Today, as I present on the theme of my presidential year, “Delivering Discoveries; Expanding the Reach of Precision Medicine,” I do it from the perspectives of a clinician—an academic physician—and perhaps with a perspective that gives me insight into our profession, as a cancer survivor.

There is no question that we are witnessing a transformation of cancer care brought about by precision medicine. All of us in this room are fortunate to be in this field and to be a part of this time of dramatic innovation in cancer research and treatment.

But if we are going to expand the reach of precision medicine, there is still a lot for us to do. Today, I will talk about insight from the past, how these insights inform the opportunities before us, and how all of us can continue to advance this field.

The cumulative effect of these efforts has been transformative, and the effect has been observed clinically in less than a decade and a half.

Today nearly half of all patients presenting with lung cancer can now be initially treated with targeted agents or immunotherapy rather than chemotherapy—half of all patients with advanced lung cancer—about 100,000 a year. And there’s more to come.

Precision medicine is impacting the lives of people living with cancer, including myself, not only in terms of survival, but also in terms of us being able to experience important and memorable events in our lives. This revolution in cancer therapy is especially impressive when one considers the state of thoracic oncology a short 16 to 18 years ago. At that time,
investigators from a cooperative group here in the United States carried out a study for patients with advanced non–small-cell lung cancer (NSCLC). They compared four different chemotherapy regimens considered at that time to be promising. The study was considered so important at that time, it was presented at the plenary session at ASCO in 2000 and published 2 years later in the *New England Journal of Medicine*.

I share this example for several reasons. For one, it shows that the patient characteristics that are now considered critical to managing patients were not even reported in the publication.

The article did not list the histology: adenocarcinoma, squamous cell, or large cell carcinoma. Everything was lumped into a single category of NSCLC.

Today’s achievement of being able to systematically identify genomic changes that can be successfully targeted goes back nearly 15 years, and it underscores the importance of well-annotated preclinical models that have played a part in this exciting journey.

It is also one of the early examples of team science that began to transform the treatment of lung cancer a decade and a half ago.

My own contribution was to help annotate the clinical histories of the patients who participated in the trials whose tumors gave rise to permanent cell lines. Generation of these annotated cell lines allowed us to hone in on those tumor cell lines likely to be sensitive to the targeted agents.

The critical clinical observations made by 2004 were that never-smoking women with adenocarcinoma and patients with lung cancer from East Asia were more likely to respond to the targeted agents against the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib.

This table, taken from one of our publications, depicts the patients’ age, histology, stage, treatment status, and their survival from the start of protocol therapy. Although not shown in this table, their smoking status and sex were collected as well. I have highlighted NCI-H325S in teal, a cell line from a woman with adenocarcinoma who didn’t smoke, and I’ll talk about the properties of the cell line later.

By linking the clinical characteristics with the properties of the cell line model, we were able to observe similar biologic behavior both in patients and in the preclinical model. By studying these annotated tumor cell lines, we were able to
show that the preclinical models were more sensitive to this class of drugs—gefitinib in this case.

The clinical observations just mentioned prompted me to retrieve the preclinical model NCI-H3255. The model was established from a woman with adenocarcinoma who had never smoked—information known from the earlier mentioned annotation—so we believed the cell line was more likely to be sensitive to the EGFR-TKI gefitinib. The growth of the cell line highlighted in the previous slide, NCI-H3255, is shifted to your left, meaning the cell line is 100-fold more sensitive to gefitinib than the other cell lines. My colleague, Dr Janne discovered a DNA mutation in EGFR, now referred to as L858R.

Other colleagues pictured here, Drs Meyerson and Sellers sequenced the same domains in EGFR as that studied in the cell line in more than 100 lung cancers. They discovered the same EGFR mutation detected in NCI-H3255 in three different adenocarcinomas of the lung in patients from Japan, a country where clinical observations showed patients were three times more likely to respond to gefitinib or erlotinib than patients from the United States.

The findings from studying the preclinical models prompted us to study the patients with exceptional responses to gefitinib. Lung cancers were identified from five patients treated at the Dana-Farber Cancer Institute/Brigham and Women’s Hospital who had dramatic responses to treatment with either gefitinib or erlotinib. One of our first exceptional responders was this patient whose tumor responded for more than 2 years while being treated with gefitinib. The CT scans of the patient are shown here, with bilateral tumor infiltrates that resolved on gefitinib shown in the right panel.

All five of the tumors studied from the patients whose tumors responded to gefitinib had mutations in the tyrosine kinase domain of EGFR, whereas the four patients who did not respond to the EGFR-TKI had a wild-type receptor. These observations ultimately contributed to a dramatic shift in the treatment of some patients with lung cancer.

Two other laboratory groups led by Drs Lynch and Haber at Massachusetts General Hospital plus Drs Pao and Varmus at Memorial Sloan-Kettering Cancer Center made observations in 2004 showing a total of 25 of 31 patients who responded to gefitinib or erlotinib had sensitizing mutations of EGFR while those without mutations did not respond. These findings have transformed lung cancer care, and these three manuscripts have now been referenced more than 24,000 times.

Fourteen years later, there are now four different EGFR-TKIs approved in the United States and around the world for patients with lung cancer with mutations of EGFR. Importantly, it is part of the initial treatment of approximately 15% of patients with NSCLC cancer here in the US, and their outcome is much better than those treated with chemotherapy.

Patients with these EGFR mutations are likely to live for 2.5 years from their diagnosis of metastatic lung cancer, whereas those without the mutation treated with chemotherapy survive for less than half the time, about 1 year. The testing for mutations in EGFR in patients with advanced nonsquamous NSCLC now takes place around the world and is a part of routine care for more than 80,000 patients in the US.

The first genomic change that could be effectively targeted was the EGFR mutation, which was discovered because:

- the L858R mutation is present in preclinical cell line models that are sensitive to gefitinib;
- patients who responded to gefitinib had the same L858R mutation as the sensitive cell line;
- those who did not respond did not have the mutation;
- the growth of the cell line highlighted in the previous slide, NCI-H3255, is shifted to your left, meaning the cell line is 100-fold more sensitive to gefitinib than the other cell lines.
- Other colleagues pictured here, Drs Meyerson and Sellers sequenced the same domains in EGFR as that studied in the cell line in more than 100 lung cancers.
- They discovered the same EGFR mutation detected in NCI-H3255 in three different adenocarcinomas of the lung in patients from Japan.
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- Lung cancers were identified from five patients treated at the Dana-Farber Cancer Institute/Brigham and Women’s Hospital who had dramatic responses to treatment with either gefitinib or erlotinib.
- One of our first exceptional responders was this patient whose tumor responded for more than 2 years while being treated with gefitinib.
- The CT scans of the patient are shown here, with bilateral tumor infiltrates that resolved on gefitinib shown in the right panel.
The successful targeting of the first oncogenic driver in lung cancer prompted further studies around the world to find additional genomic changes that can be effectively targeted.

Professor Mano led the studies that identified the next oncogenic driver in lung cancer to be successfully targeted. The presence of the translocation in both the anaplastic lymphomas and lung cancers provided compelling evidence that ALK likely played a critical role in the malignant transformation to lung cancer and lymphoma and also identified a potential target for therapy.

The preclinical models were once again central for characterizing the potential therapeutic target, and the clinical characteristics of the patients from whom these cell lines were critical for identifying the appropriate models to study.

The preclinical studies showing dramatic antitumor activity against appropriate cell lines and xenograft models prompted the development of a crizotinib as an agent that has been shown to be effective for ALK-positive NSCLC patients who respond to the targeted agent, crizotinib—and now other ALK-directed agents—there are patients whose responses now go on for years and have a dramatic impact on their lives.

As oncologists we are continually exposed to response rates and progression-free and survival curves. However, the ultimate test should be whether the targeted agents make our patients feel better while living longer. Among those patients with ALK-positive NSCLC who respond to the targeted agent, crizotinib—and now other ALK-directed agents—there are patients whose responses now go on for years and have a dramatic impact on their lives.

The preclinical studies showing dramatic antitumor activity against appropriate cell lines and xenograft models prompted the development of the first oncogenic driver in lung cancer. The preclinical xenograft model, NCI-H3122, shows tumor regressions with increasing doses of the agent directed against the rearranged ALK. Dr McDermott in Dr Settleman’s laboratory led similar studies with the same drug, as well as crizotinib in lung cancer cell lines with ALK rearrangements.

A trial comparing the outcomes of ALK-positive treated NSCLC patients who were given either crizotinib versus single agent chemotherapy was reported in 2013. This slide depicts the two-fold prolonged progression-free survival of the patients treated with crizotinib, median 7.7 months, versus those treated chemotherapy, 3 months.

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These are the images of one of my patients who participated in the clinical trial just mentioned. You can see her right-sided lesion on the left panel has resolved and she has been in remission for longer than 6 years.

We commonly think of our interventions in terms of responses, progression-free survival, or overall survival, but one must keep in mind that we are actually trying to make our patients live longer and better lives, one of the principles of precision medicine.
Loretta Benkert embodies this principle, and she is willing to share her experience and the milestones she has been able to share with her family as she survives her lung cancer and is a beneficiary of precision medicine.

Now instead of lumping all patients into one group of NSCLC as we did as late as 2002, we now need to apply our principles of precision medicine and identify different genomic changes that prompt different therapies. I am pleased to say today that there are now four different oncogenic drivers for which there are FDA- and European Medicines Agency–approved targeted therapies. These include EGFR, which makes up 15% of patients, and ALK, which makes up another 5% of patients. Crizotinib for ROS1 was added in 2016, and dabrafenib plus trametinib for V600E BRAF mutations were approved in 2017, each making up another 1%. The result of this is that today about 22% of patients with lung cancer can now be treated with oral targeted agents as their initial therapy rather than combination chemotherapy. This is a dramatic transformation in the past 14 years when everyone used to be treated with chemotherapy.

However, there remain another 78% of patients who still need effective agents directed against their cancer. NTRK and RET rearrangements are among the newest genomic changes in lung cancer and other malignancies that will likely have effective agents. Trials presented at ASCO in 2017 and now in 2018 will hopefully bring that total to 25% of patients with lung cancer. A robust infrastructure in academia, other settings involved in clinical trials, and ongoing pharmaceutical research will continue to be needed to expand the proportion of patients treated with precision medicine.

But it is not just precision medicine that is revolutionizing cancer treatment. Immunotherapy has now come of age. While the clinical success of immuno-oncology has been realized in the last 5 to 10 years, it was the result of a determined effort to bring immunotherapeutic discoveries into meaningful treatments for patients with cancer for more than three decades. The basic science discoveries two and three decades ago are now having a dramatic impact on the lives of many of our patients with lung cancer. It is basic science discoveries in immunology that have transformed our field, performed by key investigators from around the world.

Professor Honjo from Japan, depicted here, identified a surface protein, the programmed cell death receptor now known as PD-1. PD-1 is a negative regulator of immune responses and now a target for the class of agents we call checkpoint inhibitors. Other work done in the early 2000s by Drs Gordon Freeman and Arlene Sharpe, both from my institutions, plus Dr Lieping Chen, shown here, identified programmed cell death ligand 1 and 2 (also known as PD-L1 and PD-L2) which also caused negative regulation of the immune responses mediated through PD-1. Their pioneering work led to the generation of the class of therapeutic agents directed against PD-1 and PD-L1—called the checkpoint inhibitors—and are now being used throughout the world as anticancer agents.

Much of the pioneering work with checkpoint inhibitors took place in melanoma patients, and those of us working in lung cancer have been informed by their ongoing discoveries and their clinical application. I am happy to say this class of agents, checkpoint inhibitors, is also active in patients with lung cancer. I show a spider plot of NSCLC patients’ responses to the checkpoint inhibitor, nivolumab, published 6 years ago in 2012. The tumor burden is depicted over time in patients treated with the checkpoint inhibitor nivolumab. There were four of 25 patients with an objective response. These responses were durable for more than 6 months. Importantly, this initial report showed some of these responses appear to go beyond a year.

Key points

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- I am pleased to say today that there are now four different oncogenic drivers for which there are FDA- and European Medicines Agency–approved targeted therapies.
- The result of this is that today about 22% of patients with lung cancer can now be treated with oral targeted agents as their initial therapy rather than combination chemotherapy. This is a dramatic transformation in the past 14 years when everyone used to be treated with chemotherapy.
- A robust infrastructure in academia, other settings involved in clinical trials, and ongoing pharmaceutical research will continue to be needed to expand the proportion of patients treated with precision medicine.
- The basic science discoveries two and three decades ago are now having a dramatic impact on the lives of many of our patients with lung cancer.
- It is basic science discoveries in immunology that have transformed our field, performed by key investigators from around the world.
- Professor Honjo from Japan, depicted here, identified a surface protein, the programmed cell death receptor now known as PD-1.
We commonly think of our interventions in terms of responses as shown in this slide, but as I said before, we must keep in mind that we are actually trying to make our patients live better as well as longer.

The 3-year follow-up of studies comparing previously treated patients with NSCLC given the checkpoint inhibitor nivolumab, versus docetaxel chemotherapy have now been reported. Their long-term follow-up is encouraging.

Patients with previously treated NSCLC are surviving beyond 3 years when treated with the checkpoint inhibitor nivolumab. As shown in this slide, the estimated 3-year survival rates are 17% in the patients with NSCLC, and the curve remains relatively flat out toward 5 years. One is gratified that one can speak of 3-year survival in advanced lung cancer, and we await further follow-up.

I, for one, am becoming optimistic that a subset of our patients with lung cancer may actually be cured with checkpoint inhibitor therapy, a finding that is now transforming the treatment of lung cancers. It has been the holy grail of oncology to develop potentially curative treatments for advanced common solid tumors, and it may now be on our doorstep for at least some patients.

The results of the trial depicted on this slide have also had a dramatic influence on the initial treatment of our patients with advanced NSCLC.

The findings have changed the initial therapy for yet another subset of patients with lung cancer by deploying a predictive marker for the efficacy of a checkpoint inhibitor.

Patients with untreated advanced NSCLC and PD-L1 expression on at least 50% of tumor cells make up about 25% of the screened patients.

The results of the trial led to the FDA approval of pembrolizumab for first-line therapy of patients with PD-L1 expression of greater than 50%, about another 25% of the patients with NSCLC.

These are the radiographic images of one of my patients placed on one of the checkpoint inhibitor combination trials. The chest CT scan in 2016 shows extensive involvement of her mediastinal lymph nodes, tracheal compression, and the left-sided chest mass. She started treatment in July of 2016 and has a near-complete remission shown in the right panel. We commonly think of our interventions in terms of responses as shown in this slide, but as I said before, we must keep in mind that we are actually trying to make our patients live better as well as longer. But instead of me talking about how Elaine is doing that, I’d like Elaine to tell you in her own words. As Elaine has put it much better than me, the delivery of immunotherapy to our patients with advanced cancer can transform their lives, not only in terms of living longer, but also living better.

As I said at the beginning of my presentation, I come to you today not only as an oncologist and cancer researcher, but as a person experiencing cancer. My own encounter with prostate cancer has allowed me to see cancer in a very different way than we commonly see it professionally. Knowing how to decide about screening as
The son of a prostate-cancer patient, and then going through the long wait of evaluation and treatment as a patient myself, has been an eye-opening experience. I now share some of the experiences that my patients routinely experience.

My personal exposure to dealing with prostate cancer came when my dad was diagnosed in 2006. I, like many men in their 50s and 60s, was faced with what to do about prostate cancer screening and knew my dad had prostate cancer. The guidance from the US Preventive Services Task Force was not clear during that time, and I share the information as it evolved in the 2000s.

In 2008, the US Preventive Services Task Force concluded that the current evidence was insufficient to assess the balance of benefits and harms of prostate cancer screening—or an I Recommendation. In 2012—the year I ended up being diagnosed—the Task Force recommended against PSA-based screening for prostate cancer—or a D Recommendation.

Now in 2018, the Task Force just recommended that, for men aged 55 to 69 years, the decision to undergo periodic PSA-based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician—or a C recommendation.

So, this advice has been bouncing around and did not give clear guidance to someone needing to make a decision, even someone firmly embedded in the field of cancer. Despite the uncertainty hovering around the prostate cancer screening, given that my dad had prostate cancer, my internist and I decided to have the PSA checked starting in my 50s. As you can see, on November 2, 2010, when I was 57, my PSA was 2.7, below the upper limit of normal, 4.0. Then I went through what a lot of our patients go through. I signed on to my medical record on March 15, 2012, when I was 59, and saw it went from 2.7 in 2010 to 9.68 during my annual check-up. I thought I needed to verify the elevation, and checked it two weeks later on March 31, and it continued to be elevated at 10.96.

The biopsies were scheduled more than a month later in May of 2012, so I had to wait for more than a month, not knowing my status and living with the uncertainty of a potential cancer diagnosis. One of six biopsies from the one side of the prostate showed prostate cancer involving of one of six cores. These findings pointed away from observation and toward therapeutic intervention, so I opted for a surgical resection. One has to wait for another 6 weeks after biopsies, so the operation was done on June 28, 2012, more than 3 months after the initial observation of a high PSA.

I have now personally experienced what it is like going for 3 months not knowing the eventual status of my cancer, and trying to carry as normal a life as possible with the distractions of a cancer diagnosis hovering over my head with the uncertainty about my future. During these 3 months, I was seeing patients in clinic, working on papers, and submitting grants. It was a challenge for me, as it is for many of my patients, to focus on my duties as an oncologist and academician. I was experiencing the uncertainty of what would be ultimately be found, and the potential impact on my life and my expected survival.

My surgeon, Dr Chang, is depicted on the slide. He performed the prostatectomy, and the resection yielded a stage II cancer with
my photomicrograph shown on the right of the slide. As many of you in the audience know, a stage II cancer is neither the best nor the worst stage of cancer to have.

Similar to many of our patients, I have and continue to live with the uncertainty of whether my prostate cancer will come back. Now that nearly six years have passed, I feel blessed that, thus far, I have avoided many of the potentially devastating consequences of recurrent cancer. The opportunity to give this address has made me think and document here the things in my life that I could have missed had my cancer not been picked up and effectively treated. I show some highlights now that 6 years have passed since my diagnosis. I have lived to see my son Evan get married in 2016, my daughter Katherine who married in 2017, our first grandchild born in 2017.

You can see my grandson Edward and me here in 2018. I also share the photograph of the gavel passing from Daniel Hayes at the 2017 ASCO annual meeting to me.

I consider it one of the great honors of my life to be able to serve this year as the ASCO President and to be delivering this Presidential Address.

ASCO needs to continue to lead efforts to guide the selection of the testing needed for each type of cancer, provide point of care support for decision making, and generate information on the outcomes of the patients in the real world outside the academic centers.

I have seen and played a small role in the introduction of some of the four different FDA-approved targeted therapies, and been able to successfully treat many of my patients with immunotherapy. Given my own encounter with prostate cancer, I now have personal insights into the anxiety faced by many of our patients about return of their cancer. I want to remind you, as we do our work and see our patients, one must be mindful of the roles we can play beyond selecting the appropriate therapy for our patients and see to the psychological needs of our patients as well. We must acknowledge the need to continue to innovate with our treatments from ongoing research to improve the lives of our patients. We must also be aware that our patients worry not only about the efficacy of our treatments, but also that they do not want to miss the critically important events in our lives that we share with those around us.

I have been proud that I have lived to be able to serve as your president of ASCO and want to thank all of you for your attention.

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**Reference**