Come gather 'round people where ever you roam

And admit that the waters around you have grown

And accept it that soon you'll be drenched to the bone

If your time to you is worth savin'

Then you better start swimmin'
or you'll sink like a stone,

For the times they are a' changin'!
## Estimated number of cases and deaths worldwide in 2012

<table>
<thead>
<tr>
<th>Cancer type</th>
<th># cases</th>
<th># deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td><strong>1,824,701</strong></td>
<td><strong>1,589,925</strong></td>
</tr>
<tr>
<td>Breast</td>
<td>1,671,149</td>
<td>521,907</td>
</tr>
<tr>
<td>Colorectum</td>
<td>1,360,602</td>
<td>693,933</td>
</tr>
<tr>
<td>Prostate</td>
<td>1,094,916</td>
<td>307,481</td>
</tr>
<tr>
<td>Stomach</td>
<td>951,594</td>
<td>723,073</td>
</tr>
<tr>
<td>Liver</td>
<td>782,451</td>
<td>745,533</td>
</tr>
<tr>
<td>Head and neck*</td>
<td>686,328</td>
<td>375,665</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>527,624</td>
<td>265,672</td>
</tr>
<tr>
<td>Esophageal</td>
<td>455,784</td>
<td>400,169</td>
</tr>
<tr>
<td>Bladder</td>
<td>429,793</td>
<td>165,084</td>
</tr>
<tr>
<td>NHL</td>
<td>385,741</td>
<td>199,670</td>
</tr>
</tbody>
</table>

* Larynx, oral cavity, nasopharynx, pharynx

---

Significantly mutated pathways in lung adenocarcinomas

Modified based on Ding et al. Nature 2008;455;1069-1075.
Positions of Mutations Detected in EGFR Tyrosine Kinase Domain in NSCLC

EGF=endothelial growth factor; TM=transmembrane.

# NSCLC: EGFR Mutations

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>EGFR Mutations</th>
<th>Frequency of mutations(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2105</td>
<td>350</td>
<td>All</td>
</tr>
<tr>
<td>Never-smokers</td>
<td>612</td>
<td>231</td>
<td>38</td>
</tr>
<tr>
<td>Smokers</td>
<td>1382</td>
<td>116</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>814</td>
<td>244</td>
<td>30</td>
</tr>
<tr>
<td>Male</td>
<td>1287</td>
<td>106</td>
<td>8.2</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1634</td>
<td>283</td>
<td>17.3</td>
</tr>
<tr>
<td>BAC</td>
<td>147</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Large Cell</td>
<td>287</td>
<td>33</td>
<td>11.5</td>
</tr>
</tbody>
</table>
Iressa Pan-Asia Study (IPASS)

**Patients**

- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 wks
- PS 0-2
- Measurable stage IIIB / IV disease

**Endpoints**

**Primary**

- Progression-free survival (non-inferiority)

**Secondary**

- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

**Exploratory**

- Biomarkers
- EGFR mutation
- EGFR-gene-copy number
- EGFR protein expression

**Gefitinib**

(250 mg / day)

1:1 randomisation

**Carboplatin**

(AUC 5 or 6) / paclitaxel

(200 mg / m²)

3 weekly*

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles carboplatin/paclitaxel was offered to gefitinib patients upon progression PS, performance status; EGFR, epidermal growth factor receptor

Objective response rate in EGFR mutation positive and negative patients

Overall response rate (%)

**Mutation positive patients**
- Gefitinib: 71.2% (n=132)
- Carboplatin / paclitaxel: 47.3% (n=129)

**Mutation negative patients**
- Gefitinib: 1.1% (n=91)
- Carboplatin / paclitaxel: 23.5% (n=85)

EGFR M+ odds ratio (95% CI) = 2.75 (1.65, 4.60), p=0.0001

EGFR M- odds ratio (95% CI) = 0.04 (0.01, 0.27), p=0.0013

Odds ratio >1 implies greater chance of response on gefitinib
IPASS: PFS in EGFR Mutation Positive and Negative Patients

**EGFR mutation positive**

Gefitinib (n=132)  
Carboplatin / paclitaxel (n=129)  

HR (95% CI) = 0.48 (0.36, 0.64)  
\( P < .0001 \)

No. events gefitinib, 97 (73.5%)  
No. events C / P, 111 (86.0%)  
RR- 71%; 47%

**EGFR mutation negative**

Gefitinib (n=91)  
Carboplatin / paclitaxel (n=85)  

HR (95% CI) = 2.85 (2.05, 3.98)  
\( P < .0001 \)

No. events gefitinib, 88 (96.7%)  
No. events C / P, 70 (82.4%)  
RR- 1.1%; 23%

Treatment by subgroup interaction test, \( P < .0001 \)
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment Arm</th>
<th>Control Arm</th>
<th>Stage</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS (Mok TS, et al. N Engl J Med. 2009;361:947-957.)</td>
<td>1217</td>
<td>Gefitinib</td>
<td>Carboplatin/Placitaxel</td>
<td>IIIB/IV</td>
<td>5.7 vs 5.8 months (HR for EGFR mutated pts 0.48; HR for nonmutated pts 2.84)</td>
<td>18.6 vs 17.3 months (P = NS)</td>
<td>First-line</td>
</tr>
<tr>
<td>WJTOG3405 (Mitsudomi T, et al. Lancet Oncol. 2010;11:121-128.)</td>
<td>177 (M+)</td>
<td>Gefitinib</td>
<td>Cisplatin, Docetaxel</td>
<td>IIIB/IV</td>
<td>9.2 vs 6.3 months (P &lt; 0.001)</td>
<td></td>
<td>First-line</td>
</tr>
<tr>
<td>Maemondo M, et al. N Engl J Med. 2010;362:2380-2388.</td>
<td>230 (M+)</td>
<td>Gefitinib</td>
<td>Carboplatin, Paclitaxel</td>
<td>IIIB/IV</td>
<td>10.8 vs 5.4 months (HR 0.3, P &lt; 0.0001)</td>
<td>30.5 vs 23.6 months (P = NS)</td>
<td>First-line</td>
</tr>
<tr>
<td>OPTIMAL (Zhou C, et al. Lancet Oncol. 2011;12:735-742.)</td>
<td>165 (M+)</td>
<td>Erlotinib</td>
<td>Carboplatin/Gemcitabine</td>
<td>IIIB/IV</td>
<td>13.6 vs 4.6 months (HR 0.16, P &lt; 0.0001)</td>
<td></td>
<td>First-line</td>
</tr>
<tr>
<td>EURTAC (Rosell R, et al. Lancet Oncol. Jan 25, 2012 [Epub ahead of print].)</td>
<td>153 (M+)</td>
<td>Erlotinib</td>
<td>Platinum-based chemotherapy</td>
<td>IIIB/IV</td>
<td>9.4 vs 5.2 months (HR, 0.42, P &lt; 0.0001)</td>
<td>22.9 vs 18.8 months (P = 0.42)</td>
<td>First-line</td>
</tr>
</tbody>
</table>

PFS is superior, no survival advantage for first line TKI- effect of cross-over
37 patients re-biopsied at the time of progression

6/18 patients with T790M had other molecular abnormalities

5 patients had SCLC phenotype

Acquired exon 20 mutation found in >50% of patients with acquired resistance to TKI

- Increases relative affinity of mutant EGFR for ATP, may also cause steric hindrance to erlotinib

**T790M**

- More likely to show progression in lungs/pleura
- Less commonly detected in CNS
- May have better prognosis than non-T790M

**A. Post-progression survival**

<table>
<thead>
<tr>
<th>Number at risk:</th>
<th>T790M pos</th>
<th>T790M neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>58 Months following progression on TKI</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>35 Number at risk:</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

New Treatment Paradigm for EGFR Mt+ NSCLC

1\textsuperscript{st}/2\textsuperscript{nd} Gen TKI

Resistance
- Biopsy
- Evaluate for SCLC conversion, T790M status

3\textsuperscript{rd} Gen TKI
- mPFS 9-13 m
Osimertinib in First-Line Therapy for EGFR-Mt+ NSCLC

- **Median PFS, * months (95% CI):**
  - 80 mg: NC (12.3, NC)
  - 160 mg: 19.3 (11.1, 19.3)
  - Total: 19.3 (13.7, NC)

- **Remaining alive and progression-free, † % (95% CI):**
  - 12 months:
    - 80 mg: 75 (55, 88)
    - 160 mg: 69 (49, 83)
    - Total: 72 (59, 82)
  - 18 months:
    - 80 mg: 57 (36, 73)
    - 160 mg: 53 (32, 70)
    - Total: 55 (41, 67)
Alectinib vs Crizotinib in ALK Inhibitor-Naïve ALK-Positive NSCLC

Primary Endpoint: PFS by IRF (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo [95% CI]</td>
<td>NR [20.3 - NR]</td>
<td>10.2 [8.2 - 12.0]</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HR [99.6826% CI]</td>
<td>0.34 [0.17 - 0.71]</td>
<td></td>
</tr>
</tbody>
</table>

Presented by: Hiroshi Nokihara
T790M-positive aNSCLC progressed following prior EGFR-TKI or EGFR-TKI and other anti-cancer therapy

EGFRm locally advanced or metastatic NSCLC progressed following prior therapy with an approved EGFR-TKI

Osimertinib in Pre-treated T790M-Positive NSCLC

<table>
<thead>
<tr>
<th></th>
<th>AURA Ph I (80 mg) N=63</th>
<th>AURA pooled Ph II (80 mg) N=411</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS</strong>, months (95% Cl)</td>
<td>9.7 (8.3, 13.6)</td>
<td>11.0 (9.6, 12.4)</td>
</tr>
<tr>
<td>Remaining alive and progression-free, † % (95% Cl)</td>
<td>41 (29, 53)</td>
<td>48 (42, 53)</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td>NC</td>
</tr>
<tr>
<td>18 months</td>
<td>29 (18, 41)</td>
<td>NC</td>
</tr>
<tr>
<td>24 months</td>
<td>17 (8, 30)</td>
<td>NC</td>
</tr>
</tbody>
</table>

### Summary of RET Inhibitor Efficacy in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>RET testing</th>
<th>n</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (Drilon, ASCO 2015)</td>
<td>FISH/NGS</td>
<td>Stage I, 16</td>
<td>38</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Cabozantinib (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>13</td>
<td>31</td>
<td>3.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Vandetanib (Sato, ASCO 2016)</td>
<td>FISH/RT-PCR</td>
<td>19/17</td>
<td>47/53</td>
<td>4.7</td>
<td>47% 1-year</td>
</tr>
<tr>
<td>Vandetanib (Lee, ASCO 2016)</td>
<td>FISH confirmed</td>
<td>18</td>
<td>17</td>
<td>4.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Vandetanib (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>11</td>
<td>18</td>
<td>2.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Sunitinib (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>9</td>
<td>22</td>
<td>2.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Any RET inhibitor (Gautschi, ASCO 2016)</td>
<td>FISH/NGS/RT-PCR</td>
<td>41</td>
<td>23</td>
<td>2.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>
Can we use Plasma and Urine to Detect T790M Mutations in NSCLC?

- 181 samples w/matched pretreatment T790M results in tissue, plasma, & urine
  - 7 T790M-negative or inadequate by all three sample types (4%)
  - 174 T790M-positive by at least one sample type (96%)

Investigator-assessed confirmed objective response rate (*RECIST v1.1) is similar for T790M-positive patients identified by plasma, tissue, and urine

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>n</th>
<th>ORR* % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>443</td>
<td>33.9 (29.5–38.5)</td>
</tr>
<tr>
<td>Plasma</td>
<td>374</td>
<td>32.1 (27.4–37.1)</td>
</tr>
<tr>
<td>Urine</td>
<td>169</td>
<td>36.7 (29.4–44.4)</td>
</tr>
</tbody>
</table>

- Comparable duration of response and PFS whether positive by tissue, plasma, or urine
- Overall, results show tissue, plasma, & urine each detect T790M at comparable rates, no clear “gold standard”
Outliers and the 10,000 hour rule:
Lessons from our patients
Winship Cancer Institute of Emory University
Lung and Aerodigestive Cancer Research and Clinical Team
Linking basic findings to clinical trials with molecular imaging

Limited clinical activity of RAD001:
Limited target effect

Everolimus Ph1 clinical trial PET scan
Phase I: N = 29 (RAD001)
Phase I/II: N= 52 (RAD001+docetaxel)

Limited target effect:
- **p-AKT** in all 17 patients
- **pS6** only inhibited in 1 patient

Inhibitors of PI3K + mTOR
Synergistically inhibit tumor growth in xenograft

Phase I trial:
BKM120 + RAD001
to achieve complete target blockade (Proj 1, P01)

Sun et al. Cancer Res 2005

Ramalingam et al. Cancer, 2010,
Owonikoko et al. Clinical Cancer Research, 2015;
Lung cancer remains a challenge for therapeutic treatment

**Lung cancer** –
- Leading cause of death worldwide (1.3 million/yr)
- 5 yr survival rate for lung adenocarcinoma – 15%

**Targeted therapy provides hope for patients harbor certain altered oncogene drivers**
- EGFR, ALK fusions (gefitinib, erlotinib, crizotinib)
- Targets pursued by agents in clinical trials: KRAS, BRAF, ERBB2, PIK3CA, fusions of RET and ROS1

**Tumor suppressors remain a challenge for therapeutic intervention**
TP53, STK11, RB1, NF1, CDKN2A, SMARCA4, KEAP1

**Targeting tumor suppressors may offer Opportunity for novel therapeutic discovery**
“Targeting tumor suppressors: exploiting LKB1 vulnerability in lung cancer”
Advisory Boards

External
John Minna, MD - UT SW Med School
Paul Bunn, MD - U of Colorado
Thomas Roberts, PhD - Harvard Med School
J. Jack Lee, DDS, PhD - MD Anderson Cancer Center
Edward Levitt, Patient Advocate

Internal
Paul Doetsch, PhD - Winship
Dan Brat, MD PhD - Pathology
Larry Boise, PhD - Hem Med Onc
Jin-Tang Dong, PhD - Hem Med Onc
Dong M. Shin, MD - Hem Med Onc
Paula Vertino, PhD - Rad Onc
Lance Waller, PhD - Biostatistics

P01 Executive Committee
Contact PI: Haian Fu, PhD
MPI: Suresh Ramalingam, MD

Lung Cancer Oncology: Fadlo R. Khuri, MD
Research Ethics: Rebecca Pentz, PhD
Project/Core Leaders: Jing Chen PhD, Adam Marcus PhD,
Gabe Sica, MD, Michael Kutner PhD

Cores
1. Administrative
   H Fu,
   S Ramalingam
2. Molecular pathology
   M Rossi,
   G Sica
3. Biostatistics and biomedical informatics
   M Kutner,
   Z Chen

Projects
1. Cell metabolism-dependent restriction of LKB1 in lung cancer
   J Chen, J Fan
2. Interrogating the LKB1-CDK4 interaction in lung cancer
   H Fu, TK Owonikoko, W Zhou
3. Defining a combinatorial anti-metastatic strategy in LKB1-mutant lung cancer
   A Marcus, M Gilbert-Ross,
   S Ramalingam
Project 1
“Cell metabolism dependent restriction of LKB1 in lung cancer”
*Novel 6PGD Inhibitors Physcion and S3*

Project 2
“Interrogating the LKB1-CDK4 interaction in lung cancer”
*CDK4 Inhibitor palbociclib*

Project 3
“Defining a combinatorial anti-metastatic strategy in LKB1 mutant lung cancer”
*FAK Inhibitor VS-6063 + pemetrexed*
Project 1: Cell metabolism-dependent restriction of LKB1 in human lung cancer
(Leader: Jing Chen, PhD, Co-Leader: Jun Fan, PhD)

6PGD is commonly important for cell metabolism and tumor growth of lung cancer cells despite LKB1 levels.
Discovery of Protein-Protein Interaction Networks

TCGA PPI expression library of lung cancer associated genes

Lung cancer-associated genes

High throughput PPI screen

TR-FRET, H1299 lung cancer cells

PPI expression library of lung cancer associated genes

Reported PPIs
Stat. Significant PPI
High-confidence PPI
Project 2. Interrogating the LKB1-CDK4 interaction in lung cancer

(Leader: Haian Fu, PhD, Co-Leaders: Taofeek Owonikoko, MD, Wei Zhou, PhD
Key contributor: Fadlo R. Khuri, MD)

Aim 1: whether & how LKB1 inhibits CDK4

Aim 2: LKB1 status for palbociclib sensitivity in cell and mouse models

Aim 3: Palbociclib sensitivity in patient-derived organoids and tumor tissues
Project 3. Defining a combinatorial anti-metastatic strategy in LKB1-compromised lung cancer
(Leader: Adam Marcus, PhD, Co-Leaders: Suresh Ramalingam, MD, Melissa Gilbert-Ross, PhD)

Aim 2: Biology of LKB1-inactivated tumors

Aim 1: FAKi + Pemetrexed in GEMM and PDX

Aim 3: Phase I/II Trial with FAKi + Pemetrexed
Shared Core Resources

Preclinical Studies

- Project 1: 6PGD/Phycion, S3
- Project 2: CDK4/palbociclib

Biostatistics Core

MolPath Core

Project 3: FAK/VS-6063

Admin Core

Clinical Trial

NCI Lung Cancer Mutation Consortium (S. Ramalingam, M. Rossi)
NCI Chemical Biology Consortium (H. Fu)
The Cancer Genome Atlas (S. Ramalingam, M. Behera, G. Slca)
NCI CTD² Network (H. Fu, F. Khuri)
National Clinical Trials Network (S. Ramalingam)
Project 1
6PGD
Cancer metabolism

Project 2
CDK4
proliferation

Project 3
FAK
metastasis

6PGD inhibitor discovery

LKB1

6PGDi to reverse LKB1

CDK4i in GEMM, patient tumor organoids, combination with FAKi

CDK4i to target LKB1

6PGD controls FAK via LKB1

Lys-Ac & activity of 6PGD in patients

CDK4 impact on FAKi

Phase II trial with FAKi

Palbociclib for lung cancer

Inter project interactions

NCI Lung Cancer Mutation Consortium

NCI CTD^2 Network

Molecular Pathology Core

Biostatistics Core
Integration of Emory lung cancer research into functional genomics and chemical biology initiatives

**NCI Chemical Biology Consortium**

- From genomics to potential drug targets
- From targets to new anticancer agents

**CTD²** Cancer Target Discovery and Development

**New agents**

**Assays HTS**

**New cancer targets**
14-3-3 represents a hub in oncogenic signaling networks. 14-3-3 promotes tumorigenesis in part by driving Akt-controlled survival machinery & antagonizing apoptotic proteins.
PPI network mapping:
To define the 3\textsuperscript{rd} dimension of the cancer genome

- Genomic alterations
- Gene/protein expression
- Re-wired PPI network in cancer
- PPI interface as drug target
- Targeted therapy
“THE PESSIMIST COMPLAINS ABOUT THE WIND; THE OPTIMIST EXPECTS IT TO CHANGE; THE REALIST ADJUSTS THE SAILS.”

WILLIAM A. WARD
Therapeutic Opportunities:
Targeting Tumor Suppressor Genes with Oncolytic Viruses

- Gene therapy, siRNA, oncolytic viruses (eg ONYX-15)
- Phase II trial combining Onyx-015 with chemotherapy
- Oncolytic viruses demonstrate reversal of premalignancy
- Phase III trial of Onyx-015 plus chemotherapy in nasopharynx cancer using in China showed a dramatic advantage in ORR

Reovirus Growth in a Ras Activated Cell

Pre-treatment

Rapid progression in <3 weeks before Study

After 3 cycles

UK Phase II REOLYSIN/Carbo/Taxol Combination
Pt 2016 – Partial Response in HNSCC
Role of PD-1 in Suppressing Antitumor Immunity

Activation (cytokines, lysis, prolif., migration)

Inhibition (anergy, exhaustion, death)
Nivolumab in Advanced NSCLC

Eligible NSCLC patients randomized between 3 nivolumab dose levels (n = 129)

- Nivolumab 1 mg/kg IV q 2 weeks (n = 33)
- Nivolumab 3 mg kg IV q 2 weeks (n = 37)
- Nivolumab 10 mg/kg IV q 2 weeks (n = 59)

- Accrual has completed
- Patient assessment is ongoing
- Current analysis is for patients treated through March 5, 2013, all of whom received first treatment at least 1 year before the analysis

IV = intravenously
Nivolumab (BMS-936558) Phase 1 Study

### Table: Dose Response

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>ORR(^{ab}) (%) (n/N)</th>
<th>Estimated Median DOR (Weeks) (Range)</th>
<th>Stable Disease Rate (\geq 24) Wks (%) (n/N)</th>
<th>Median PFS Months (95% CI)</th>
<th>Median OS Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses</td>
<td>17.1 (22/129)</td>
<td>74.0 (6.1+, 133.9+)</td>
<td>10.1 (13/129)</td>
<td>2.3 (1.9, 3.7)</td>
<td>9.9 (7.8, 12.4)</td>
</tr>
<tr>
<td>1</td>
<td>3.0 (1/33)</td>
<td>63.9 (63.9, 63.9)</td>
<td>15.2 (5/33)</td>
<td>1.9 (1.8, 3.6)</td>
<td>9.2 (5.6, 11.1)</td>
</tr>
<tr>
<td>3</td>
<td>24.3 (9/37)</td>
<td>74.0 (16.1+, 133.9+)</td>
<td>8.1 (3/37)</td>
<td>1.9 (1.7, 12.5)</td>
<td>14.9 (9.5, NE)</td>
</tr>
<tr>
<td>10</td>
<td>20.3 (12/59)</td>
<td>83.1 (6.1+, 132.7+)</td>
<td>8.5 (5/59)</td>
<td>3.6 (1.9, 3.8)</td>
<td>9.2 (5.2, 12.4)</td>
</tr>
</tbody>
</table>

\(^a\) Includes patients with progressive disease (PD) at baseline who had a subsequent non–PD response.  
\(^b\) Includes patients with PD at baseline who had a subsequent non–PD response.
Nivolumab in Advanced Squamous Cell NSCLC: Phase 2 Study
Overall Survival with Nivolumab in Advanced Squamous Cell NSCLC
Nivolumab Vs. Chemotherapy (CheckMate 017)

**Scheme**

- Adv Squamous NSCLC
  - Prior Platinum-based ChemoTx
    - Nivolumab
      - N=135 Pts
    - Docetaxel
      - N=137 Pts

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9.2 m HR = 0.59</td>
<td>6.0 m</td>
</tr>
<tr>
<td>p</td>
<td>0.00023</td>
<td></td>
</tr>
</tbody>
</table>

Spigel et al, ASCO 2015
Pembrolizumab: KEYNOTE-001 Study:
NSCLC Expansion Cohorts (N = 307)

Response assessment every 9 weeks

- Primary measure: ORR by RECIST v1.1 per independent central review
- Secondary measure: immune-related response criteria (irRC) per investigator assessment
Evaluable patients were those with measurable disease at baseline per central review who had ≥1 post baseline tumor assessment. Analysis cut-off date: March 3, 2014.

Response Rate by Level of PD-L1 Expression (RECIST 1.1, Central Review)

- Total (N=129)
- Strong Positive (n=41)
- Weak Positive (n=46)
MPDL3280 (Anti PDL1) Phase I study
KEYNOTE-024: Pembrolizumab vs chemotherapy in first-line therapy for stage IV NSCLC* with PD-L1 TPS ≥50%

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>73</td>
<td>10.3</td>
<td>0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.37-0.68)</td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>116</td>
<td>6.0</td>
<td>NR</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*ECOG PS 0-1; no activating EGFR mut or ALK translocation; no untreated brain mets; no active autoimmune disease
KEYNOTE-021G: Carboplatin/pemetrexed +/- pembrolizumab in first-line therapy for stage IIIB/IV NSCLC*

**PFS, %**

- **Pembro + chemo**: 77% (63%) at 13.0 mo, 63% at 8.9 mo
- **Chemo alone**: 60% at 8.9 mo

**OS, %**

- **Pembro + chemo**: 92% at 13.0 mo, 75% at 7.0 mo
- **Chemo alone**: 92% at 13.0 mo, 72% at 7.0 mo

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>23</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>33</td>
</tr>
</tbody>
</table>

*Provision of sample for PD-L1 assessment; ECOG PS 0-1; no activating EGFR mut or ALK translocation; no untreated brain mets; no ILD or pneumonitis
CheckMate 026: Nivolumab vs chemotherapy in first-line therapy for stage IV/recurrent PD-L1–positive NSCLC* 

<table>
<thead>
<tr>
<th>(≥5% PD-L1+)</th>
<th>Nivolumab (n = 211)</th>
<th>Chemotherapy (n = 212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>4.2 (3.0, 5.6)</td>
<td>5.9 (5.4, 6.9)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>14.4 (11.7, 17.4)</td>
<td>13.2 (10.7, 17.1)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>26.1 (20.3, 32.5)</td>
<td>33.5 (27.2, 40.3)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>24.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38.4</td>
<td>47.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>8.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Median time to response, months (range)</td>
<td>2.8 (1.2, 13.2)</td>
<td>2.6 (1.2, 9.8)</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
<td>12.1 (8.8, NE)</td>
<td>5.7 (4.2, 8.5)</td>
</tr>
</tbody>
</table>

*≥1% PD-L1 expression; No EGFR/ALK muts sensitive to available targeted tx; CNS mets permitted if adequately treated
OAK: Atezolizumab vs docetaxel in previously treated locally advanced or metastatic NSCLC*; OS by PD-L1 expression

On-study Prevalence

<table>
<thead>
<tr>
<th></th>
<th>16%</th>
<th>31%</th>
<th>55%</th>
<th>45%</th>
</tr>
</thead>
</table>

Subgroup
- TC3 or IC3
- TC2/3 or IC2/3
- TC1/2/3 or IC1/2/3
- TC0 and IC0

Median OS, mo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 or IC3</td>
<td>20.5</td>
<td>8.9</td>
</tr>
<tr>
<td>TC2/3 or IC2/3</td>
<td>16.3</td>
<td>10.8</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3</td>
<td>15.7</td>
<td>10.3</td>
</tr>
<tr>
<td>TC0 and IC0</td>
<td>12.6</td>
<td>8.9</td>
</tr>
</tbody>
</table>

ITT* 0.73

Hazard Ratio 0.73

*1-2 prior lines of chemotherapy including at least 1 platinum-based; any PD-L1 status

Barlesi et al. ESMO 2016
Pembrolizumab appears promising in the front line setting for patients with highly positive PD-L1 expression (≥50% tumor cells positive for PD-L1 in KEYNOTE-024)

In contrast, nivolumab did not show benefit in CheckMate 026, which used 1% PDL1 positivity as the cutoff

Consider a divide and conquer approach based on PD-L1 expression and driver oncogene status

- What is the proportion of NSCLC patients with TPS ≥50%? (23-30% in the KEYNOTE studies)
- What is the tumor PD-L1 expression in patients with driver oncogenes (EGFR, ALK, ROS) – initial treatment targeted agent or checkpoint inhibitor?
- Use of different cutoff points or alternative biomarkers?

Translating KeyNote 024 into clinical practice: inclusion criteria: PD-L1 TPS 50%, no EGFR/ALK mutation, PS 0-1, no (untreated) brain mets
• Earlier detection remains a significant challenge
• Lack of a defined premalignant lesion – AAH?
• Value of ctDNA or other biomarker?
• Development of screening processes for genetically driven tumors

• *Watson for Genomics* to analyze genomic data
• New York Genome Center study
• IBM/VA partnership as part of the Cancer Moonshot program
Reduced Lung Cancer Mortality with Low-Dose CT Screening

National Lung Screening Trial

53,454 subjects at high risk for lung cancer

- Low-dose CT
  - 3 annual screenings

- Single-view chest radiography
  - 3 annual screenings

- Compared with radiography, the two annual incidence screenings with low-dose CT resulted in a decrease in the number of advanced-stage cancers diagnosed and an increase in the number of early-stage lung cancers diagnosed

- Pooled data from 2 randomized phase 3 trials (STARS and ROSEL) that closed early due to slow accrual
- Small patient size (N=58)
- Larger trials are needed

How can we make lung cancer management affordable, particularly for low and middle income nations?

Countries in the developing world bear the greatest burden of new cancer cases as well as deaths.

By 2030, the developing world is expected to account for 70% of newly reported cancer cases.

- **How can we make lung cancer management affordable, particularly for low and middle income nations?**

Peter Bach MD, MSKCC.
American Cancer Society. Global cancer facts & figures.
Trends in Current Cigarette Smoking by High School Students* and Adults** — United States, 1965-2014

*Percentage of high school students who smoked cigarettes on 1 or more of the 30 days preceding the survey (Youth Risk Behavior Survey, 1991-2013).

**Percentage of adults who are current cigarette smokers (National Health Interview Survey, 1965-2014).
The disproportionate increase in the number of cigarettes smoked in China is a combined effect of China’s population growth and an increase in smoking intensity.
E-cigarette use among current smokers in 27 European countries, 2012

Prevalence of water pipe usage

Florida Department of Health; 2012 Florida Youth Tobacco Survey.
tobaccoatlas.org
Legislation: **National Tobacco Control Law 174** included ban on indoor waterpipe use in public places based on AUB-led research (2011)

Policy alerts by **American Lung Association** (2007); **US Centers for Disease Control** (2011); **American Cancer Society** (2014)

Prohibition of indoor use of waterpipes in various cities


**Framework Convention on Tobacco Control**: resolution on waterpipe tobacco smoking in the 6th Conference of Parties (FCTC COP6/10, 2014)
• 16% of the world's population are protected by comprehensive national smoke-free laws

• As of October 1, 2016, there were 1,713 smoke-free campuses in the US, of which 1,427 -- around two-thirds -- were fully tobacco-free

• Several statewide policies exist, including in Arkansas, Illinois, Iowa, and Louisiana

• Along with many other universities worldwide, AUB will become a smoke-free campus by January 1, 2018
Field Carcinogenesis: The Rationale for Cancer Chemoprevention

- Normal
- Damaged Tissue
- DNA Adducts
- Mutations
- Polysomy
- Damaged Tissue
- CLONES (3p, 9p, 17p)
- Aneuploidy
- Premalignancy
- Bronchial Metaplasia
- Clonal Outgrowth
- New Clones
- First Primary
- Treatment
- Second Primary
- SPT

W Hittelman, MDACC
Tobacco as a Potent Molecular Probe: Tobacco Smoke-mediated Induction of Cyclooxygenase-2 (COX-2) is Dependent on Activation of EGFR

Stage I/II NSCLC
Complete surgical resection

COX-2 Overexpression in primary tumor

Celecoxib 400 mg BID X 7 days

Metabolic responders (Urinary PG metabolites)
Celecoxib 400 mg BID
Placebo QD

No metabolic response
Off study

Khuri et al. CCR 2001;7:861-867.

Dannenberg et al. JCO 2005;23:254-266.
Prevention of Head and Neck Cancer SPT with Adjuvant High-Dose 13cRA

100 subjects
NED after primary SCCHN tx

13-cRA
50-100 mg/M2/day
x 12 months

Placebo
x 12 months

Time to development of SPT
Isotretinoin in chemoprevention of bronchial squamous metaplasia

86 subjects
Dysplasia/Metaplasia

13-cRA
1 mg/kg
x 6 months

Placebo
x 6 months

Mean metaplasia index before and after treatment.

---- isotretinoin
- - - placebo

NSCLC Prevention: Failure of Chemoprevention in Unselected Patients

Selenium supplementation in resected stage I NSCLC

1561 subjects
Resected Stage I NSCLC

Selenized yeast
200 mg/day
x 4 years
N=1040

Placebo
x 4 years
N=521

Overall Survival

RTOG 91-15: Low Dose 13cRA for Prevention of SPT in Early Stage HNSCC

1190 subjects
NED after primary tx for Stage I-II HNSCC

13-cRA
30 mg/day
x 3 years

Placebo
x 3 years

SPT free survival by treatment(04/14/03)

13cRA ( E/N = 126 / 590 )
Placebo ( E/N = 129 / 600 )
P-value = 0.764

Selenium Supplementation in Resected Stage I Lung Cancer

1561 subjects
Resected Stage I NSCLC

Selenized yeast
200 mg/day
x 4 years
N=1040

Placebo
x 4 years
N=521

Overall Survival

Karp et al. JCO 2013; Sep 3.
Large-Scale Aerodigestive Cancer Chemoprevention Trials

- CARET (β-Carotene and Retinol)
- ATBC (α-Tocopherol and β-Carotene)
- Euroscan (Retinyl Palmitate and NAC)
- NCI Intergroup (13cRA)-Lung and Head & Neck trials
- Selenium

Major Findings

- β-carotene increases lung cancer incidence in current smokers, but not in former smokers
- 13cRA has no impact on reduction of incidence of second primary tumors in patients of any smoking status
- Data suggest that 13cRA is beneficial in non-smokers and possibly beneficial in former smokers for reduction of locoregional recurrence and improving survival, but harmful in current smokers
Airway Epithelial Gene Expression in Lung Cancer Diagnosis

- 80-gene biomarker that distinguishes smokers with and without lung cancer

- Hierarchical clustering of biomarker probe-set expression in 2 independent test sets (a and b).

- Classification was correct for 83% of test samples and 80% of prospective validation set samples.
Evaluated 137 SNPs from 20 genes involved in the PI3K/PTEN/AKT/mTOR pathway in 440 HNSCC patients (enrolled in the 13-cRA HN SPT study) and assessed for SPT/recurrence risk and response to 13-cRA

- 22 loci associated with the risk of SPT/recurrence
- 6 loci also associated with benefit from 13-cRA

Effect of TSC1-variant genotypes on event-free survival in placebo group

Effect of 13-cRA treatment in patients with common TSC1 genotype

Genetic variations in PI3K/PTEN/AKT/mTOR pathway modify HNSCC SPT/recurrence risk

Hildebrandt et al. CCR 2012;18:3705-3713.
• Progress in targeted therapies for oncogenic drivers
• Immunotherapy in the first line setting based on PD-L1 expression and oncogenic driver status?
• Chemoprevention approaches are largely unsuccessful in continuing smokers
• CT screening in high risk patients
• How do we provide access to new targeted and immuno-therapies and CT screening in less wealthy nations?
• Global tobacco control measures are crucial
Men May Be Able to Avoid Dementia By Marrying Intelligent Women, Researchers Say

Men who marry intelligent women are less likely to develop dementia