The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of *EGFR* Mutation–Positive Non–Small Cell Lung Cancer: Status in 2016

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Disclosure: Dr. Tan reports personal fees from Celgene, Eisai, and Pfizer; grants and personal fees from Novartis; and grants from GlaxoSmithKline, AstraZeneca, and Bayer outside the submitted work. Dr. Yom reports grants from the National Comprehensive Cancer Network Foundation, Genentech, and Clinigen; royalties from UpToDate, and honoraria from the American Society of Radiation Oncology outside the submitted work. Dr. Tsao reports grants and personal fees from AstraZeneca Canada during the conduct of the study; grants and personal fees from Pfizer Canada; and personal fees from Bristol-Myers Squib, Merck, and Hoffmann LaRoche outside the submitted work. Dr. Kelly reports receiving the following outside the submitted work: personal fees and nonfinancial support from Boehringer Ingelheim; personal fees from Clovis; personal fees and compensation for serving on advisory boards and for research of clinical trials from Lilly; grants, personal fees, nonfinancial support and compensation from Genentech for attending advisory board meetings, travel, conducting research of clinical trials, and serving on a data monitoring committee; personal fees from Transgene; personal fees, nonfinancial support, and compensation from Celgene for attending advisory board meetings, travel, and conducting research of clinical trials; personal fees and compensation from Synta for attending advisory board meetings and conducting research of clinical trials; personal fees, nonfinancial support, and compensation from AstraZeneca for attending advisory board meetings, travel, conducting research of clinical trials, and serving on a data monitoring committee; personal fees and nonfinancial support from Ariad; compensation for conducting research of clinical trials from Millennium, Novartis, EMD Serono, AbbVie, and Gilead; and author royalties UpToDate. Dr. Wistuba reports grants and personal fees from Genentech/Roche, personal fees from AstraZeneca and Clovis during the conduct of the study, and he also reports personal fees from Glaxo Smith Kline, Celgene, Bristol-Myers Squibb, Synta, Boehringer Ingelheim, Medscape, Asuragen, Ariad, and HTG Molecular, as well as grants from HTG Molecular and Oncoplex outside the submitted work. Dr. Yatabe reports personal fees from AstraZeneca, Novartis, and Merck, Sharp, and Dohme, as well as from Pfizer, Chugai Pharma, Taiho, and Roche outside the submitted work. Dr. Mack reports personal fees from AstraZeneca, Novartis, Guardant Health, MolecularMD, and Apton Biosystems and grants from Boehringer Ingelheim outside the submitted work. Tetsuya Mitsudomi reports personal fees from AstraZeneca and grants and personal fees from Chugai and Boehringer Ingelheim during the conduct of the study; he also reports grants and personal fees from Pfizer, Ono, and Taiho and personal fees from Merck, Sharp, and Dohme and from Bristol-Myers Squibb and Eli Lilly outside the submitted work. Dr. Herbst reports personal fees from Genentech, Merck, Boehringer Ingelheim, Pfizer, and AstraZeneca during the conduct of the study. Dr. Gandara reports grants and other from Genentech, AstraZeneca, and Boehringer-Ingelheim outside the submitted work. Dr. Carbone reports personal fees from Ariad, AstraZeneca, Bayer HealthCare, Biothera, Boehringer Ingelheim, Clovis Oncology, Genentech of Roche, Guardant Health, Inivata, Janssen Diagnostics, Merck, Novartis, Peregrine Pharmaceuticals, Synta Pharmaceuticals, and Teva Pharmaceuticals and grants and personal fees from Bristol-Myers Squib during the conduct of the study. Dr. Bunn Jr. reports personal fees from Astra Zeneca, Genentech, and Clovis during the conduct of the study. Dr. Mok reports personal fees from the following companies outside the submitted work: AstraZeneca; Roche/Genentech; Lilly; Merck Serono; ACEA Biosciences; Bristol-Myers Squib; AVEO and Biodesix; Pfizer; Boehringer Ingelheim; Novartis Pharmaceuticals; GlaxoSmithKline; Clovis Oncology; Amgen; Janssen; BioMarin Pharmaceuticals; SFJ Pharmaceuticals; Merck, Sharp, and Dohme; Vertex Pharmaceuticals; Prime Oncology; Sanomics Ltd.; geneDecode; and Oncogenex. Dr. Hirsch reports grants from AstraZeneca during the conduct of the study and compensation outside the submitted work from AstraZeneca, Genentech/Roche, Bristol-Myers Squib, Lilly, Pfizer, and Boehringer-Ingelheim for participating in advisory board meetings; in addition, he is chief executive officer of the International Association for the Study of Lung Cancer.

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ISSN: 1556-0864

http://dx.doi.org/10.1016/j.jtho.2016.05.008

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Received 25 April 2016; revised 12 May 2016; accepted 13 May 2016
Available online - 23 May 2016

ABSTRACT

Mutations in the epidermal growth factor receptor gene (*EGFR*) represent one of the most frequent "actionable" alterations in non–small cell lung cancer (NSCLC). Typified by high response rates to targeted therapies, EGFR tyrosine kinase inhibitors (TKIs) are now established first-line treatment options and have transformed the treatment paradigm for NSCLC. With the recent breakthrough designation and approval of the third-generation EGFR TKI osimertinib, available systemic and local treatment options have expanded, requiring new clinical algorithms that take into account individual patient molecular and clinical profiles. In this International Association for the Study of Lung Cancer commissioned consensus statement, key pathologic, diagnostic, and therapeutic considerations, such as optimal choice of EGFR TKI and management of brain metastasis, are discussed. In addition, recommendations are made for clinical guidelines and research priorities, such as the role of repeat biopsies and use of circulating free DNA for molecular studies. With the rapid pace of progress in treating *EGFR*-mutant NSCLC, this statement provides a state-of-the-art review of the contemporary issues in managing this unique subgroup of patients.

Keywords: Non–small cell lung cancer; EGFR mutation; Tyrosine kinase inhibitor; Therapy; Resistance; Brain metastases

Introduction

Since the seminal discovery of activating epidermal growth factor receptor gene (*EGFR*) mutations in 2004,[1,2] the management paradigms and outcomes of lung cancer have changed dramatically. One of the key conceptual advances has been the identification of subsets of patients with non–small cell lung cancer (NSCLC) who exhibit differential responses to specific therapies. The significant impact of mutation-specific targeted therapies directed against an expanding list of "actionable" alterations has necessitated rapid integration of molecular profiling into clinical practice. One of the striking observations arising from molecular screening of patient populations globally has been the difference in prevalence of *EGFR* mutations across ethnicities.[3,4] For example, the prevalence of *EGFR* mutations ranges from between 5% and 10% in whites to between 60% and 70% in never-smoking Asian patients with adenocarcinoma—notably leading to regional differences in molecular profiling algorithms, as well as to varying levels of feasibility in conducting biomarker-selected trials.[5]

As a classic oncogene-driven solid tumor, *EGFR* mutation–positive NSCLC has a unique disease course typified by high response rates to tyrosine kinase inhibitors (TKIs).[6] Several phase III studies comparing first- and second-generation epidermal growth factor receptor (EGFR) TKIs with chemotherapy have demonstrated significantly higher response rates and longer progression-free survival (PFS), establishing EGFR TKIs as a first-line treatment of *EGFR*-mutant NSCLC.[6–13] However, resistance to TKIs almost invariably occurs and several molecular mechanisms have been described, with the *EGFR* T790M somatic mutation being the most frequent alteration detected in approximately half of progressing tumors.[14–16] Next-generation EGFR TKIs have since been developed specifically to target the T790M mutation,[17,18] and they have demonstrated high and durable responses in patients with advanced *EGFR*-mutant NSCLC who have been previously treated and in whom first- or second-generation EGFR TKIs have failed. The median overall survival (OS) after first- or second-generation EGFR TKIs has reached 2 to 3 years and is likely to be extended further with the recent approval of