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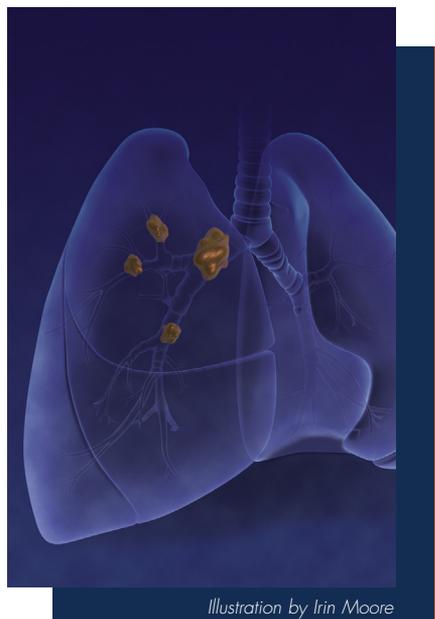


Illustration by Irin Moore

CLINICAL Lung Cancer

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Clinical Commentary

- 63 Chemo-immunotherapy: The Beginning of a New Era in Lung Cancer
Dipesh Uprety

Original Studies

- 66 LACE-Bio: Validation of Predictive and/or Prognostic Immunohistochemistry/Histochemistry-based Biomarkers in Resected Non–small-cell Lung Cancer
Lesley Seymour, Gwénaél Le Teuff, Elisabeth Brambilla, Frances A. Shepherd, Jean-Charles Soria, Robert Kratzke, Stephen Graziano, Jean-Yves Douillard, Rafael Rosell, Anthony Reiman, Benjamin Lacas, Beranger Lueza, Sarit Aviel-Ronen, Anne McLeer, Thierry Le Chevalier, Robert Pirker, Martin Filipits, Ariane Dunant, Jean-Pierre Pignon, Ming-Sound Tsao, on behalf of the LACE-Bio Steering Committee
- There are no validated molecular tools to allow patient selection for adjuvant chemotherapy after complete resection of non–small-cell lung cancer. Immunohistochemistry biomarkers shown in one trial to have a prognostic/predictive effect on overall survival were tested. The majority of the promising biomarkers could not be validated, and none were predictive of benefit. Immunohistochemistry assays from single trials may be misleading.
- 74 Results of a Phase II Placebo-controlled Randomized Discontinuation Trial of Cabozantinib in Patients with Non–small-cell Lung Carcinoma
Beth A. Hellerstedt, Nicholas J. Vogelzang, Harriet M. Kluger, Christopher A. Yasenachak, Dana T. Aftab, David A. Ramies, Michael S. Gordon, Primo Lara, Jr
- Cabozantinib is an inhibitor of receptor tyrosine kinases, including MET, vascular endothelial growth factor receptors, AXL, RET, and ROS1. We assessed cabozantinib in 60 patients with non–small-cell lung carcinoma enrolled in a phase II randomized discontinuation trial. Tumor regression was observed in most patients, including patients with KRAS and epidermal growth factor receptor mutations. The safety profile was consistent with that reported for cabozantinib in other solid tumors.

- 82 Impact of Exon 19 Deletion Subtypes in EGFR-Mutant Metastatic Non–Small-Cell Lung Cancer Treated With First-Line Tyrosine Kinase Inhibitors**
Sabrina Rossi, Luca Toschi, Giovanna Finocchiaro, Vincenzo Di Noia, Maria Bonomi, Eleonora Cerchiaro, Giovanni Luca Ceresoli, Giordano Domenico Beretta, Ettore D'Argento, Armando Santoro
Patients affected by oncogene-addicted metastatic non–small-cell lung cancer harboring the uncommon epidermal growth factor receptor (EGFR) mutation seem to have similar survival outcomes compared to those with common EGFR mutations and have disease that responds either to gefitinib or afatinib.
- 88 Association of Tumor Mutational Burden With DNA Repair Mutations and Response to Anti–PD-1/PD-L1 Therapy in Non–Small-Cell Lung Cancer**
Young Kwang Chae, Andrew A. Davis, Kirtee Raparia, Sarita Agte, Alan Pan, Nisha Mohindra, Victoria Villaflor, Francis Giles
Tumor mutational burden (TMB) has emerged as a biomarker for response to immune checkpoint blockade in clinical trials. We broadened the potential impact of TMB by evaluating the utility of commercial comprehensive genomic profiling in non–small-cell lung cancer in clinical practice. We analyzed 72 patients and 34 treated with anti–programmed cell death 1/programmed death ligand 1 therapy, with higher TMB predicting longer overall survival.
- 97 Pneumonectomy in Stage IIIA-N2 NSCLC: Should It Be Considered After Neoadjuvant Chemotherapy?**
Monica Casiraghi, Juliana Guarize, Alberto Sandri, Patrick Maisonneuve, Daniela Brambilla, Rosalia Romano, Domenico Galetta, Francesco Petrella, Roberto Gasparri, Cesare Gridelli, Filippo De Marinis, Lorenzo Spaggiari
This study aims to analyze the outcome of patients with stage IIIA-N2 non–small-cell lung cancer who underwent pneumonectomy to prove its safety and feasibility, in particular after induction chemotherapy. Based on the acceptable morbidity and mortality rate and the long-term survival, pneumonectomy should not be excluded for selected patients as a matter of principle.
- 107 Stereotactic Body Radiotherapy for Early-Stage Multiple Primary Lung Cancers**
John Nikitas, Todd DeWees, Sana Rehman, Chris Abraham, Jeff Bradley, Cliff Robinson, Michael Roach
Outcomes of patients with early-stage multiple primary lung cancers (MPLC) were reviewed from a prospective database at a high-volume institution. Compared to patients receiving a single course of stereotactic body radiotherapy (SBRT), MPLC patients receiving multiple courses of SBRT or receiving surgery followed by SBRT had no significant detriment in survival, freedom from disease progression, or toxicity.
- 117 Prognostic Significance of Total Lymphocyte Count, Neutrophil-to-lymphocyte Ratio, and Platelet-to-lymphocyte Ratio in Limited-stage Small-cell Lung Cancer**
Ryoko Suzuki, Xiong Wei, Pamela K. Allen, James D. Cox, Ritsuko Komaki, Steven H. Lin
We sought markers of survival and disease control among patients treated for limited-stage small-cell lung cancer. High pretreatment total lymphocyte count was linked with superior (and high neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with inferior) median and 2-year overall survival, findings confirmed in multivariate Cox regression. Baseline lymphopenia was an indicator of poor prognosis in patients with limited-stage small-cell lung cancer.
- 124 Dynamic Monitoring and Predictive Value of Circulating Tumor Cells in EGFR-Mutated Advanced Non–Small-Cell Lung Cancer Patients Treated With First-Line EGFR Tyrosine Kinase Inhibitors**
Tao Jiang, Jing Zhao, Chao Zhao, Xuefei Li, Jiqiao Shen, Juan Zhou, Shengxiang Ren, Chunxia Su, Caicun Zhou, Mary O'Brien
We prospectively investigated the dynamic monitoring and predictive value of circulating tumor cells (CTCs) in epidermal growth factor receptor (EGFR)-mutated advanced non–small-cell lung cancer (NSCLC) patients treated with first-line EGFR tyrosine kinase inhibitors (TKIs). Folate receptor–positive CTC counts can be used for both the dynamic monitoring and prediction of outcome in EGFR-mutated NSCLC patients treated with EGFR-TKIs, which could serve as an alternative or supplement to computed tomographic scanning.

Current Trial Reports

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Takashi Ninomiya, Nobuhisa Ishikawa, Koji Inoue, Toshio Kubo, Masayuki Yasugi, Takuo Shibayama, Tadashi Maeda, Kazunori Fujitaka, Masahiro Kodani, Toshihide Yokoyama, Shoichi Kuyama, Nobuaki Ochi, Yutaka Ueda, Seigo Miyoshi, Toshiyuki Kozuki, Yoshihiro Amano, Tetsuya Kubota, Keisuke Sugimoto, Akihiro Bessho, Tomoya Ishii, Kazuhiko Watanabe, Isao Oze, Katsuyuki Hotta, Katsuyuki Kiura

139 A Phase II Study of Nivolumab in Patients With Advanced Non–small-cell Lung Cancer who Responded to Prior PD-1/L1 Inhibitors: West Japan Oncology Group 9616L (WJOG9616L)

Hiroaki Akamatsu, Shunsuke Teraoka, Yasuhiro Koh, Takeharu Yamanaka, Nobuyuki Yamamoto, Kazuhiko Nakagawa

Available Exclusively Online at www.clinical-lung-cancer.com

e133 Lorlatinib Salvages CNS Relapse in an ALK-Positive Non–Small-Cell Lung Cancer Patient Previously Treated With Crizotinib and High-Dose Brigatinib

Mandy R. Sakamoto, Justin M. Honce, Deborah L. Lindquist, D. Ross Camidge

e137 Pathologic Complete Response to Neoadjuvant Crizotinib in a Lung Adenocarcinoma Patient With a *MET* Exon 14 Skipping Mutation

Julia K. Rotow, Gavitt A. Woodard, Anatoly Urisman, Caroline E. McCoach, Trever G. Bivona, Brett M. Elicker, David M. Jablons, Collin M. Blakely

e142 Identification and Development of a Lung Adenocarcinoma PDX Model With *STRN-ALK* Fusion

Hongzheng Ren, Xiaonan Hou, Patrick W. Eiken, Jin Zhang, Karlyn E. Pierson, Asha A. Nair, Jaime I. Davila, Helena Kovarikova, Jin Sung Jang, Sarah H. Johnson, Julian R. Molina, Randolph S. Marks, Ping Yang, Joanne E. Yi, Aaron S. Mansfield, Jin Jen

e148 Monitoring Treatment Response to Erlotinib in *EGFR*-mutated Non–small-cell Lung Cancer Brain Metastases Using Serial O-(2-[¹⁸F]fluoroethyl)-L-tyrosine PET

Diana S.Y. Abdulla, Matthias Scheffler, Vanessa Brandes, Maximilian Ruge, Sabine Kunze, Sabine Merkelbach-Bruse, Lucia Nogova, Sebastian Michels, Rieke Fischer, Richard Riedel, Reinhard Büttner, Thorsten Persigehl, Stefan Grau, Norbert Galldiks, Alexander Drzezga, Carsten Kobe, Jürgen Wolf

e152 Treatment and Outcomes of Primary Pericardial Mesothelioma: A Contemporary Review of 103 Published Cases

Elizabeth McGehee, David E. Gerber, Joan Reisch, Jonathan E. Dowell

e158 Spread Through Air Spaces (STAS): A New Pathologic Morphology in Lung Cancer

Ke Ma, Cheng Zhan, Shuai Wang, Yu Shi, Wei Jiang, Qun Wang

e163 Radiologic Criteria in Predicting Pathologic Less Invasive Lung Cancer According to TNM 8th Edition

Shinya Katsumata, Keiju Aokage, Shoko Nakasone, Takashi Sakai, Satoshi Okada, Tomohiro Miyoshi, Kenta Tane, Ryuichi Hayashi, Genichiro Ishii, Masahiro Tsuboi

The optimal radiologic criteria of selecting a candidate for sublobar resection is still unclear. Our study indicated that tumors of clinical T1a or less and consolidation-to-tumor ratio, calculated with the maximum solid component diameter divided by the maximum tumor diameter, of 0.5 or less can predict pathologic less invasive (with no nodal involvement and no vessel invasion) lung cancer (specificity, 30.7%). Lung cancers with these radiologic criteria will be appropriate candidates for limited resection.

e171 De Novo MET Amplification in Chinese Patients With Non–Small-Cell Lung Cancer and Treatment Efficacy With Crizotinib: A Multicenter Retrospective Study

Zhengbo Song, Hong Wang, Zongyang Yu, Peihua Lu, Chunwei Xu, Gang Chen, Yiping Zhang

We investigated the clinicopathologic characteristics, treatment, and prognosis of non–small-cell lung cancer patients with de novo mesenchymal–epithelial transition (MET) amplification. The results demonstrated that patients with MET amplification had a trend toward a high prevalence of the solid predominant subtype of adenocarcinoma and of brain metastases. Patients with de novo MET amplification benefit from crizotinib treatment, especially those with high-level amplification.

e177 High Receipt of Statins Reduces the Risk of Lung Cancer in Current Smokers With Hypercholesterolemia: The National Health Insurance Service–Health Screening Cohort

Yu-jin Kwon, Na-Young You, Jae-Woo Lee, Joungyoun Kim, Hee-Taik Kang

Recent studies have presented conflicting data on the effect of the receipt of statins on lung cancer risk. This current study found that high statin receipt could prevent lung cancer in Korean men with hypercholesterolemia, especially those who are current smokers. A better understanding of statin receipt in the effects of lung cancer risk according to smoking status will help clinicians.

e186 Activity of EGFR TKIs in Caucasian Patients With NSCLC Harboring Potentially Sensitive Uncommon EGFR Mutations

Antonio Passaro, Arsela Prelaj, Laura Bonanno, Marcello Tiseo, Alessandro Tuzi, Claudia Proto, Rita Chiari, Danilo Rocco, Carlo Genova, Claudio Sini, Diego Cortinovis, Sara Pilotto, Lorenza Landi, Chiara Bennati, Andrea Camerini, Luca Toschi, Carlo Putzu, Giulio Cerea, Gianluca Spitaleri, Federico Cappuzzo, Filippo de Marinis

Uncommon epidermal growth factor receptor (EGFR) mutations reported in non–small-cell lung cancer, accounting approximately 10%-15% of all EGFR mutations, are a heterogeneous group characterized by different clusters: exon 20 insertion and mutations, exon 18 mutations, and complex mutations. Although available data confirming the intrinsic resistance of exon 20 insertions to EGFR tyrosine kinase inhibitors (TKIs) of first- and second-line generation, data about exon 18 and complex mutations are suggesting the activity of EGFR TKIs. In this clinical study, we showed exon 18 and EGFR complex mutations might be considered sensitive uncommon mutations, showing interesting survival results.

e195 The Association Between Imaging Features of TSCT and the Expression of PD-L1 in Patients With Surgical Resection of Lung Adenocarcinoma

Tong Wu, Fei Zhou, Adilah K. Soodeen-Laloo, Xing Yang, Yingran Shen, Xi Ding, Jinpeng Shi, Jie Dai, Jingyun Shi

In this study we identified 350 patients with pathologically confirmed adenocarcinoma. Of 350 specimens, 74 (21.1%) were programmed death-ligand 1-positive. In multivariate analysis, absence of surrounding ground glass opacity ($P = .022$), shape ($P = .008$), pleural indentation ($P = .007$), tumor mean computed tomography value ($P = .004$), and the ratio of consolidation mass to tumor mass ($P = .003$) were significantly associated with programmed death-ligand 1 expression.

e208 Natural Disease History, Outcomes, and Co-mutations in a Series of Patients With BRAF-Mutated Non–small-cell Lung Cancer

Nathaniel J. Myall, Solomon Henry, Douglas Wood, Joel W. Neal, Summer S. Han, Sukhmani K. Padda, Heather A. Wakelee

BRAF mutations occur infrequently in non–small-cell lung cancer, and therefore, our understanding of the natural history of tumors harboring these mutations remains limited. In this retrospective study, we report the outcomes, treatment responses, and co-occurring mutations in a series of patients with *BRAF*-mutated non–small-cell lung cancer. In our cohort, survival rates at 2 and 5 years were 56% and 13%, respectively, suggesting more favorable outcomes in a subset of patients.