Cancer Drug Development in the Era of Precision Medicine



INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER Conquering Thoracic Cancers Worldwide



Janet Freeman-Daily, MS, Eng Moderator



William Pao, MD, PhD Speaker



INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER Conquering Thoracic Cancers Worldwide

Disclosures

ASI

- William Pao, MD discloses he is an employee of Roche and has ownership/stock interest in Roche. The rights to EGFR T790M testing were licensed by MSKCC on his behalf and others.
- Janet Freeman-Daily, MS, Eng discloses she receives travel expenses from STAT News and Turning Point Therapeutics and is on an advisory board for Genentech.



Traditional view of lung cancer up to early 2000s

2 main types, based upon microscopic examination

- Small Cell Lung Cancer (SCLC)
- Non-Small Cell Lung Cancer (NSCLC)
 - > Adenocarcinoma
 - > Squamous cell carcinoma
 - > Large cell carcinoma





Effect of chemotherapy in advanced NSCLC plateaued



Schiller et al '02



Pao et al '04

2002: Dramatic response to gefitinib



February 6, 2002

February 11, 2002

Why were female Asians with adenocarcinomas and no smoking history most likely to respond?



Achilles heel in a common solid tumor: a genetic "driver"

2004: EGFR mutations associated with sensitivity to gefitinib and erlotinib







adapted from https://www.roche.com/about/priorities/personalised_healthcare/comprehensive-genomic-profiling.htm

CONQUERING THORACIC CANCERS WORLDWIDE

2004: Disease progression in patients who responded to gefitinib or erlotinib (acquired resistance)



We learned from patients with chronic myelogenous leukemia (CML) who took the TKI imatinib (FDA approved in 2000)

- Patients with CML have a high rate of response to treatment with imatinib
- A proportion of patients acquire resistance after an initial response
- There are a small number of conserved changes in the ABL tyrosine kinase domain which confer resistance
- Other patients with acquired resistance have amplification of the BCR-ABL gene



Search for clues: IRB Protocol MSKCC #04-103

> Eligibility

- > Previously received erlotinib or gefitinib
- > Radiologic partial or complete response to treatment with erlotinib or gefitinib
- > Radiologic progression of disease while on treatment
- Adequate amount of tissue (obtained prior to treatment with TKI) available for sequencing of EGFR
- > Procedure
 - > Review imaging studies to confirm partial or complete response
 - > Determine adequacy of pre-treatment material
 - > CT-PET study
 - > Core needle or excisional biopsy of most metabolically active site of disease

VA Miller



Why do patients' tumors shrink and then grow again?



Day 0

4 months





Growing bone lesion

Growing lung lesion

CONQUERING THORACIC CANCERS WORLDWIDE

Pao et al '05

Deep understanding of acquired resistance led to rational way to overcome resistance



From first report in 2005 to approval of EGFR T790M mutant-specific TKI in 2015





Pao et al '05; Kobayashi et al '05; Cross et al '14

2009: Iressa Pan-Asia Study (IPASS) showed the value of routine lung tumor testing



Mok et al '09

CONQUERING THORACIC CANCERS WORLDWIDE

2020: Great progress in molecularly tailored therapy for oncology



Excludes surface antigen targets such as CD20, CD38, etc.

AR

CONQUERING THORACIC CANCERS WORLDWIDE



2020: Impact of targeted therapies in lung cancer



Incidence and incidence-based mortality decreasing

Survival trends among men and women increasing

Howlader et al '20

Biomarker testing can help guide therapy Different inhibitors are effective at various disease stages



Example: patient with ALK-fusion positive lung cancer



Shaw et al '16

2017: Unprecedented survival in some melanoma patients on immunotherapy (checkpoint inhibitor therapy)



CONQUERING THORACIC CANCERS WORLDWIDE

Overall survival improved in NSCLC with introduction of checkpoint inhibitor therapy (CIT)



EMA- or FDA-approved CIT-based regimens in first-line NSCLC



Data from approved regimens only. Median OS is the most recently reported. Year refers to first presentation of trial data.

 $\label{eq:anti-PDL1/PD-based combinations includes anti-PDL1/PD1 + chemotherapy \pm anti-VEGF and anti-PDL1/PD1 + anti-CTLA4 \pm a$

Bunn & Kelly. Clin Cancer Res 1998; Sandler, et al. N Engl J Med 2006; Scagliotti, et al. J Clin Oncol 2008; Mok, et al. ELCC 2019 (Abs 1020); Peters, et al. ESMO 2019 (Abs LBA4); Spigel, et al. ESMO 2019 (Abs LBA78)

Paz-Ares, et al. ESMO 2019 (Abs LBA82); West, et al. Lancet Oncol 2019; Reck, et al. AACR 2020 VM1 (Abs CT216); Reck, et al. ASCO 2020 (Abs 9501); Rodriguez-Abreu, et al. ASCO 2020 (Abs 9582); Brahmer, et al. ESMO 2020 (Abs LBA51)



CIT improving OS in extensive-stage SCLC



Reck, et al. ESMO 2019 (Abs 1736O); Liu, et al. ESMO 2020 (Abs 1781MO) Paz-Ares, et al. ASCO 2020 (Abs 9002)

NSCLC today: Multiple options for molecularly defined subsets

Evolution of lung cancer classification



Pao & Girard. Lancet Oncol 2011; Johnson, et al. ASCO 2013; Foundation Medicine Inc Database, Accessed November 2018 (all NSCLC).

CONQUERING THORACIC CANCERS WORLDWIDE

Liquid biopsies will further enable precision medicine 30% of LC patients have insufficient biopsy material





- · Allows for serial liquid biopsy testing to follow tumor evolution and resistance
- RWD cohort paired with NGS testing provides additional natural history & epidemiological data
- Primary endpoint in the ALK+ cohort met; filed in Q1 2020

Mok T. et al., WCLC 2017; NGS=next generation sequencing; ctDNA=circulating tumor DNA; Atezo = atezolizumab, cobi = cobimetinib; vemu = vemurafenib; RWD=real world data; bTMB=blood tumor mutational burden; MSI=microsatellite instability

Real world data & synthetic controls also have an impact Accelerated access to alectinib in 20+ countries by >1 year



Alectinib was associated with significantly prolonged OS compared to ceritinib in the real world and ASCEND 2 trial



Overall survival analysis comparing alectinib Ph II data with real world external control to demonstrate value of alectinib relative to standard of care for patients with ALK+ metastatic lung cancer



Journal of Comparative Effectiveness Research

Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib

Jessica Davies*.¹, Michael Martinec², Paul Delmar², Mathieu Coudert³, Walter Bordogna², Sophie Golding², Reynaldo Martina⁴ & Gracy Crane¹ ¹Roche Products Ltd, 6 Racon Way, Shire Park, Welwyn Garden City, AL7 1TW, UK ²F. Hoffmann-La Roche Ltd, Basel, Switzerland ³F. Hoffmann-La Roche Ltd, Boulogne-Billancourt Cedex, France ⁴Department of Biostatistics, University of Liverpool, Liverpool, UK *Author for correspondence: Tel.: +44. 7584 587 922; Jessica.davies@roche.com

CI=confidence interval; HR=hazard ratio; NR=not reached; OS=overall survival; RWD=real world data; Davies, J. et al. 2018 Journal of Comparative Effectiveness Research

Scientific breakthroughs and new paradigms are leading to improved outcomes in lung cancer

- → Histology-based diagnosis / chemotherapy
 → therapeutic plateau in early 2000s
- > Molecular-based diagnosis / molecular targeted therapy
 - \rightarrow significant advances since early 2000s
 - > From all-comers to molecular subsets
 - > Patient biopsies before and after treatment key to gaining biological insights
- > Cancer immunotherapy
 - \rightarrow significant advances since early 2010s
 - Even greater survival rates, but there is still much work to do to understand who benefits the most and how we can do even better
- > New approaches
 - \rightarrow liquid biopsies, real-world data