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IASLCNEWS
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

INSIDE

GLOBAL RESEARCH

Adjuvant Gefitinib Extended Disease-Free Survival in Patients With Stage II/IIIA Non-Small Cell Lung Cancer With *EGFR*-Activating Mutations

By Cynthia L. Kryder, MS, CCC-Sp

Editor Note: *IASLC Lung Cancer News is pleased to provide the following overview, which is followed by expert commentary by Dr. Heather Wakelee, Dr. Yi-Long Wu, and Dr. Julie Mazières (see page 10).*

In patients with resected stage II-IIIA non-small cell lung cancer (NSCLC), cisplatin-based adjuvant chemotherapy over the last decade has become the standard of care, based on clinical trials that have demonstrated a statistically significant survival benefit in patients with completely resected stage IB, II, or III NSCLC.[1] Results from a recent clinical trial suggest that targeted therapy with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa) may be a better option than chemotherapy to improve disease-free survival (DFS) in patients with sensitizing *EGFR* mutations.[2]

In advanced NSCLC, the presence of *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations is predictive of treatment benefit with an EGFR tyrosine kinase inhibitor with multiple trials showing a statistically significant and clinically meaningful response and PFS benefit compared to standard chemotherapy. Consequently, these mutations are referred to as sensitizing *EGFR* mutations. About 10% to 15% of Caucasian patients with NSCLC and up to 50% of Asian patients have sensitizing *EGFR* mutations.[3] Accordingly, experts recommend testing for *EGFR*-sensitizing mutations in all patients with nonsquamous NSCLC or NSCLC not otherwise specified (NOS).[4]

Gefitinib is an oral tyrosine kinase inhibitor that is well established in Asia for the treatment of advanced NSCLC. It was reapproved in the United States in July 2015 for first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations. This approval was based on the results of a phase IV, open-label, single-arm trial.[5] At the Annual Meeting of the American

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MEETING NEWS PREVIEW

IASLC 18th World Conference on Lung Cancer

At the upcoming IASLC WCLC 2017 Conference, Co-Presidents Dr. Hisao Asamura, MD, and Dr. Keunchil Park, MD, PhD, will welcome delegates from more than 100 countries who will gather to witness and discuss the latest developments in thoracic malignancy research.

The WCLC 2017 motto "Synergy to Conquer Lung Cancer" captures the collaborative spirit of the conference, which will be both a scientific and educational event.

The world's largest meeting dedicated to lung cancer and other thoracic malignancies, attendees include surgeons, medical oncologists, radiation oncologists, pulmonologists, radiologists, pathologists, epidemiologists, basic research scientists, nurses and allied health professionals, as well as patients.

In response to the rapid advancement of the science of lung cancer, the IASLC has decided to hold the World Conferences annually. The IASLC WCLC in Yokohama will be the second of the yearly Conferences, following the IASLC World Conference in Vienna, Austria, in 2016.

Under Dr. Asamura and Dr. Park's leadership, the latest research will be presented in the following areas:

- Advanced NSCLC
- Biology/Pathology
- Chemotherapy/Targeted Therapy
- Clinical Design, Statistics and Clinical Trials
- Early Stage NSCLC
- Epidemiology/Primary Prevention/ Tobacco Control and Cessation
- Immunology and Immunotherapy
- Locally Advanced NSCLC
- Mesothelioma
- Nursing/Palliative Care/Ethics
- Patient Advocacy
- Pulmonology/Endoscopy
- Radiology/Staging/Screening
- Radiotherapy
- SCLC/Neuroendocrine Tumors
- Surgery
- Thymic Malignancies/Esophageal Cancer/Other Thoracic Malignancies

In addition, the conference program includes research presentations on Clinical Trials in Progress; Pro-Con sessions for various controversial issues; Ground Rounds; and Meet-the-Expert sessions.

At the conference, please keep up-to-date by reading synopses of presented studies in *IASLC WCLC Daily News*, the onsite meeting newspaper. Also, look for highlights from the conference in the December 2017 issue of *IASLC Lung Cancer News*. ✦

ADVOCACY AND SURVIVORSHIP

Second Annual Lung Cancer Awareness Month to Publicize Research Advances and Hope

By Keightley Amen, BA, ELS

This November, survivors around the world will celebrate the second annual Lung Cancer Awareness Month (LCAM) Consortium. Together, they will celebrate a unique, new initiative that spreads hope and shares progress in the fight against lung cancer. Led by IASLC, a rapidly growing partnership of advocacy groups and survivors is telling the world: "Hope Lives—More Research. More Survivors."

The joint public-awareness campaign aims to teach the public that everyone can get lung cancer, reduce the stigma associated with the disease, raise money for research, and reduce mortality and

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THOUGHT LEADER PERSPECTIVE

A Surprising Career Advances Cancer Research: Margaret Foti, MD, PhD (hc)

When Margaret Foti began a job as an editorial assistant for the journal *Cancer Research*, with a communications degree and a fervor for the biological sciences, she could not have known then that she had just launched a remarkable, meaningful, and particularly impactful decades-long career. Just 4 years after her entry into the field, she became the youngest managing editor of *Cancer Research*, eventually moving up the ranks to chief executive officer of the journal's publisher, the American Association for Cancer Research (AACR).

Serving as CEO since 1982, Dr. Foti, PhD, MD (hc), has helped AACR grow from 3,000 members to more than 38,000 laboratory, translational, and clinical researchers; population scientists; other healthcare professionals; and patient advocates working in 108 countries. The organization's annual operating revenues have increased to $108 million, and its scientific events have blossomed from one annual meeting to more than 25 conferences and educational workshops yearly. AACR's portfolio of peer-reviewed scientific journals also has increased—from one journal, *Cancer Research*, to eight, adding to the list *Cancer Epidemiology, Biomarkers & Prevention*; *Clinical Cancer Research*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research*; *Cancer Prevention Research*; *Cancer Discovery*; and *Cancer Immunology Research*. AACR also now publishes *Cancer Today*, a magazine for cancer patients, survivors, and their caregivers.

To further AACR's mission, Dr. Foti has spurred numerous key partnerships with organizations that have similar goals, including the International Association for the Study of Lung Cancer (IASLC). Together, the associations present the Joint International Conference on Lung Cancer Translational Science: From the Bench to the Clinic. The fifth biennial event will take place January 8–11, 2018, in San Diego, California.

The partnership with IASLC is of major importance to AACR, Dr. Foti said. "With its focus on conquering lung cancer, both nationally and internally, IASLC is a powerhouse of scientists and physicians who are working to markedly reduce the burden of lung cancer. Through its partnership with IASLC, AACR wishes to work together to make even more inroads against this terrible disease." Discussions are under way to increase AACR-IASLC collaborations in a number of areas, including joint meetings and other salient initiatives.

Margaret Foti

Limited research funding is one of the most significant challenges facing both organizations, Dr. Foti indicated, so AACR advocates for increased federal spending for cancer research and the related sciences. One of her major ongoing goals is to help incorporate cutting-edge cancer science and medicine into regulatory science and policy to accelerate drug development, drug approval, and clinical research as well as to ensure that the voices of cancer researchers, patients, survivors, and caregivers are heard on Capitol Hill. In 2007, AACR opened an office in Washington, DC, to lobby legislators on funding for scientific research. Dr. Foti said she is very proud of the work being accomplished there, at the society's headquarters in Philadelphia, and at its other offices in Boston, Toronto, and Shanghai.

Dr. Foti also leads the AACR's Scientific Partnership with Stand Up To Cancer (SU2C), a charitable initiative that supports groundbreaking translational research aimed at getting new cancer treatments to patients more quickly. With SU2C's Scientific Advisory Committee, AACR facilitates expert peer review, grants administration, and scientific oversight of various types of SU2C grants, including large team science grants (Dream Teams) and Innovative Research Grants to young investigators.

Among her accomplishments at AACR, Dr. Foti is most proud of the organization's successful work in science policy at the national level, fundraising for cancer research through the AACR Foundation, and the scientific emphasis on drug development, translational research, and science-based clinical trials, all of which are making significant contributions to saving more lives from cancer. Dr. Foti has personal experience with how research can change the lives of cancer patients and their families and caregivers. Her sister was treated 18 years ago for late-stage ovarian cancer at Fox Chase Cancer Center in Philadelphia and "is alive today because of the remarkable advances in cancer research," she said.

In addition to serving on many boards in cancer research, civic service, and publishing, Dr. Foti has garnered numerous national and international honors and awards, most notably honorary degrees in medicine and surgery from the University of Rome La Sapienza and the University of Catania in Sicily as well as an honorary degree in medicine from the University CEU of San Pablo in Madrid. In 2007, she received the inaugural AACR award established in her name. The Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research recognizes contributions to accelerating progress in cancer research, efforts that raise national or international awareness of cancer research, and other salient actions that demonstrate a sustained commitment to the conquest of cancer—much like the story of Dr. Foti's career. ✦

Her sister was treated 18 years ago for late-stage ovarian cancer at Fox Chase Cancer Center in Philadelphia and "is alive today because of the remarkable advances in cancer research."

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IASLC MISSION

To embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment, and all other aspects of lung cancer and other thoracic malignancies; to provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public; to use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world.

IMMUNOTHERAPY

Exploring the Potential of Immuno-oncology Combination Therapy

By Cynthia L. Kryder, MS, CCC-Sp

Editor Note: *The article is part of a newly launched ongoing series about immuno-oncology (IO) combination therapy, future articles of which will address PD-L1 and CTLA-4 combinations as well as IO in a curative setting, the Blueprint project, managing toxicities, as well as other related topics.*

Immunotherapy, in particular blockade of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the programmed cell death 1 pathway (PD-1/PD-L1), has been shown to be an effective treatment as monotherapy for some forms of cancer, especially lung cancer. Improved response rates and extended survival seen with immunotherapy have led investigators to explore the synergistic potential of combination immunotherapy to inhibit complementary immunosuppressive pathways simultaneously. With its established antitumor activity and favorable toxicity profile, PD-1/PD-L1 inhibition has served as the foundation for most combination immunotherapy strategies.

Rationale for Combination Immunotherapy

Combination immunotherapy aims to increase the percentage of patients who respond to treatment, to identify new tumor types that do not respond to monotherapy alone, and to improve the quality of clinical responses compared with monotherapy. Evidence suggests that PD-1 pathway inhibitors and other immune checkpoint inhibitors are most effective in tumors that are recognizable by the immune system. When tumors produce tumor antigens that are not sufficiently distinct from self-antigens, the tumor avoids detection by the immune system, and a spontaneous tumor response to treatment is absent. Combination strategies that involve complementary immunosuppressive pathways may enhance the tumor responses achieved with monotherapy and improve response rates in patients with lung cancer. One immunotherapy combination was recently approved and additional immunotherapy combinations are under investigation in patients with lung cancer.

Dual PD-1 Inhibition and Chemotherapy in Nonsquamous Non-Small Cell Lung Cancer

In May 2017, the U.S. Food and Drug Administration (FDA) approved pembrolizumab (Keytruda), an anti-PD-1 therapy, in combination with pemetrexed (Alimta) and carboplatin for the first-line treatment of metastatic nonsquamous non-small cell lung cancer (NSCLC), irrespective of PD-L1 expression. This approval was based on the results of the KEYNOTE-021 trial, cohort G.[1] Updated results presented at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting showed that the front-line combination of pembrolizumab, pemetrexed, and carboplatin reduced the risk of progression or death by 50% and nearly doubled objective response rates (ORR) compared with chemotherapy alone.[2] After 14.5 months of follow-up, the median progression-free survival (PFS) had not been reached in the triplet arm (95% CI, 8.5–not reached) compared with 8.9 months with chemotherapy alone (95% CI, 6.2–10.3). The 12-month PFS rate was 56% in the triplet arm compared with 34% with chemotherapy alone (HR, 0.50; 95% CI, 0.29–0.84; $P = 0.0038$). The ORR was 56.7% with pembrolizumab and 30.2% with chemotherapy alone ($P = 0.0016$). In addition, the hazard ratio for overall survival had dropped from 0.90 to 0.69, with a similar drop in the *P* value from 0.37 to 0.13, suggesting some further separation in outcomes favoring the pembrolizumab combination.

Dual PD-1/PD-L1 and EGFR Inhibition in Nonsquamous NSCLC

The phase Ib I4X-MC-JFCQ trial is investigating the combination of pembrolizumab and necitumumab (Portrazza), an epidermal growth factor receptor (EGFR) antibody, in patients with metastatic NSCLC who have received at least one prior line of therapy.[3] At an interim analysis of 34 patients with nonsquamous NSCLC, the ORR was 29.4%. With a median follow-up of 6.0 months, the median PFS was 6.9 months, and the 6-month rate was 55.1%.

Dual PD-1/PD-L1 and CTLA-4 Inhibition in Small Cell Lung Cancer

Preclinical evidence has provided a strong rationale to investigate the combination of PD-1/PD-L1 and CTLA-4 inhibition in different tumor types.[4] Dual blockade of PD-1/PD-L1 and CTLA-4 has proven effective in patients with advanced melanoma, and 2 studies are exploring this combination in patients with small cell lung cancer (SCLC).[5,6]

The phase I/II CheckMate 032 trial evaluated dual immunotherapy with nivolumab (Opdivo), a PD-1 inhibitor, and ipilimumab (Yervoy), a CTLA-4 immune checkpoint inhibitor, in 159 patients with recurrent SCLC.[7] In the nonrandomized portion of the trial, 98 patients received nivolumab monotherapy and 61 patients received the combination. The ORR was 25% with the combination and 11% with monotherapy. Based on these initial results, a randomized cohort of 247 patients with SCLC was added. In the subsequent SCLC expansion cohort, patients were randomized 3:2 to nivolumab monotherapy or the combination and stratified by number of prior therapies. Preliminary efficacy data for this population were presented at the 2017 ASCO Annual Meeting. In the expansion cohort, the response rate to nivolumab plus ipilimumab was 21% compared with 12% with nivolumab monotherapy. These response rates were similar to those seen in the nonrandomized portion of the trial; however, longer follow-up is needed to validate these results.

Also underway is CheckMate 451, a randomized, phase III trial of nivolumab monotherapy or nivolumab plus ipilimumab as maintenance therapy in extensive-stage SCLC following first-line chemotherapy. Primary endpoints are overall survival and PFS. Results have not yet been reported.[8]

Dual PD-1/PD-L1 and Indoleamine 2,3-dioxygenase 1 (IDO1) Enzyme Inhibition

IDO1 is a key immunosuppressive enzyme that modulates the antitumor immune response by promoting regulatory T cell generation and blocking effector T cell activation, thereby facilitating tumor growth by allowing cancer cells to avoid immune surveillance. Epacadostat is a selective oral inhibitor of the IDO1 enzyme. The ongoing phase I/II ECHO-202 trial is evaluating the combination of pembrolizumab and epacadostat in patients with advanced squamous and nonsquamous NSCLC.[9] Patients previously treated with anti-PD-1 or anti-CTLA-4 therapies are excluded from this trial. Enrollment is complete for the phase I dose escalation and dose expansion portions of the trial. Preliminary results show an ORR of 35% with the combination, irrespective of PD-L1 status, for all patients combined.

Safety Concerns With Immunotherapy Combinations

Immunotherapies present distinct safety challenges, as immune responses may be raised against normal tissues as well as against tumor cells. Checkpoint inhibitors have been associated with several inflammatory conditions similar to autoimmune-like disorders, which may indicate a disruption of self-tolerance to normal tissues. Adverse events reported in patients treated with immunotherapies commonly involve certain organ systems, including the skin, endocrine organs, liver, gastrointestinal tract, nervous system, eyes, respiratory system, and hematopoietic cells.[10] In addition to the synergistic therapeutic activity seen with immunotherapy combinations, there also may be substantive incremental toxicity, depending on the patient population and the dose and administration schedule employed. Standard dosing approaches may not work when combining immunotherapies, and patients need to be closely monitored so that safety concerns can be identified early and intervention delivered as soon as possible. By and large, steroids ameliorate these toxicities, but there are also concerns that steroids may potentially abrogate the positive effects of immunotherapy.

Clinical data thus far have shown the potential benefits that may be achieved with immunotherapy combinations. Nevertheless, further research is needed to better define the mechanisms of action of these combinations and to test various dosing schedules so that patients may benefit from these treatments. In addition, the risk-benefit profiles of immunotherapy combinations, as well as their economic impact, will need to be evaluated before novel combinations become standard of care. ✦

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ALLIED HEALTH

Role of Allied Health Professionals in the Multidisciplinary Lung Cancer Team

By Carol Brimacombe, State Registered Occupational Therapist (SROT)

The emerging role of allied health professionals in the multidisciplinary thoracic cancer team (MDT) is only just being acknowledged by the wider oncology community. How best to define and integrate their role into disease management remains a challenge.

In the United Kingdom (UK), patients with cancer are supported by specialist nurses with expertise in each specific tumor site. In Oxfordshire, a county in Southern Central England with a population of nearly 700,000 and covering just over 1,000 square miles, the lung cancer nursing team sees over 300 patients newly diagnosed with lung cancer annually, many of whom experience the inevitable decline in health and functional status that comes with a diagnosis of advanced lung cancer. The nursing team had long been acutely aware of the threat that this disease imposes on an individual's independence and dignity and of the added pressures on family and caregivers struggling to support a loved one. The lung cancer nurses and the wider MDT completed an internal review of the service being offered to patients. A lack of timely therapy provision was identified as an area of need. It was concluded that having an occupational therapist (OT) join the team would significantly expand and diversify the service that could be offered to patients. Lung cancer therapy goals were identified as:

a) Work with patients and carers to anticipate functional needs rather than waiting for a crisis to occur
b) Provide a rapid, flexible and responsive service to those with existing needs
c) Include a keyworker role outside of traditional therapy expertise who supports patients at diagnosis, helps with treatment decisions, and provides information

While all MDT members share a keyworker role, which includes supporting people through their diagnostic journey, having an OT be present and involved from the point of diagnosis onward is an original way of working for an OT and the MDT.

Funding for the post was obtained from Macmillan, a leading UK-based cancer charity, and an OT position, I was recruited and embedded into the nursing team and employed full time as an Advanced Therapist Practitioner (ATP). Referrals were received from all members of the MDT, inpatient teams, primary and palliative care. Interventions included home assessment, outpatient clinic review, breathlessness and anxiety management, and provision of aids, support, education, and advice.

Data were gathered from 305 new lung cancer patients, 165 (54%) of whom had identified therapy needs. An additional 40 (13%) were seen by the ATP as part of a generic keyworker role. The number of referrals (205) resulted in a total of 1,005 interventions averaging 5 per person. The value of the role was measured 3 ways: User Feedback Event, Satisfaction Questionnaire, and a Stakeholder Questionnaire. Outcomes were overwhelmingly positive; two of the principal benefits included the speed of response from referral to first contact and the advantages, on both a practical and human level, of being assessed at home.

It was concluded that having an occupational therapist (OT) join the team would significantly expand and diversify the service that could be offered to patients.

Case Example:
Mr. W, a patient with advanced, incurable mesothelioma, was referred to the ATP by the lung cancer specialist nurse following review at a pleural clinic where he presented with increasing functional difficulties. Previously active and independent, Mr. W and his wife were struggling to come to terms with his progressive disease and consequent decline in function.

ATP actions:

- Made 3 x home visits to build trust and rapport and assess Mr. W's functional level within his home environment
- Identification of Mr. W's extreme risk of falls and acknowledgment of his initial reluctance to make any changes to his home
- Recognition of Mr. W's trouble managing bladder function and maintaining functional independence
- Provision of equipment, including bed lever, Mowbray toilet frame, urine bottle, and walking frame, to help maintain his independence, dignity, and function
- Urgent referral made to and liaison with District Nursing for pressure care assessment
- Urgent referral made to and liaison with Community Palliative Care
- Communication conduit with patient's primary pleural consultant to confirm outcome/advice from clinic appointment, which ATP communicated to the primary care physician on same day

Outcome:
Although Mr. W died 2 weeks after the first meeting, his wife was pleased with the services provided. At the first meeting, his wife had said that she felt "desperate and lost." A week later she indicated that, whilst the situation was still horrible, she felt that everything was in place for her husband's care, and she felt in control.

Carol Brimacombe

It should be noted that interactions of this sort, if implemented properly, can allow terminally ill thoracic oncology patients to die at home with dignity and without unnecessary hospitalizations. The Oxfordshire experience provides a template for the rest of the UK as well as the rest of the world. ✦

BREAKING NEWS BRIEFS

- Alectinib received FDA priority review designation for first-line treatment of patients with ALK-positive, locally advanced or metastatic NSCLC. The supplemental new drug application included results from the phase III ALEX and J-ALEX studies, which were designed to evaluate alectinib as first-line treatment for patients with ALK-positive, locally advanced or metastatic NSCLC as detected by an FDA-approved test. (8/03/17)

- Durvalumab (Imfinzi) received FDA breakthrough therapy designation for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC). This designation was based on interim results of the randomized phase III PACIFIC trial. The double-blind, placebo-controlled, multicenter study evaluated durvalumab as a sequential treatment for patients with locally advanced, unresectable NSCLC whose disease had not progressed after standard platinum-based chemotherapy with adjuvant radiation therapy. (7/31/17)

- Pembrolizumab received from the Scottish Medicines Consortium for routine use in treatment of advanced NSCLC. Approximately 5,000 cases of lung cancer are diagnosed annually in Scotland, which makes its incidence there among the highest in the world. Lung cancer in Scotland is also the most frequent type of cancer diagnosed compared with cancer incidence rates rest of the United Kingdom. (07/10/17)

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FDA CORNER

New Strategy for Tobacco Regulation

By Erik J. MacLaren, PhD

On July 28, 2017, the U.S. Food and Drug Administration (FDA) announced a new, multi-year strategy intended to reduce tobacco-related disease and mortality. As part of this new strategy, the agency will begin developing a plan to reduce nicotine in combustible cigarettes to non-addictive levels and delay implementation of some new product regulations.[1] The primary goals of these actions are to make it easier for current smokers to quit, to reduce the risk of nicotine addiction in new smokers, and to gather more evidence for the benefits and risks newer nicotine-delivery methods, such as e-cigarettes, might pose for addicted smokers.

In a speech to employees of the FDA in May, Dr. Gottlieb identified reducing smoking rates as a key goal in the agency's mission to protect public health.[2] The new strategy announced at the end of July is intended to focus on nicotine as the underlying cause of tobacco addiction and to recognize differences in the health risks posed by combustible cigarettes versus electronic devices such as e-cigarettes. Writing in the *New England Journal of Medicine*,[3] Scott Gottlieb, MD, the FDA Commissioner, and Mitch Zeller, JD, director of the FDA's Center for Tobacco Products, provided more details about this strategy, explaining that the ultimate goals are to reduce the addictiveness of cigarettes while exploring how potentially less harmful nicotine-delivery devices should be regulated to maximize harm reduction among smokers.

To reduce the addictiveness of combustible cigarettes, the FDA will seek to regulate nicotine yields in combustible cigarettes using authority granted by the Family Smoking Prevention and Tobacco Control Act of 2009. This legislation empowered the agency to set product standards, including standards for nicotine yields, in the interest of public health. Although the FDA cannot require the complete removal of nicotine from cigarettes, it can limit nicotine to levels that are non-addictive or minimally addictive.

To begin creating new nicotine standards, the FDA will first issue an Advance Notice of Proposed Rulemaking seeking stakeholder input on the potential public health benefits and possible unintended consequences of lowering nicotine in cigarettes. Dr. Gottlieb and Mr. Zeller wrote that the FDA will consider data from peer-reviewed studies of very-low-nicotine cigarettes in setting any potential standard. Scientific evidence about possible adverse effects of decreasing nicotine levels, such as compensatory smoking, the migration of smokers to other tobacco products, or the emergence of a black market for high-nicotine cigarettes, will also be explored.

In concert with developing new regulations regarding nicotine yields, the FDA will delay the deadline for manufacturers of newly regulated products such as cigars and e-cigarettes to submit tobacco product review applications until 2021 or 2022, respectively. Current requirements for cigarettes and smokeless tobacco, and all other requirements for cigars and e-cigarettes, will be unaffected.

In their editorial, Dr. Gottlieb and Mr. Zeller explained the need for the postponement by noting that there is a "continuum of risk for nicotine-containing products" and citing the possibility that electronic nicotine-delivery methods could offer a low-risk alternative to cigarettes. Encouraging the development of new nicotine-containing products as alternatives to combustible cigarettes will likely stoke the ongoing debate over the benefits of harm reduction versus the risks of normalizing nicotine addiction. Dr. Gottlieb and Mr. Zeller acknowledged the "strongly held views" on both sides of this debate, and indicated that more time was needed to gather information on the potential benefits and risks of these alternative technologies in order to best regulate them. ✦

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CANCER LEADERSHIP

IASLC Leader Elected President of ESMO for 2020–2021: Solange Peters, MD, PhD

The European Society for Medical Oncology (ESMO) has elected an emerging leader in thoracic oncology—and an IASLC board member—to lead the organization in 2020–2021. ESMO President-Elect Solange Peters, MD, PhD, is head of the medical oncology service and chair of thoracic oncology in the Oncology Department at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland.

Dr. Peters is very active in ESMO and serves on its executive board and chairs several committees, including the organization's Women for Oncology Committee. She is also a member of the American Association for Cancer Research and European Organisation for Research and Treatment of Cancer. In addition to serving on IASLC's board, Dr. Peters is deputy editor of IASLC's *Journal of Thoracic Oncology*.

Dr. Peters spoke with *IASLC Lung Cancer News* about key issues in oncology.

IASLC: Where is oncology going as a field? What are the major issues and priorities?

Dr. Peters:

- **Issue 1:** Bridging cancer research, diagnosis, and treatment for integrated cancer care

As ESMO becomes a global society, it needs to foster a greater integration of professionals from different geographic, socio-economic, and ethnic backgrounds, to create a vibrant community that considers relevant issues from the global perspective. ESMO is committed to promoting an environment where equal access to information and optimal cancer treatment are priorities, at a time when these considerations might be weakened in several specific political and economic contexts.

- **Issue 2:** Specialized education to support oncologists and help them keep up in such a quickly evolving field

I believe that ESMO should prioritize adaptation of its activities to regional needs, for example co-developing preceptorships with ESMO members in lower-resource countries, adapting oncology curricula and guidelines to local prevailing conditions. I will support the expansion of ESMO's educational meetings to satisfy the needs of those regions that will most benefit from ESMO's resources and know-how. Such an expansion of activities will be critically assessed, to positively impact the actual delivery of cancer care without interfering with local organizations and culture.

Furthermore, ESMO has started to integrate basic researchers into its faculty, meetings, and educational activities. These efforts could be gradually reinforced, and this would also be a stimulus to promote and support academic research as well as strengthen information in the basic sciences, something which is greatly needed for the modern management of cancer patients.

- **Issue 3:** Sustainable cancer care and equal access to quality treatment

One of the most important topics to be addressed in the next 10 years is the availability of essential cancer medicines for patients, in Europe and globally. There is growing evidence of inequalities and complex barriers to access for many innovations in cancer therapy in Europe, as healthcare systems are increasingly challenging their cost, with out-of-pocket payments for cancer care growing exponentially as a result. ESMO should act as an advocate in this field, helping the profession to guide health authorities. ESMO can—impartially—provide the scientific content and specific expertise to health authorities and governmental agencies, pharmaceutical companies, patient advocates, national collaborative groups, insurance companies, and cancer caregivers across disciplines to improve or secure access to optimal cancer care. However, ESMO must first describe and report on the incredible variety and heterogeneity of public policies and healthcare models across Europe, to understand the issues encountered by each nation or region, and then establish models that can be adapted to different local conditions.

Beyond specific geographical disparities, the global sustainability of healthcare systems is threatened by the emergence of extremely expensive treatments. Costs have to be analyzed at an international level. ESMO is in a unique position to be able to describe how funding and cost-related negotiations are managed across European countries, and to develop optimal and acceptable models to be proposed or deployed at national and regional levels.

The necessary starting point for the measurement of value of any innovation is to determine whether it offers real benefits to patients. It has become clear that we can no longer afford to accept novel therapies with marginal benefits carrying disproportionate price tags. The ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) is intended to help decision-makers prioritize paradigm-changing new drugs for reimbursement. ESMO is one of several organizations initiating requests for more transparency from pharmaceutical companies regarding pricing, and helping to facilitate fair pricing.

IASLC: How will the insights and challenges you've experienced as a leader in thoracic oncology influence your leadership of ESMO?

Dr. Peters: As our understanding of the complex molecular biology underlying different cancers advances—with lung cancer being one of the first diseases facing such challenges—the potential for personalized therapies continues to grow, but so do the costs of each patient's cancer treatment. More and more government authorities must seek a balance between treatment costs and clinical benefit when assessing reimbursement policies; as a result, doctors face increasingly tough decisions.

To offer the most appropriate treatment to cancer patients, oncologists and other decision-makers need to be supported with the highest standard of guidance. And this holds particularly true as doctors face the very complex aspects of personalized oncology, tumor molecular characterization, and immunogenicity prediction—aspects that we are currently systematically discussing in the field of thoracic tumors.

Thoracic malignancies have taught me that we need to provide excellent, up-to-date, and very clear information to allow oncology specialists and stakeholders to make informed decisions and to offer the highest-quality treatments to cancer patients, regardless of their specific environment.

IASLC: What are your thoughts on research involving industry and academia?

Dr. Peters: We need to support and promote independent academic research. Commercially sponsored clinical trials only assess the viability of compounds that are chosen by a commercial entity that funds the entire process. By their design and focus, these trials need to fufill commercial interests and market expectations, which do not always coincide with patients' needs. As soon as or even before novel treatments and compounds obtain formal market authorization, academia should be able to take both existing and new medicines and conduct further research to optimize their use, develop new combinations, and focus on patients and their needs.

Solange Peters

ESMO and other organizations established the CAREFOR initiative to improve academic clinical trials. This should be expanded to other collaborative national and international research organizations; ESMO should serve as a platform for closer interactions and evaluation of new models for clinical research. This will ensure that ESMO will continue to disseminate the best science as well as identify and promote key opinion leaders in multidisciplinary cancer care. ✦

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RADIATION ONCOLOGY

Proton-Beam Therapy Versus Photon-Beam Therapy: The Debate Continues

By Cynthia L. Kryder, MS, CCC-Sp

For patients who present with inoperable, locally advanced lung cancer, photon-based chemoradiation remains the standard of care. Despite advanced radiation-delivery techniques, such as multi-leaf collimators, intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT), radiation oncologists continue to explore ways to extend the ALARA principle, that is, the desire to deliver tumoricidal radiation doses to intended targets while minimizing the radiation doses to adjacent healthy tissues. This has led radiation oncologists to investigate the potential of proton beam radiation therapy. In patients with non-small cell lung cancer (NSCLC), proton-beam therapy may enable safe dose escalation while sparing chest organs at risk and simultaneously maintaining adequate target coverage. In so doing, the collateral damage of standard radical thoracic radiotherapy can, theoretically, be mitigated.

Photons Versus Protons

Although the therapeutic index of modern, highly conformal photon radiotherapy has increased, the physics of photons make it impossible to avoid the exit dose downstream from the target, which is a physical limitation of the photon beam. In comparison, protons travel through tissue quickly and stop abruptly when reaching tissues at a very specific depth. Unlike photons, which deposit their radiation doses close to their entrance into the body, protons deposit most of their energy at the end of their paths, in a phenomenon known as the Bragg peak, the point at which the majority of energy deposition occurs. Before the Bragg peak, the deposited dose is about 30% of the Bragg peak maximum dose. Thereafter, the deposited dose falls to practically zero, yielding a nearly nonexistent exit dose. The integral dose with proton therapy is approximately 60% lower than any photon-beam technique.[1] Thus, proton therapy delivers radiation to tumors and areas in very close proximity, decreasing integral radiation dose to normal tissues and theoretically avoiding collateral damage.

Despite these potential advantages, a fundamental issue with protons is the ability to stop the proton at the tumor. As any external beam travels through the body toward its target, it passes through tissues of different densities. Proton-beam therapy is much more sensitive to tissue density than photon therapy. Likewise, at greater depths the lateral margins of the proton beam become less sharp due to considerable scattering.[2] Any change in tissue composition, such as organ motion, lung expansion, or alteration in bone position from one treatment to the next, can affect target coverage and dose to surrounding structures. To account for tissue heterogeneity and to reduce the potential for tumor underdosing, radiation oncologists often add a margin of uncertainty, meaning that the beam is designed to overshoot the target to guarantee good coverage.[3] This could, however, negate the tissue-sparing advantage of proton-beam therapy and/or dilute its therapeutic effects.

Another difference between photon-beam therapy and proton-beam therapy is the expense. Proton-beam therapy is an expensive technology. Including a cyclotron, multistory gantries, and several treatment rooms, the average cost for a proton facility ranges between US$140 million and US$200 million.

Assessing the Clinical Advantage of Proton-Beam Therapy

Given its lower integral dose and steeper dose gradient, proton therapy is an appealing therapeutic option. However, dosimetry advantages alone will not be enough to convince payors and patients to adopt this costly technology. Proton-beam therapy must demonstrate a measurable clinical advantage when compared with standard photon therapy.

Clinical trials are underway to do just that. Zhongxing Liao, MD, of the Department of Radiation Oncology at the University of Texas MD Anderson Cancer Center, is the principal investigator of a multicenter, prospective, randomized phase III trial that will compare overall survival after photon versus proton chemoradiotherapy in patients with unresectable locally advanced NSCLC.[4] This randomized trial will compare the overall survival (OS) in patients with stage II-IIIB NSCLC after image-guided, motion-managed photon radiotherapy (Arm 1) or after image-guided, motion-managed proton radiotherapy (Arm 2), both given with concurrent platinum-based chemotherapy. A total of 560 patients are expected to be enrolled. The primary endpoint is OS; secondary endpoints include 2-year progression-free survival, adverse events, quality of life, cost-effectiveness, and changes in pulmonary function.

EXPERT COMMENT

The photon versus proton conundrum continues in the latter part of 2017, and it now must evolve in the context of promising new data with immune enabling drugs such as checkpoint inhibitors. Personally, I believe it is unlikely that further dose escalation to the target area will result in significant benefits in local control and overall survival from a radiobiologic perspective despite potential advantages in dose deposition by proton therapy, so newer directions are needed. From a cost perspective, is a 140-200 million monetary outlay for protons the way to get us to the promised land? Or will molecular and immunological discoveries offer the best avenue for success? Perhaps radiation, whether through protons or photons, will be the match rather than the flame for immune enabling drugs; therefore, dose escalation may be less important. Building on the theme of potential clinical advantages between photon or proton intensity modulated therapy, the question is whether less integral dose scatter within normal tissue with the use of protons will result in less chronic immunosuppression and thus potentiate checkpoint inhibition over photon irradiation. This is an amazing opportunity to study the changes in lymphocyte:neutrophil ratios during and after treatment. The bar has jumped with the anticipated results of the PACIFIC trial in locally advanced NSCLC, and we must jump with it.

—David Raben, MD

A second ongoing trial seeks to determine whether the dose of radiation to the tumor, but not the surrounding healthy tissue, could be increased by using IMRT or intensity-modulated proton beam therapy (IMPT).[5] In phase I of the study, investigators will identify the maximum tolerated dose (MTD) of IMPT and IMRT. In phase II, researchers will compare the efficacy of IMPT and IMRT when both treatments are combined with standard chemotherapy. The primary outcome measure is MTD; the secondary outcome measure is progression-free survival.

Future Outlook

The ability of proton-beam therapy to precisely target tumors and spare underlying tissues from radiation exposure in patients with a variety of cancers has already been demonstrated. Exactly if and how proton-beam therapy fits into the treatment of patients with lung cancer remains to be determined. Harnessing the power of proton-beam therapy in the treatment of NSCLC may be challenging given that protons must be delivered to the lungs, which are targets in motion that are surrounded by tissues of different densities. Future studies will need to assess not only side effects and outcomes, but they will also need to provide data to support the development of dose algorithms and motion-management techniques.

Given the capital investment and operating costs associated with proton-beam therapy, examining the economic advantages and liabilities of this new technology is necessary. Clear data about its cost effectiveness based on different clinical and treatment scenarios will enable providers, payors, and patients to make informed decisions about treatment. ✦

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THOUGHT LEADER PERSPECTIVE

ADJUVANT Trial of Gefitinib Versus Chemotherapy in Resected *EGFR*-Mutations Non-Small Cell Lung Cancer

By Heather Wakelee, MD

Heather Wakelee

For most of the world, four cycles of cisplatin-based adjuvant chemotherapy is the standard of care for patients with resected stage II and IIIA non-small cell lung cancer (NSCLC), and is offered to many patients with stage IB tumors at least 4 cm in size or larger. This approach provides only a modest survival benefit with meta-analyses revealing a 4–5% absolute survival benefit at 5 years with adjuvant chemotherapy.[1,2] Attempts to improve outcomes with the addition of other agents to cisplatin doublets have been disappointing, including the negative ECOG-ACRIN E1505 adjuvant trial with bevacizumab[3] and the MAGRIT trial with the MAGE-A3 vaccine.[4] In subsets of patients with known driver mutations, the use of targeted agents in the adjuvant setting is an area of active investigation.

In metastatic NSCLC, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) produce superior response and progression-free survival (PFS) compared with platinum doublet chemotherapy for patients with tumors with activating *EGFR* mutations (*EGFR*mut) such as exon 19 deletion (del19) and the exon 21 mutation L858R.[5,6]

Retrospective data and non-randomized trials of adjuvant EGFR TKIs have been promising, but limited. The first phase III adjuvant EGFR TKI trial was RADIANT; however, patients were selected for EGFR expression by IHC/FISH and not by *EGFR* mutation status.[7] The primary endpoint was disease-free survival (DFS) in the full data set of patients randomized to erlotinib versus placebo after completion of any planned adjuvant chemotherapy, with secondary analyses focused on patients with del19 or L858R *EGFR* mutations in their tumor. In the entire study population, no differences were found in either DFS or overall survival (OS), but in the *EGFR*mut subset (N=161) DFS favored erlotinib (HR 0.61, 95% CI = 0.384–0.981, *P*= 0.0391). Based on trial statistical design this DFS benefit was not statistically significant. No OS benefit was reported for the *EGFR*mut subset, though OS results remain immature. Most concluded from RADIANT that adjuvant EGFR TKI was not a standard treatment option, and further investigation was warranted.

ADJUVANT (CTONG 1104) is the first randomized phase III trial focused exclusively in patients with resected *EGFR* mutant (+) NSCLC. Dr. Yi-Long Wu gave a wonderful presentation of the data at ASCO 2017. The study was restricted to patients with resected stage II-IIIA (N1-N2) *EGFR* mutation (+) NSCLC. The patients were evenly split between del19 and L858R mutations, and the majority underwent a lobectomy (82% and 84% on the chemotherapy and gefitinib arms, respectively). Prognostic factors were well balanced, but it is important to note that nearly two-thirds of the patients (>64%) had N2 disease. The study included 220 patients who were randomized 1:1 to gefitinib at 250 mg daily for 24 months or to cisplatin (75 mg/m^2 day 1) plus vinorelbine (25 mg/m^2 day 1,8) every 3 weeks for up to 4 cycles. DFS was the primary endpoint. Of 483 patients assessed for eligibility, 222 patients were evenly randomized with 111 assigned to each arm, but the treatment refusal rate was much higher on the chemotherapy arm with only 87 (78%) receiving chemotherapy while 106 (95%) received assigned gefitinib. Thus of the 222 patients treated, of whom 64% had stage IIIA disease, only 39% of them received any chemotherapy. The majority of patients who initiated therapy completed treatment with 84% of the 87 who received chemotherapy completing 4 cycles and 68% of those on gefitinib completing at least 18 months of therapy.

The study met its primary endpoint: median DFS was 28.7 months for gefitinib versus 18.0 months with chemotherapy (HR for recurrence 0.60, 95% CI 0.42–0.87, p.005). However, there was no clear "tail" as the vast majority of patients had recurrent disease by 48 months and the 3-year DFS was only 34% with gefitinib versus 27% on the chemotherapy arm. At first glance these results are very impressive. However, one must remember that the majority of patients on this study had stage IIIA disease, and many of these patients never received any chemotherapy. It is noteworthy that the forest plot revealed that patients with N1 disease did not have as favorable a benefit with gefitinib with a HR of 0.89 (95% CI 0.45–1.76, p.743); the most significant benefit was in the N2 nodal group with a HR of 0.52 (95% CI 0.34–0.80, p.003). Many of the N2 patients likely had more extensive disease.

Toxicity was as expected with higher rates of grade 3 events with chemotherapy, mostly hematologic, though it is noteworthy that the chemotherapy duration was only 4 cycles (approximately 3 months) versus 2 years for gefitinib. Not surprisingly, health-related quality of life favored gefitinib. The OS data were immature and not presented. The conclusion was that "adjuvant gefitinib could be the preferred approach in patients with resected N1/N2 *EGFR*-mutant NSCLC." The question though is really about what happens after recurrence. By year 3, a significant majority of patients had recurred. Presumably, those on the chemotherapy arm would then go on to receive an EGFR TKI, while those on gefitinib might or might not receive chemotherapy. Hence, the survival outcomes based on these approaches will be critical to determining the best possible strategy. If the gefitinib was merely treating undetected metastatic disease, the superior DFS versus chemotherapy is not surprising as PFS superiority for EGFR TKIs versus chemotherapy in the metastatic setting is well established. The real question for an adjuvant trial is whether or not the intervention actually impacts cure rates and survival. For that answer we need longer follow-up from this trial.

ADJUVANT (CTONG 1104) is not the only adjuvant EGFR TKI study proceeding globally. Multiple others are listed in Table 1. The WJOB6401L study in Japan is the most similar to ADJUVANT, with a nearly identical design; the outcome will clearly influence interpretation of the ADJUVANT (CTONG 1104) results. Other trials, including many with the EGFR TKI icotinib in China, are not only looking at whether an OS benefit can be obtained with adjuvant molecularly targeted therapy but are also assessing the duration of therapy and the potential to use EGFR TKIs instead of or after chemotherapy in selected patients. The largest North American study is the US NCI National Clinical Trials Network (NCTN) ALCHEMIST trial. The study screens patients with resected early stage (IB-IIIA) NSCLC for *EGFR*-activating mutations and *ALK* translocations. If either is identified, then, after completion of all planned adjuvant chemotherapy or radiation therapy, patients are randomized to targeted TKI therapy for 2 years or to observation. Both sub-studies are expected to enroll approximately 400 patients and are powered for an OS endpoint. The results of these trials will more clearly establish the role, if any, for adjuvant TKI therapy.

Does ADJUVANT provide enough data to support the conclusion "adjuvant gefitinib could be the preferred approach in patients with resected N1/N2 *EGFR*-mutant NSCLC"? Personally, I believe that until the OS results show a

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Table 1. Ongoing Phase III Targeted and Immunotherapy Adjuvant Trials

Trial	Description	Primary Endpoint(s)
C-TONG 1104 ADJUVANT NCT01405079	*gefitinib vs cisplatin/vinorelbine	3-year DFS
GASTO1002 NCT01996098	*chemo then icotinib vs observation	5-year DFS
BD-IC-IV-59 NCT02125240	*chemo then icotinib vs placebo	2-year DFS
WJOG6401L IMPACT	*gefitinib vs cisplatin/vinorelbine	5-year DFS
ADAURA NCT02511106	+/- chemo then *osimertinib vs placebo	DFS
ALCHEMIST A081105/E4512	+/- chemo then *erlotinib vs observation: *ALK*^ crizotinib vs observation	OS

All include stage II-IIIA
DFS: disease-free survival; OS: overall survival
*EGFR deletion 19 or exon 21 L858R mutation only
ALK^ : Positive for ALK translocation by FISH

THOUGHT LEADER PERSPECTIVE

Adjuvant Gefitinib Extended Disease-Free Survival in Patients With Stage II/IIIA Non-Small Cell Lung Cancer With *EGFR*-Activating Mutations

By Julien Mazieres, MD, PhD

The standard of care for patients post-resection for lung cancer is adjuvant chemotherapy, usually a platinum-based regimen.[1] The deciphering of lung oncogenesis has led to the routine use of targeted therapy in metastatic lung cancer but, to date, the use of these agents in the adjuvant setting is controversial and not recommended. A recent phase III trial specifically addressed this issue. The phase III ADJUVANT trial was the first randomized trial to compare gefitinib (250 mg per day for 24 months) with standard vinorelbine plus cisplatin (4 cycles) in 222 patients with completely resected stage II-IIIA (N1-N2) non-small cell lung cancer (NSCLC) with confirmed *EGFR*-activating mutations. The primary endpoint was disease-free survival (DFS) in the intent-to-treat population. Briefly, the authors have reported a significantly longer DFS in the gefitinib arm, but no significant improvement in overall survival.[2]

An optimistic view is that a subset of patients with resected stage NSCLC can benefit from EGFR inhibitors with fewer side effects than chemotherapy. A more realistic analysis suggests that 24 months of oral treatment can postpone recurrence, but does not improve survival.

Thus, this trial will not change the practice patterns as we aim in this setting to cure patients and not just delay disease recurrence. This trial underscores the limits of targeted therapies in NSCLC and suggests that EGFR TKIs are not able to definitively eradicate *EGFR*-mutated tumors. Thus, oncogenic addiction is probably more a dogma than a biological reality, and acquisition of resistance is invariably associated with targeted therapies.

In metastatic *EGFR*-mutated NSCLC, targeted therapy is used as first-line treatment as it provides a clear advantage compared to standard chemotherapy. However, virtually all patients will eventually develop resistance within a median of 12 months. Recent in vitro findings suggest that resistance can occur through two non-exclusive mechanisms: (i) by selection of pre-existing mutated clones, and (ii) through an adaptive mechanism during the early stage of treatment. We will focus on this latter mechanism.

Across multiple cell lines, in response to a variety of strong drug challenges, small subpopulations of cells have been reported to survive by initially entering a drug-tolerant, so-called persister state (drug-tolerant persisters) in which there is little to no population growth.[3] Crucially, after long-term treatment without appreciable cell growth, a fraction of persisters gain the ability to expand despite the presence of the inhibitor, and acquire genetic resistance to form drug-tolerant expanded persisters (DTEP). It has been hypothesized that survival and expansion through a drug-tolerant state could be part of an initial strategy that mediates the acquisition of bona fide, genetically driven, resistance mechanisms.[4] However, the diversity of resistance mechanisms compatible with evolution through a persister bottleneck is unclear.

The results of this phase III trial suggest that gefitinib is able to reduce micro-metastasis for a certain period of time, but is not able to eradicate these micro-metastases probably due to the induction of adaptive resistance in most of the patients. My perspective is that we need to overcome this resistance through novel therapeutic strategies. Immunotherapy, which is currently being tested in many perioperative trials, will probably help to improve the outcome of these patients. ✦

Julien Mazieres

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ADJUVANT Gefinitib from page 1

Society for Clinical Oncology (ASCO) in June 2017, Yi-Long Wu, MD, of the Guangdong General Hospital, in China, presented new data from the randomized ADJUVANT trial that suggest that gefitinib might play a significant role in the adjuvant setting, as well.

The ADJUVANT Trial

The phase III ADJUVANT (Chinese Thoracic Oncology Group 1104) trial was the first randomized trial to compare gefitinib head-to-head with vinorelbine plus cisplatin in 222 patients with completely resected stage II-IIIA (N1-N2) NSCLC with confirmed *EGFR*-activating mutations.[2] Patients received gefitinib 250 mg once daily for 24 months or the vinorelbine-cisplatin combination every 3 weeks for four cycles. Patients were stratified according to lymph node status and *EGFR*-mutation status. The primary endpoint was DFS in the intent-to-treat population. Secondary endpoints included 3-year DFS, 5-year DFS, overall survival (OS), 5-year OS, safety, health-related quality of life, and exploratory biomarker analyses.

At a median follow-up of 36.5 months (range 0.1 to 62.8 months), patients who received gefitinib had significantly longer DFS than those receiving chemotherapy. Median DFS was 28.7 months (95% confidence interval [CI] 24.9 to 32.5) for gefitinib compared with 18.0 months for vinorelbine plus cisplatin (95% CI 13.6 to 22.3; hazard ratio 0.60; 95% CI 0.42 to 0.87; P=0.005). Significantly more patients in the gefitinib arm were disease-free at 3 years compared with the chemotherapy arm, 34% versus 27%, respectively (P=0.013). The number of overall survival events was 76 (34.2%); consequently, the survival data were immature for assessment. A significant correlation between lymph node status (pN1/N2) and DFS (P<0.05) was seen in a subgroup analysis of patients in the gefitinib arm.

With regard to adverse events (AEs), patients treated with gefitinib had fewer grade 3 or higher AEs than those in the chemotherapy arm (12.3% vs 48.3%; P<0.001). All-grade AEs occurred in 57.5% of patients treated with gefitinib, compared with 80.5% of the chemotherapy group. Hematologic AEs, nausea, vomiting, and anorexia were more frequent with chemotherapy; however, rash, elevated liver enzymes, and diarrhea occurred more often with gefitinib. No gefitinib-treated patients developed interstitial lung disease.

Implications for Practice

The results of the ADJUVANT trial show that a subset of patients with resected stage II-IIIA (N1-N2) NSCLC can benefit from targeted treatment that has fewer side effects than chemotherapy. In the US, where it is not standard practice to perform *EGFR* mutation testing immediately after surgery, these data point to the potential benefit of testing tumors immediately after surgery rather than waiting until cancer recurs or metastasizes to determine whether treatment with an EGFR inhibitor can be initiated in earlier-stage disease.

Nevertheless, whether practice patterns will change as a result of these data is open for debate. A key unanswered question is what effect will adjuvant gefitinib have on overall survival? Dr. Wu and colleagues will continue following the patients in the ADJUVANT trial to fully measure this key parameter. Others question the omission of standard chemotherapy in the investigational arm prior to the administration of gefitinib.

Additional factors that may impact clinical practice are treatment length and cost. In the ADJUVANT trial, patients in the gefitinib arm received treatment for 2 years, compared with 12 weeks for patients in the chemotherapy cohort. Longer treatment may be a burden to patients and could lead to decreased treatment compliance as well as cumulative toxicities. In this regard, a TWIST analysis in each arm measuring time without progression as well as toxicities of treatment could prove instructive. In addition, as a specialty pharmaceutical, gefitinib costs more than an average outpatient drug and certainly more than chemotherapy; its estimated wholesale cost is approximately US$7,000 per month.[6]

Although adjuvant gefitinib was less toxic and more effective than chemotherapy in preventing recurrence

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THOUGHT LEADER PERSPECTIVE

Q&A with Yi-Long Wu, MD

Yi-Long Wu

What is the current standard of care in the adjuvant setting post-resection of high-risk NSCLC in your practice or nationally?

Current Chinese Lung Cancer Diagnosis and Treatment Guideline from the Chinese Society of Clinical Oncology (CSCO) recommends adjuvant platinum-based doublet chemotherapy as the standard of care (SOC) for completely resected stage II-III NSCLC. This includes node-positive tumors as well as T3 or T4N0 NSCLC. We generally do not recommend adjuvant chemotherapy for node-negative tumors under 7 cm. In clinical practice, some patients refuse chemotherapy after surgery. They prefer traditional Chinese medicine treatment, although this is not considered SOC in China.

ADJUVANT trial (CTONG 1104) provides clear evidence that adjuvant gefitinib can prolong disease-free survival by approximately 10 months with lower toxicity and better quality of life (QoL) compared to standard platinum-based chemotherapy in *EGFR*-mutant (*EGFR*-mt [+]) NSCLC. This study justifies an alternative treatment strategy for *EGFR*-mt (+) patients with N1-N2 resected NSCLC who are averse to or ineligible for chemotherapy. Based on our data, I will recommend adjuvant gefitinib for *EGFR*-mt (+) NSCLC patients with N2 disease because chemotherapy in this setting yields a median DFS of only 9–12 months. This population remains at very high risk. I believe most patients and most thoracic surgeons in China would accept this recommendation.

The absence of a documented OS advantage is not a deterrence. Almost all EGFR TKIs clinical trials in advanced NSCLC have shown a striking PFS advantage compared to SOC chemotherapy, but no difference in OS. Despite the absence of a clear OS benefit, most practitioners accept these results, and first-line EGFR TKIs are now the SOC for recurrent or metastatic *EGFR*-mt (+) NSCLC patients. Why should we not apply similar criteria to the adjuvant setting for *EGFR*-mt (+) resected NSCLC? For this reason, we selected DFS as the primary endpoint, and this strategy has been adopted in other similar trials. In this situation, with crossover to an EGFR TKI expected in the control arm at the time of disease progression, we believe that all patients with driver genes will live longer than they have previously. In addition, we need to acknowledge that many factors beyond *EGFR* status and the nature of treatment will influence OS. While OS is important, a DFS advantage will likely lead to clinical benefits, both physical and psychological.

In East Asia, driver genes account for approximately 40% of the NSCLC patient population. This is a huge population, proportionally larger than similar populations seen outside of East Asia. Now that our trial has been reported, there are two therapeutic options for these patients after surgery: adjuvant TKI or chemotherapy. For so-called wild-type patients, adjuvant chemotherapy is the only treatment we recommend outside of a clinical trial.

There are still unanswered questions. In the adjuvant setting, we still need to figure out a way to better select patients for adjuvant TKIs as well as determine how long such treatment should be given. Is there an optimal sequence for adjuvant TKIs and chemo? In addition, we need to determine the optimal therapeutic adjuvant approach for "wild-type" patients whose tumors do not harbor an oncogenic driver. In this regard, checkpoint inhibitors may ultimately play an important role.

Do you restrict adjuvant therapy to node (+) patients or also include those with lesions 4 cm or larger?

For adjuvant chemotherapy, we restrict patients with stage II-III. Stage II-III NSCLC not only includes node positive, but also T3 or T4 with N0. If only lesion 4 cm with N0 (stage IB), we do not give adjuvant chemotherapy.

Does the phase III trial presented at ASCO, showing a DFS advantage for gefitinib over platinum-based chemo, alter practice either locally or nationally?

ADJUVANT trial (CTONG 1104) provides clear evidence that adjuvant gefitinib could postpone disease recurrence by 10 months, decrease toxicity, and increase QoL. We provide an option for patients with N1-N2 resected NSCLC, and in my mind, I will recommend adjuvant gefitinib for patients with N2 disease. Because median DFS of N2 is only 9–12 months, this population is very high risk. I think most patients and thoracic surgeons will accept this recommendation.

From a philosophical perspective, is OS the ultimate arbiter of benefit? Or can DFS be considered a surrogate? In other words, is DFS alone sufficient to leverage particular regimens?

Almost all EGFR TKIs clinical trials on advanced NSCLC showed PFS is superior with chemotherapy, but there is no difference in OS. Everybody accepts these results, and first-line EGFR TKIs is now the standard of care for *EGFR*-mt (+) NSCLC patients. Why are we overcritical of the adjuvant setting for *EGFR*-mt (+) resected NSCLC? In our trial and another ongoing adjuvant target trial, DFS is always designed as the primary endpoint. All patients with driver genes will live longer than before, and many factors will influence OS. In this situation of no difference in OS, I think DFS is very important because patients will get benefit both physically and psychologically.

Are the standards different in those with oncogenic drivers compared to the larger "wild-type" population?

In East Asia, patients with NSCLC and driver genes account for 40%. This is also a huge population. After our trial, there were two options for these patients after surgery: adjuvant TKI or chemotherapy. For those so-called wild-type patients, adjuvant treatment is only chemo.

What future research directions should we be pursuing in the adjuvant setting?

For the adjuvant setting, I think we need to select precisely which patient could benefit from adjuvant TKIs and determine how long treatment is needed. What is the optimal sequence of adjuvant TKIs and chemotherapy? and so on. And on the other hand, when treating patients with wild-type in the adjuvant setting—could checkpoint inhibitors play an important role for these patients? ✦

ADJUVANT Gefinitib from page 11

following surgery in patients with sensitizing *EGFR* mutations, practitioners await the results of ongoing and future clinical trials to determine the optimal role of gefitinib in the treatment of NSCLC. Based on NCCN guidelines, it has not yet entered standard practice in the US. ✦

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NCI CORNER

Tools for Smoking Cessation

By Erik J. MacLaren, PhD

Scott Gottlieb, MD, Commissioner of the U.S. Food and Drug Administration, said in a recent speech, "*There's probably no single intervention or product we're likely to create in the near future that can have as profound an impact on reducing illness and death from disease as our ability to increase the rate of decline in smoking.*"[1] One of the many ways the National Cancer Institute (NCI) contributes to the goal of reducing smoking is through its Tobacco Control Research Branch (TCRB), which leads and collaborates on research, and disseminates evidence-based findings to prevent, treat, and control tobacco use.

In collaboration with other Federal organizations, TCRB created and maintains the Smokefree.gov Initiative (www.smokefree.gov), the largest Federal mobile behavioral health intervention program. Smokefree.gov offers free, accurate, evidence-based smoking cessation treatment and professional assistance to help individuals, including specific vulnerable populations such as teens, women of reproductive age, Spanish speakers, military/veterans, and older adults.

A wealth of consumer-friendly articles on key smoking cessation topics—including preparing to quit, managing withdrawal, and choosing cessation support methods—serves as the foundation of Smokefree.gov. In addition, Smokefree.gov offers digital tools for those wishing to quit, such as a *Create My Quit Plan* builder and quizzes that assess topics like nicotine dependence or stress levels. QuitGuide (for adults) and quitSTART (for teens), are smartphone apps that conform to US Clinical Practice Guidelines. They each provide 24/7 on-demand support and skills building to improve users' chances of successfully quitting. They also allow users to tag specific locations and times of day to get support when they need it most.

The Initiative also maintains SmokefreeTXT, a 6–8 week text messaging intervention that provides smoking cessation treatment and includes advice and encouragement to smokers attempting to quit. Eleven other smoking cessation text programs have been modeled from SmokefreeTXT to help vulnerable smoking populations. Two recently developed programs assist smokers in practicing quitting and building skills and confidence for quitting permanently. HealthyYouTXT offers 3 tailored programs for smokers interested in addressing related health behaviors around eating healthier, increasing physical activity, and managing their weight.

The NCI's Cancer Information Service supports a smoking quit line (1-877-44U-QUIT), a national service with trained information specialists who offer multiple resources to quit smoking, including information, counseling, and referrals. As a complement to this, the NCI also offers access to state-run programs via 1-800-QUIT-NOW, which automatically redirects callers to a local quit line.


Erik Augustson

Erik Augustson, PhD, MPH, a Behavioral Scientist and Program Director in the TCRB, spoke with *IASLC Lung Cancer News* about the future of digital tools for smoking cessation, including mobile health (mHealth) treatments such as smartphone apps. "One primary area in which I expect to see improvement is in our ability to maintain engagement in mHealth treatments with smokers across time, which will improve outcomes," said Dr. Augustson. He explained that several research groups around the country, including his own, are working on integrating natural language processing and artificial intelligence into mHealth treatments to achieve this goal.

Another key direction identified by Dr. Augustson is improvement in the integration between digital resources and those delivered by real people. One possibility, he said, would be "providing the counselor with data summaries collected within the mHealth platforms to improve the ability of the counselor and smoker to work collaboratively in developing and implementing quit plans." The goal of such integration would not be to reduce the active role of real people in delivering treatment but to allow the greater personalization of treatment plans and improve outcomes. ✦

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LCAM from page 1

suffering by disseminating information about recent scientific advancements.

Silvia Novello, professor of medical oncology in the Department of Oncology at the University of Turin in Italy, stressed the importance of getting the word out. "A lot has been achieved, but a lot more needs to be done. We believe everyone can have an impact, so let's join our efforts and work together to make lung cancer a chronic disease and to help lung cancer patients not to feel isolated and discriminated against, *because lung cancer doesn't discriminate*!"

The flagship of the initiative, LCAM.org, shares stories of survivors to inspire and inform others about many facets of the disease; for example: "Become Your Own Best Advocate," "Lung Cancer Can Happen to Anyone," "Always Seek a Second Opinion," and "Three Years and Thriving." The stories are intended to showcase the diversity of those affected by the disease: all races, young and old, smokers and non-smokers.

Janet Freeman-Daily, a lung cancer survivor and a member of the LCAM working group, has made it "pretty much a full-time job" to help others fighting the disease. Diagnosed in May 2011 with non-small cell lung cancer, Freeman-Daily has had no evidence of disease in four years and counting. "Advocacy gives me a purpose," she said. "When you face death and realize you might not even have a year left, you start to wonder: *Why am I here and what difference do I make*? Even if I have days when I'm not feeling so good, I can still do something worthwhile. I can get online and help other patients."

She helps countless others by writing, speaking, getting involved with research projects, tweeting factoids, and building a Facebook community, and now by helping the LCAM initiative find patient stories and get the word out.

The campaign also profiles other lung cancer advocacy organizations that support patients and caregivers, provide physicians with more information about screening and clinical trials, and educate the public and healthcare community about tumor testing and targeted therapy. It is building momentum quickly:

- More than 40,000 people are following LCAM on Facebook
- At LCAM.org, more than 60 survivors and caregivers have shared their stories, and the site has had more than 30,000 visits
- More than 20 global partners are participating in the campaign
- During the 2016 LCAM campaign, more than 25,000 pins, T-shirts, bracelets, and posters were distributed
- Print newspaper ads have reached a circulation of almost 700,000
- The campaign's videos have been viewed by more than 78,000
- The LCAM YouTube Channel has featured 15 videos, which have received more than 2,000 views

However, Freeman-Daily said there are still so many obstacles to overcome. "Sometimes you wonder if you're making any difference. Sometimes you get tired of all the barriers you run into," she said, citing a lack of knowledge about clinical trials, limited access in rural areas and for minority groups, doctors telling patients to "get their affairs in order" rather than telling them to be tested for EGFR, ALK, ROS-1 and other genetic markers, scarce funding for research, the small survivor community and therefore small advocacy community, and the stigma that lung cancer is self-inflicted.

"The awareness month is good because you see the number of people who are living longer, being able to show a positive picture of lung cancer, not just the smoking stuff. It does give people hope."

In its second year, LCAM will focus on adding more global partners, including additional advocacy groups and medical institutions as well as more international participants from Israel, Latin America, Australia, and more. The partners also plan to expand the diversity of featured patients and participants, develop additional educational and marketing materials (photos, videos, and an educational webinar), build social media interaction and sharing, showcase more scientific advances, and increase sponsorship to build staff and the advertising campaign.

Novello implored others to get involved worldwide to keep the momentum going. "Lung cancer is the first cause of death due to solid cancer in several countries, and all the efforts in terms of primary prevention, proper diagnosis, and adequate treatment need to be shared to cope with the disease," she said. "To make this message universal and to disseminate it, it is extremely important to join the IASLC in its program of awareness in November."

To learn more or participate, visit LCAM.org, sign up on the site (http://lcam.org/contact/) to receive email updates, follow the campaign on Facebook (https://www.facebook.com/LCAM.org/) or Twitter (https://twitter.com/LCAM_org), or contact Kristin.Schultz@iaslc.org. ✦

The LCAM initiative is supported by independent educational grants from Eli Lilly and Company; Bristol-Myers Squibb; Merck & Co., Inc.; and Helsinn.

EVOLVING STANDARDS OF CARE

Evolution in Treatment of Brain Metastases in Mutation-Driven Non-Small Cell Lung Cancer

By Jason K. Molitoris, MD, PhD, Anthony D. Nehlsen, MD, and Minesh P. Mehta, MD

Up to 40% of patients with advanced non-small cell lung cancer (NSCLC) will develop brain metastases (BM); this contributes significantly to decrement in survival and quality of life. Optimal BM treatment in patients with targetable rearrangements in *ALK* and mutations in *EGFR* is in a state of dramatic flux because of the underlying disease biology, availability of effective, blood-brain barrier penetrant targeted agents, new evidence on therapeutic outcomes after stereotactic radiosurgery (SRS), whole-brain radiation therapy (WBRT), and ongoing evaluation of cognitive preservation strategies.

Large retrospective data cohorts of NSCLC patients with BM demonstrate an overall "improvement" in median survival (MS) from 7 to 12 months in patients treated between 1985–2005 and 2006–2014; whether this is a genuine improvement or a function of selection bias and earlier detection remains speculative. Dramatically longer survival times are seen in patients harboring actionable mutations, with a MS of 14 months in non-mutated patients, 23 months for *EGFR*-mutated patients, and 45 months for *ALK*-rearranged patients.[1] An update to the NSCLC disease-specific graded prognostic assessment (ds-GPA) now includes mutational status, with a median survival of nearly 4 years for the most favorable patients.[2] As survival increases in general, and specifically in mutation-driven tumors, there are competing priorities in the management strategies for BM: improving survival and achieving durable intracranial control while minimizing toxicity.

In the US and increasingly around the world, there is a clear trend towards the utilization of SRS and delayed use of WBRT. The recently reported NCCTG-N0574 trial, which randomized patients with 1 to 4 BM to SRS+/–WBRT, demonstrated similar OS, and WBRT was associated with worse cognition at 3 months, which persisted for long-term survivors at 1 year.[3] However, this came at the cost of a significantly shorter time to intracranial failure with SRS, compared to SRS+WBRT. As SRS alone increases in utilization, the risk of intracranial progression increases, the time-to-intracranial failure shortens, and the need for more reliable follow-up increases, usually entailing more frequent surveillance MRIs; each of these considerations must be balanced for individual patients. Alternative strategies to preserve cognitive function while instituting WBRT include the use of the N-methyl-D-aspartate (NMDA)-receptor agonist, memantine, with WBRT, which has led to a delay in cognitive deterioration.[4] In a recently published phase II trial, hippocampal-avoidance WBRT also preserved cognition, compared to historical controls.[5] An ongoing phase III trial is evaluating the addition of hippocampal-avoidance in combination with WBRT and memantine.

The prolonged survival and availability of well-tolerated tyrosine kinase inhibitors (TKI), most of which cross the blood-brain barrier, has led investigators to question whether radiotherapy now has any upfront role in the management of BM in *ALK*-rearranged or *EGFR*-mutated NSCLC, particularly in patients with minimal symptomatology. A recent multi-institutional review of *EGFR*-mutated NSCLC with BM compared patients treated with upfront SRS or WBRT followed by TKI or TKI with delayed radiation. MS was significantly longer for patients receiving either upfront SRS (46 months) or WBRT (30 months), compared to TKI with delayed radiation (25 months).[6] While patients in the SRS and TKI groups were similar, patients in the WBRT group had poor prognostic features, and still outperformed upfront TKI treatment alone. While these findings are retrospective, they are cautionary and underscore the potential for increased importance of early intracranial control in patients, thereby ensuring prolonged survival.

Recent data have demonstrated intriguing evidence for the intracranial activity of TKIs in *ALK*-rearranged NSCLC BM. Crizotinib initially demonstrated mild CNS penetration and responses in a study evaluating 275 patients with asymptomatic BM who received either RT+crizotinib or crizotinib alone[7] Patients who did not receive RT had significantly shorter time to intracranial progression (7 vs 13 months). More recently second- and third-generation TKIs have demonstrated superior intracranial response rates. In a pooled analysis, alectinib demonstrated a 64% CNS response.[8] The recently presented ALEX study reported that, compared to crizotinib, alectinib had improved CNS response (81% vs 50%) and decreased 12-month incidence of BM (9% vs 41%).[9] Similarly, ceritinib has demonstrated responses in 34% to 61% of patients, and intracranial PFS of 8.3 months.[10,11] Several retrospective studies evaluating outcomes for upfront vs delayed CNS RT have largely failed to demonstrate survival differences.[12,13] However, caution is warranted in over-interpreting these data, as the patients who underwent delayed CNS RT typically had lower disease burden and better prognosis.

Therefore, in patients with *EGFR* mutations, until more evidence is obtained, it is our preference to treat BMs in these patients similarly to non-mutated patients. We are more inclined to treat those patients with a "limited" number of lesions with SRS, provided close follow-up is achievable, and those with "numerous" lesions with WBRT, both in concert with an EGFR TKI. In those with ALK fusion proteins, the choice of BM treatment currently is more challenging. We believe that prospective clinical trial data are required prior to recommending therapeutic de-escalation, and we therefore would caution against withholding CNS RT outside of a clinical trial environment.

We are hopeful that the newer agents with increased CNS penetration may lead to situations where early response to targeted therapy could "down stage" patients from treatment with WBRT to SRS, alter dose fractionation of WBRT, and/or allow for increased use of cognitive-sparing WBRT techniques. We might learn from these clinical trials that perhaps, in some well-selected patient subsets, RT could even be withheld or postponed. At present, however, without additional data, making this leap is somewhat dangerous, and therapeutic de-escalation outside a clinical trial context places the patient at risk. These risks putatively include an increased risk of intracranial failure, shorter time to intracranial failure, worsening cognitive function and neurologic sequelae from increased intracranial failure, and possibly even a decrement in survival. ✦

EXPERT COMMENT

The authors provide a well-written summary of the current status of brain metastases in mutation-positive NSCLC. The newer TKI appear more effective but the improved survival may be due to better control of systemic disease, not the brain metastases. Until randomized data show otherwise, SRS for CNS metastases remains the standard of care.

—Paul W. Sperduto, MD, MPP, FASTRO

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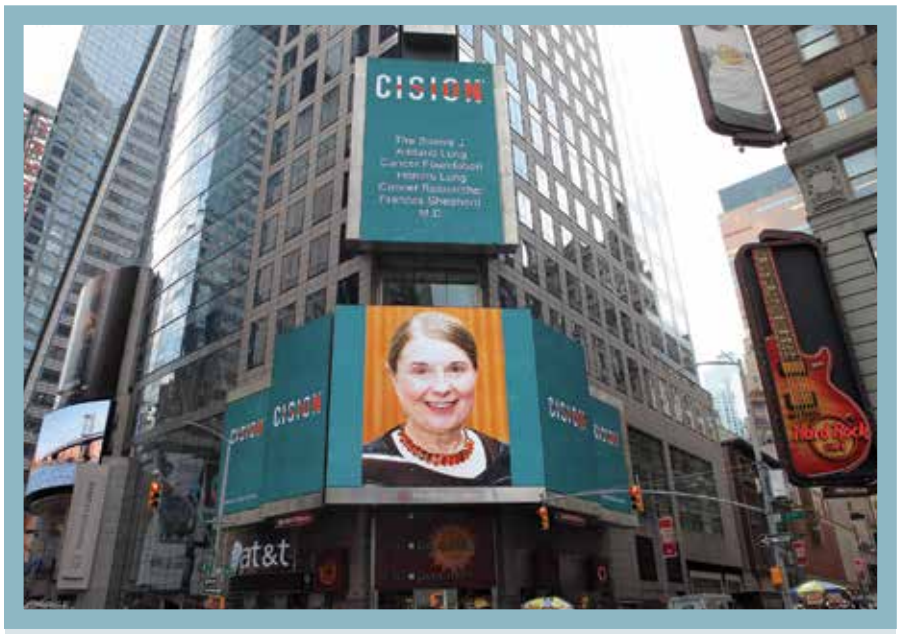
Names and News

Raymond Osarogiagbon, MBBS, FACP, incoming chair of IASLC's membership committee will receive the 2017 Association of Community Cancer Center Clinical Research Award. This award is given in recognition of research that has significantly and positively impacted the oncology patient, family, and community. Dr. Osarogiagbon is director of the Multidisciplinary Thoracic Oncology Program at the Baptist Cancer Center in Memphis, Tennessee; a Research Professor at the University of Memphis School of Public Health; a Research Member of the Vanderbilt Ingram Cancer Center; and a member of the Lung Cancer Disparities Center of the Harvard School of Public Health. Dr. Osarogiagbon also was recently appointed to the US National Cancer Institute's newly formed Cancer Prevention Steering Committee (CPSC).

Deric Savior, MD, has been appointed Head of Medical Oncology, Fox Chase Cancer Center at Temple University Hospital (TUH). Prior to this appointment, Dr. Savior led the Fox Chase thoracic oncology section at TUH, Philadelphia, USA, where he has served on the Cancer Committee, Institutional Review Board, Diversity Committee, and in the Faculty Senate.

Jean-Charles Soria, MD, PhD, has been appointed Senior Vice President, Head of Oncology Innovative Medicines at Medimmune, AstraZeneca. He will oversee research, translational sciences and early drug development in oncology within Medimmune. Prior to this appointment, Dr. Soria served as a Professor of Medicine and Medical Oncology at South-Paris University. He was also a tenure-track and full-time cancer specialist at the Institut Gustave Roussy where he served as Chair of the Drug Development Department and a member of the lung cancer unit with a focus on targeted therapies. Dr. Soria is Editor-in-Chief of the *Annals of Oncology*.

PJ Souquet, MD, was appointed President of The French Cooperative Thoracic Intergroup (Intergroupe Francophone de Cancèrologie Thoracique IFCT). Dr Souquet, is Head of Service at the Hospices Civils de Lyon, Lyon, and Associate Professor of Medecine, at South-Lyon University, France..



Frances A. Shepherd, OC, OOnt, MD, FRCPC, is the recipient of two recent oncology awards: She received the Tenth Annual Addario Foundation Keynote Lecture Award, which recognizes luminaries in the lung cancer field working to improve and prolong the lives of those with the disease, and its eradication. In addition, Dr. Shepherd was presented with the 2017 ESMO Women for Oncology award, given to acknowledge an individual who has significantly supported the career development of women in oncology.

Internationally known for her key role in the design and conduct of research studies evaluating new therapies and treatment strategies in lung cancer, Dr. Shepherd served as President of International Association for the Study of Lung Cancer (IASLC) from 2003 to 2005. In 2012, she won the British Thoracic Oncology Group International Award for Contributions to Lung Cancer Research, the Royal College of Physicians and Surgeons of Canada Whiteman Award and Visiting Professor and a Queen Elizabeth II Diamond Jubilee medal. In 2015, she was made an Officer of the Order of Canada.

Dr. Shepherd is Senior Staff Physician at The Princess Margaret Cancer Centre, Toronto, Canada, where she holds the Scott Taylor Chair in Lung Cancer Research. She is Full Professor of Medicine at the University of Toronto.

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Wakelee Perspective from page 8

clear benefit to support this approach, we should not move away from the proven benefits of chemotherapy. However, in the setting where a patient refuses chemotherapy, the ADJUVANT data strongly support that EGFR TKI treatment is better than no treatment. Given the preponderance of stage III patients in ADJUVANT, and lack of benefit in N1 patients in the forest plot from the trial, it is not clear how this will translate to patients diagnosed at earlier stages. We must exercise caution in how this study is interpreted and presented to patients. ADJUVANT clearly demonstrates that for patients with resected *EGFR*mut NSCLC with N2 involvement, gefitinib is an appropriate therapy, but given the extremely high rates of recurrence, it is not clear that this is truly adjuvant therapy, versus early initiation of treatment for occult metastatic disease. We must also not forget that nearly a quarter of patients assigned to the chemotherapy arm (22%) refused treatment and thus were treated with surgery alone, clearly an inferior strategy for stage IIIA NSCLC.

ADJUVANT (CTONG 1104) is an important, well-conducted study of adjuvant gefitinib in patients selected for resected *EGFR* mutation (+) NSCLC, and the first of this class of studies to be completed. The authors are to be congratulated on the presentation of this important trial. However, except in the subset of patients with resected *EGFR* mut (+) N2 disease who refuse chemotherapy, I believe we should wait before making adjuvant gefitinib a standard approach. We need to see a clear OS benefit, and we need to see the results of the many other ongoing trials, before changing global practice. ✦

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