Plenary Session 6: Translation of Big Data into Clinical Opportunities

The Impact of Next Generation Sequencing on the Outcomes of Patients with Lung Cancer

June 28th, 2016

Bruce E. Johnson, MD
The following relationships exist related to this presentation:

- Bruce E. Johnson is a paid consultant for Chugai, AstraZeneca, Genentech, Clovis, Novartis, Merck, Amgen, and Boehringer Ingelheim.
- Bruce E. Johnson has provided expert testimony for Genentech.
- Bruce E. Johnson receives post-marketing royalties for a patent on epidermal growth factor receptor testing.
- Bruce E. Johnson is an equity holder in the KEW Group, a company founded to provide genomic testing and interpretation to oncology practices in the United States.
The Impact of Next Generation Sequencing on the Outcomes of Patients with Lung Cancer

- EGFR mutations (15%)
- ALK rearrangements
- Other Oncogenic Drivers - BRAF, MET
- Outcomes
The Impact of Next Generation Sequencing on the Outcomes of Patients with Lung Cancer

EGFR Mutation
Woman with Adenocarcinoma Treated with Gefitinib

Exon 19 Deletion Mutation of EGFR

January 2002

October 2004
Epidermal Growth Factor Receptor Mutations

25 of 31 Patients with Response to Gefitinib had EGFR Mutation

Pao et al. 2004

Paez et al. 2004

Lynch et al. 2004
Current Standards and Studies for EGFR+ Metastatic NSCLC; 5 Year Survivors

Median: 30.80 months
(95% CI: 29.23–32.70)

No. at risk: 1657, 1307, 871, 434, 192, 77

Inoue et al. Jap J Clin Oncol 2016; epub March
The Impact of Next Generation Sequencing on the Outcomes of Patients with Lung Cancer

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52 Year Old Woman with ALK+ NSCLC Treated with Crizotinib

September 2011

April 2016
ALK+ Non-Small Cell Lung Cancer; Ceritinib

Kim et al. Lancet Oncol 2016; 17:452-463
ALK+ Non-Small Cell Lung Cancer; Ceritinib

April 2014-FDA Approved Ceritinib With ALK Rearrangements in NSCLC

Kim et al. Lancet Oncol 2016; 17:452-463
ALK+ Non-Small Cell Lung Cancer; Alectinib

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (N=103)</th>
<th>Crizotinib (N=104)</th>
</tr>
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<tbody>
<tr>
<td>Events, n (%)</td>
<td>25 (24.3%)</td>
<td>58 (55.8%)</td>
</tr>
<tr>
<td>Median, mo</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>0.34 [0.17 - 0.71]</td>
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</tbody>
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Progression-free survival rate (%)

10.2 months

No. of patients at risk
Alectinib 103 102 93 76 49 36 27 9 1
Crizotinib 104 102 86 65 40 21 14 4 1

Hiroshi Nokihara ASCO 2016
- EGFR mutations (15%)
- ALK rearrangements
- Other Oncogenic Drivers- BRAF, MET
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66-Year-Old Male Patient (former smoker) With *BRAF* V600E Mutation Treated With Dabrafenib + Trametinib

Images courtesy of B. Johnson, et al, Dana-Farber Cancer Center, Boston

*Presented by: David Planchard, MD, PhD*
Maximizing Change in Target Lesion by Best Investigator-Assessed Confirmed Response

Patients

Overall response rate: 63% (95% CI, 49-76)

NE patients did not have a follow-up scan required for confirmation.
Progression-Free Survival of V600E BRAF NSCLC Rxed with Dabrafenib and Trametinib

Presented by: David Planchard, MD, PhD

**Progression-Free Survival by Investigator Assessment**

**Time From First Dose, months**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>57</th>
<th>49</th>
<th>43</th>
<th>34</th>
<th>31</th>
<th>20</th>
<th>13</th>
<th>7</th>
<th>6</th>
<th>2</th>
<th>0</th>
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<tbody>
<tr>
<td>No. censored</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>14</td>
<td>19</td>
<td>20</td>
<td>25</td>
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Dashed lines represent 95% CIs. Median follow-up of 11.6 months.

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, median (95% CI), mo</td>
<td>9.7 (6.9-19.6)</td>
</tr>
<tr>
<td>Number of progressions or deaths, n (%)</td>
<td>32 (56)</td>
</tr>
</tbody>
</table>
Exons: ABL1, AKT1, AKT2, AKT3, **ALK**, ALOX12B, APC, AR, ARAF, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATRX, AURKA, AURKB, AXL, B2M, BAP1, BCL2, BCL2L1, BCL2L12, BCL6, BCOR, BCORL1, BLM, BMPR1A, **BRAF**, BRCA1, BRCA2, BRD4, BRIP1, BUB1B, CARD11, CBL, CBLB, CCND1, CCND2, CCND3, CCNE1, CD274, CD58, CD79B, CDC73, CDH1, CDK1, CDK2, CDK4, CDK5, CDK6, CDK9, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK2, CIITA, CREBBP, CRKL, CRLF2, CRTC1, CRTC2, CTNNB1, CX1, CYLD, DDB2, DDR2, Dicer1, DIS3, DMD, DNMT3A, **EGFR**, EP300, EPHA3, EPHA5, EPHA7, ERBB2, ERBB3, ERBB4, ERCC2, ERCC3, ERCC4, ERCC5, ESR1, ETV1, ETV4, ETV5, ETV6, EWSR1, EXT1, EXT2, EZH2, FAM46C, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FAS, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FH, FKBp9, FLCN, FLT1, FLT3, FLT4, GATA3, GATA4, GATA6, GLI1, GLI2, GLI3, GNA11, GNAQ, GNAs, GPC3, GSTM5, H3F3A, HNF1A, HRAS, ID3, IDH1, IDH2, IGF1R, IKZF1, IKZF3, JAK2, JAK3, KDM6A, KDM6B, KDR, KIT, KRAS, LMO1, LMO2, LMO3, MAP2K1, MAP2K4, MAP3K1, MAPK1, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, **MET**, MITF, MLH1, MLL, MLL2, MPL, MSH2, MSH6, MTO1, MUYH, MYB, MYBL1, MYC, MYCL1, MYCN, MYD88, NBN, NF1, NF2, NFE2L2, NFKBIA, NFKBIZ, NKX2-1, NOTCH1, NOTCH2, NPM1, NRAS, NTRK1, NTRK2, NTRK3, PALB2, PARK2, PAX5, PDCD1LG2, PDGFR, PDGFRB, PHF6, PHOX2B, PIK3C2B, PIK3CA, PIK3R1, PIM1, PMS1, PMS2, PNRC1, PRAME, PRDM1, PRF1, PRKAR1A, PRKCI, PRKCD, PRPF40B, PRPF8, PSMD13, PTC1, PTEF, PTK2, PTPN11, RAD21, RAF1, RARA, RB1, RBL2, REL, RET, RFWD2, RPN2, **ROS1**, RPL26, RUNX1, SBDS, SDHAF2, SDHB, SDHC, SDHD, SETBP1, SETD2, SF1, SF3B1, SH2B3, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMC3, SMO, SOCS1, SOX2, SOX9, SRC, SRSF2, STAG1, STAG2, STAT3, STAT6, STK11, SUFU, SUZ12, SYK, TCF3, TCF7L1, TCF7L2, TERT, TET2, TNFAIP3, TP53, TSC1, TSC2, U2AF1, VHL, WRN, WT1, XPA, XPC, XPO1, ZNF217, ZNF708, ZRSR2.

Introns: ABL1, AKT3, **ALK**, BCL2, BCL6, BRAF, CIITA, EGFR, ETV1, EWSR1, FGFR1, FGFR3, FUS, IGH, IGL, JAK2, **MET**, MLL, MYC, NPM1, PAX5, PDGFR, PDGFRB, RAF1, RARA, RET, ROS1, TRA, TRB, TRG.

Courtesy of Neal Lindeman and Jeff Golden
1. 6376 cancers underwent targeted NGS between August 2013 and May 2015

2. Cohort included 968 non-squamous NSCLCs

3. *MET* exon 14 mutations were identified in 28 of 933 nonsquamous NSCLCs (3.0%)
Case: METex14 Mutation

Normal MET Signaling

- HGF/SF
- Cbl
- Grb2
- Receptor activation
  (RAS-MAPK, PI3K-AKT, Src, STAT3)
- Receptor internalization
- Receptor degradation

Exon 14 Mutated/Skipped

- Exon 14 skipping
- Tyr1003
- Ex14 skipping
- Loss of c-Cbl binding site
- Decreased ubiquitination
- Impaired receptor degradation
- Increased MET signaling

Mark Awad J Clin Oncol Mar 1, 2016:721-730
Case: METex14 Mutation Treated with Crizotinib

D

Pretreatment

E

During crizotinib treatment (at 2 months)

Mark Awad J Clin Oncol Mar 1, 2016:721-730
Presented by: Alexander Drilon MD

Maximum Response to Crizotinib in Patients with MET Exon 14-Altered Lung Cancers (n=16 with measurable disease at baseline and ≥1 response assessment scan)

- **Partial response (PR):** confirmed
- **Stable disease (SD):** includes 4 unconfirmed PRs
- **Stable disease and 0% change from baseline**
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Eligibility

• Patients with Stage III B or IV or Recurrent Adenocarcinomas of the Lung

• Patients with SWOG Performance Status 0, 1, or 2

• Adequate Tumor Tissue for Genomic Characterization

• Histological Confirmation of Adenocarcinoma
Lung Cancer Mutation Consortium Results

A) All patients with adenocarcinoma, genotyping, and follow-up

B) Patients with an oncogenic driver mutation who did and did not receive targeted therapy, and patients without an oncogenic driver

Log-rank $P<.001$

No. at risk
All patients 938 680 375 195 115 66
Study Design

1000 patients
Stage IV
ECOG PS 0-2
Lung Adenocarcinomas
Sufficient Tissue (Paraffin)
Informed Consent

Central Confirmation of Adenocarcinoma Diagnosis
(1 slide)

Planned Analyses
CLIA-Certified lab at LCMC site:
KRAS, EGFR, BRAF, HER2, PIK3CA,
NRAS, MAP2K1,
AKT1, MET amplification,
Rearrangements in ALK, RET, and
ROS1, MET* and PTEN IHC**

* Ventana SP44 ** Cell Signaling 138G4

Report to LCMC Virtual Database

Use Results to Select Therapy
Recommend Clinical Trial of Agent Specific for Target

Report to Physician
Mutational Frequencies in LCMC II

- KRAS: 25%
- PTEN loss: 15%
- MET exp: 59%

IHC assays | % pos cases
---|---
PTEN loss | 15%
MET exp | 59%

**Note:**
- sEGFR = sensitizing
- oEGFR = other
- veBRAF = V600E
- oBRAF = other
- r = rearrangement
Some Modulators Can Be Identified

EGFR sensitizing mutation with targeted therapy

No TP53 mutation

With TP53 mutation

n= 51
Median survival 2.9 vs. NR

121 cases EGFR (+)
Only SensEGFR (+) = 91
With TTx = 72
15 with no TTx or missing information
With survival AND TP53 data = 51
Of these, 40 by NGS

Assay Coverage Matters

Of NGS cases: TP53 positive rate= 48%
Of non-NGS cases: TP53 positive rate= 8% (4 hotspots)
We are likely under-observing TP53 mutation status
French Cooperative Thoracic Intergroup

18,679 Analyzed Samples 2012-2013

Barlesi et al. Lancet 2016
French Cooperative Thoracic Intergroup

![Graph showing median overall survival (months) with gene alteration present: 16.5 (95% CI 15.0-18.3) and gene alteration absent: 11.8 (95% CI 10.1-13.5) HR 0.78 (95% CI 0.70-0.86); p<0.0001.]

**Number at risk**
- Gene alteration present: 3498, 2141, 1423, 594, 165, 9, 0
- Gene alteration absent: 1126, 617, 333, 124, 24, 4, 0
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