Cancer Drug Development in the Era of Precision Medicine
Disclosures

› **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

State of the art cancer clinical trial pre 2002

Schiller et al '02
2002: Dramatic response to gefitinib

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

Diagram showing the EGFR ligand binding, Tyrosine kinase, and autophos regions with specific mutations at Exon: 18 19 20 21 22 23 24

- G719A/C deletion
- LREA
- L858R, L861Q

Lynch et al ’04; Paez et al ’04; Pao et al ’04
Four major types of genome changes can cause cancer

Types

- **Base substitution**
- **Insertions and deletions**
- **Copy number alterations**
- **Rearrangements**

Examples

- EGFR L858R
- EGFR Exon 19 deletion
- MET amplification
- ALK fusion

adapted from https://www.roche.com/about/priorities/personalised_healthcare/comprehensive-genomic-profiling.htm
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
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
Why do patients’ tumors shrink and then grow again?

Pao et al ’05

Growing bone lesion  Growing lung lesion
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
2020: Great progress in molecularly tailored therapy for oncology

<table>
<thead>
<tr>
<th>Target</th>
<th>Cancer type</th>
<th>Molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR</td>
<td>Prostate cancer</td>
<td>multiple</td>
</tr>
<tr>
<td>ALK fusion</td>
<td>Lung adeno</td>
<td>crizotinib, alectinib, ceritinib, brigatinib, loratinib, ensartinib</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>CML</td>
<td>imatinib, dasatinib, nilotinib, bosutinib, ponatinib</td>
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<tr>
<td>BRAF V600E</td>
<td>Melanoma, hairy cell leukemia, lung adeno</td>
<td>vemurafenib, dabrafenib, encorafenib (+ MEKi)</td>
</tr>
<tr>
<td>BRCA mutant/LOH</td>
<td>Breast, epith ovarian, fallop tube or 1ry perit cancer</td>
<td>olaparib, rucaparib, niraparib, talazoparib</td>
</tr>
<tr>
<td>BTK C481S</td>
<td>CLL</td>
<td>ARQ531, LOXO305</td>
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<tr>
<td>EGFR 19 del and L858R</td>
<td>Lung adeno</td>
<td>gefitinib, erlotinib, afatinib</td>
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<tr>
<td>EGFR T790M</td>
<td>Lung adeno</td>
<td>osimertinib, almonertib, alflutinib</td>
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<tr>
<td>ER/PR</td>
<td>HR+ breast cancer</td>
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<tr>
<td>FGFR mutat</td>
<td>Urothelial</td>
<td>erdafitinib</td>
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<tr>
<td>HER2 amp</td>
<td>Breast ca</td>
<td>trastuzumab, pertuzumab, ado-trastuzumab emtansine, lapatinib, neratinib</td>
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<tr>
<td>IDH1 mutant</td>
<td>AML</td>
<td>ivosidenib</td>
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<td>KIT/PDGFR mutant</td>
<td>GIST</td>
<td>imatinib, dasatinib</td>
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<tr>
<td>KIT D816V, PDGFRA D842V</td>
<td>GIST</td>
<td>avapritinib, ripretinib</td>
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<tr>
<td>KRAS G12C</td>
<td>Multiple</td>
<td>sotorasib, MRTX849</td>
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<tr>
<td>MET splice/amp</td>
<td>Lung adeno</td>
<td>crizotinib, tepotinib, capmatinib</td>
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<td>RET fusion</td>
<td>Lung adeno, thyroid ca</td>
<td>selpercatinib, pralsetinib</td>
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<tr>
<td>ROS1 fusion</td>
<td>Lung adeno</td>
<td>crizotinib, entrectinib</td>
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<tr>
<td>TRK fusion</td>
<td>Lung adeno, other</td>
<td>larotrectinib, entrectinib</td>
</tr>
</tbody>
</table>

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

Chapman et al. NEJM '11

Chemo vs Targeted Therapy
Chapman et al. '11

CPI mono vs CPI doublet
Wolchok et al. '17
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.


CIT improving OS in extensive-stage SCLC

<table>
<thead>
<tr>
<th>OS rate</th>
<th>CIT + Chemo</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5-year</td>
<td>32–34%</td>
<td>21–25%</td>
</tr>
<tr>
<td>2-year</td>
<td>~22%</td>
<td>14–17%</td>
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</table>

1.5-year OS rate CIT + Chemo 32–34% 21–25%
2-year OS rate CIT + Chemo ~22% 14–17%

Trials of CIT regimens in limited-stage SCLC are ongoing

Trials of anti-CTLA4 combinations have not yet been successful in first-line ES-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

- 2004: Unknown, EGFR, KRAS
- 2014: Unknown, KRAS, EGFR, MET, PIK3CA, ALK, RET, BRAF, HER2, ROS, NTRK
- Today: KRAS, EGFR, NTRK, PD-L1 positive


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

Ph III trial design (B-FAST) for 1L treatment naive NSCLC

Blood based biomarkers
- Liquid biopsy test that detects the 4 main classes of genomic alterations (324 genes), bTMB, MSI
- Comprehensive genomic profiling including resistance mutations or fusions in NSCLC
- Guides therapy selection and clinical trials

- 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

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
  → significant advances since early 2000s
    › From all-comers to molecular subsets
    › Patient biopsies before and after treatment key to gaining biological insights

› Cancer immunotherapy
  → 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
  → liquid biopsies, real-world data