy combination therapy and were largely maintained throughout the treatment period and through Opdivo maintenance therapy.

Relative to the current standard of care, patients in the Opdivo plus low-dose Yervoy arm reported fewer kidney cancer symptoms as measured by the NCCN Functional Assessment of Cancer Therapy-Kidney Symptom Index. This benefit was significant at all but one post-baseline time point through two years of follow-up (P<0.05). Time to deterioration in FKSI-19 total score was also significantly delayed with Opdivo plus low-dose Yervoy versus sunitinib (HR 0.54; 95% CI, 0.46–0.63; P < 0.0001).

An additional analysis showed similar results with a significant benefit seen for Opdivo plus low-dose Yervoy relative to sunitinib on change from baseline at a pre-planned 25-week landmark. Assessed by FKSI-19 total score, with a mean difference of 3.55 (1.65 vs -1.9; P<0.0001), the analysis showed that patients in the Opdivo plus low-dose Yervoy arm experienced significantly better health-related quality of life scores in regard to disease-related symptoms, treatment side effects and functioning.

Additionally, longitudinal changes from baseline in health-related quality of life between treatment arms at 25 weeks, as assessed by the Functional Assessment of Cancer Therapy-General, also demonstrated a significant advantage for Opdivo plus low-dose Yervoy, with a mean difference of 3.71 (1.52 vs -2.19; P<0.0009) in the total score between arms.

Confirmatory results from FACT-G also showed significantly higher scores in the combination arm across a number of measures, including physical, functional and emotional well-being. Collectively, these data suggest a significant and consistent patient reported benefit of the combination relative to standard of care.