The Evolving Role of Molecular Markers in Managing Non-Small Cell Lung Cancer

Nathan A. Pennell, M.D., Ph.D.
Assistant Professor
Solid Tumor Oncology
Cleveland Clinic Taussig Cancer Institute

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www.cancergrace.org
Objectives

• The many faces of “non-small cell lung cancer”
• What is a molecular marker?
• The current status of molecular testing in lung cancer practice today
• Promising molecular markers coming in the near future
Lung Cancer Classification

1900-2000

88%

12%

SCLC

NSCLC
WHO Histologic Classification of Non-small Cell Lung Cancer

Squamous cell carcinoma.
- Papillary.
- Clear cell.
- Small cell.
- Basaloid.

Adenocarcinoma.
- Acinar.
- Papillary.
- Bronchioloalveolar carcinoma.
  - Nonmucinous.
  - Mucinous.
  - Mixed mucinous and nonmucinous or indeterminate cell type.
- Solid adenocarcinoma with mucin.
- Adenocarcinoma with mixed subtypes.
- Variants.
  - Well-differentiated fetal adenocarcinoma.
  - Mucinous (colloid) adenocarcinoma.
  - Mucinous cystadenocarcinoma.
  - Signet ring adenocarcinoma.
  - Clear cell adenocarcinoma.

Large cell carcinoma.
- Variants.
  - Large-cell neuroendocrine carcinoma.
  - Combined large-cell neuroendocrine carcinoma.
  - Basaloid carcinoma.
  - Lymphoepithelioma-like carcinoma.
  - Clear cell carcinoma.
  - Large cell carcinoma with rhabdoid phenotype.
  - Adenosquamous carcinoma.
- Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.
- Carcinomas with spindle and/or giant cells.
- Spindle cell carcinoma.
- Giant cell carcinoma.
- Carcinosarcoma.
- Pulmonary blastoma.
- Carcinomas of salivary-gland type.
- Mucoepidermoid carcinoma.
- Adenoid cystic carcinoma.
- Others.
- Unclassified carcinoma.

Classifying NSCLC: 2000 and 2010

- **2000**: NSCLC NOS

- **2010**
  - EGFR mutant: 10%
  - ALK trans+: 4%
  - KRAS mutant: 20%
  - Bevacizumab Eligible: 20%
  - NSCLC NOS: 10%

EGFR: Epidermal growth factor receptor
ALK: Anaplastic lymphoma kinase
Why is it important to classify tumors beyond simply “NSCLC”? 
The Ultimate Goal: Personalized Medicine

• Matching the specific type of tumor with the perfect treatment.

• Question: how to identify the right key?

• The (or one) answer: Molecular markers
What is a Molecular Marker?

- Molecular characteristic (protein, DNA, or RNA) of the tumor or patient that carries a **prognostic** or **predictive** value.
  - **Prognostic** marker – Indicates better or worse outcome irrespective of treatment (stage, sex or performance status)
  - **Predictive** marker – The presence or absence of the marker predicts how the patient will do with a specific treatment (**EGFR** mutation and Tarceva/Iressa).
What are the current markers in lung cancer practice?

- Epidermal growth factor receptor (EGFR) mutation
- KRAS mutation

<table>
<thead>
<tr>
<th>Marker</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutant</td>
<td>10%</td>
</tr>
<tr>
<td>ALK trans+</td>
<td>4%</td>
</tr>
<tr>
<td>KRAS mutant</td>
<td>20%</td>
</tr>
<tr>
<td>Bevacizumab Eligible</td>
<td>10%</td>
</tr>
<tr>
<td>NSCLC NOS</td>
<td>4%</td>
</tr>
</tbody>
</table>
EGFR: Potential Consequences of Dysregulation

MAPK = mitogen-activated protein kinase.

Inhibiting EGFR: Small molecule tyrosine kinase inhibitors (TKIs)

– Tarceva (erlotinib) and Iressa (gefitinib).
BR.21 Trial– Phase III trial of erlotinib (Tarceva) vs BSC in 2\textsuperscript{nd}-3\textsuperscript{rd} line NSCLC

NSCLC Patients who had failed 1 or 2 prior lines of chemotherapy

\begin{itemize}
  \item \textbf{Randomize} 1
  \item \textbf{Randomize} 2
  \item Tarceva 150 mg daily
  \item Placebo
\end{itemize}

Shepherd, NEJM 353:123, 2005
BR.21: Phase III trial of erlotinib vs supportive care in 2nd-3rd line NSCLC

Median survival
Erlotinib 6.7 mo
Placebo 4.7 mo

Shepherd, NEJM 353:123, 2005
BR.21: Survival by Smoking History

Never Smoked

- **HR=0.42 (95% CI, 0.28-0.64)**
- Erlotinib (n=104)
  - RR=24.7%
- Placebo (n=42)

Current and Ex-Smokers

- **HR=0.87 (95% CI, 0.71-1.05)**
- Erlotinib (n=358)
  - RR=3.9%
- Placebo (n=187)
EGFR-TKI: Clinical Characteristics

- Consistent benefit seen across multiple studies in:
  - Never Smokers
  - Adenocarcinoma
  - Women
  - Asian ethnicity

- What are the molecular markers that might PREDICT who would benefit from an EGFR TKI?
Candidate Markers for EGFR TKIs

- Clinical Criteria
- *EGFR* Mutation
- *EGFR* Gene Copy Number
- Proteomic Patterns
- *KRAS* mutation (negative)
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Hasserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
**EGFR Mutations**

- Mutations enhance activation of the EGFR.
- Leads to cancer cell “addiction” to the signal from the mutated receptor.
- Hence, NSCLC cells harboring *EGFR* mutations are exquisitely sensitive to TKIs like Tarceva or Iressa.
- ORR of >70% and median survival approaching 2 years with TKI treatment.
EGFR Mutations

Predictive of benefit or only prognostic of better outcome regardless of treatment?
EGFR Mutations or Clinical Predictors?  
IPASS (Iressa Pan Asian Study)

**Chemonaïve**
- Age ≥ 18 years
- Adenocarcinoma
- Never or light ex-smokers
- Life expectancy ≥ 12 weeks
- PS 0-2
- Measurable stage III B / IV

**Primary Endpoint**
- Progression-free survival (non-inferiority)

**Secondary Endpoints**
- 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

N=1217

Mok et al., NEJM 2009, 361(10).
Progression-free survival in ITT population

- Gefitinib
- Carboplatin / paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>453 (74.4%)</td>
<td>497 (81.7%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.741 (0.651, 0.845) p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

- Median PFS (months)  5.7  5.8
- 4 months progression-free  61%  74%
- 6 months progression-free  48%  48%
- 12 months progression-free  25%  7%

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib

Mok et al., ESMO 2008
Progression-free survival 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<0.0001
No. events gefitinib, 97 (73.5%)
No. events C/P, 111 (86.0%)
Median PFS G, 9.5 months
Median PFS C/P, 6.3 months

EGFR mutation negative

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

HR (95% CI) = 2.85 (2.05, 3.98)  
p<0.0001
No. events gefitinib, 88 (96.7%)
No. events C/P, 70 (82.4%)
Median PFS G, 1.5 months
Median PFS C/P, 5.5 months

Treatment by subgroup interaction test, p<0.0001

Cox analysis with covariates; HR <1 implies a lower risk of progression on gefitinib; ITT population

Mok et al 2008
Overall survival in ITT population (follow-up ongoing)

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>223 (36.6%)</td>
<td>227 (37.3%)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.91 (0.76, 1.10)</td>
<td></td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>18.6</td>
<td>17.3</td>
</tr>
<tr>
<td>6 month OS</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>12 month OS</td>
<td>68%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Cox analysis with covariates
HR <1 implies a lower risk of death on gefitinib
OS, overall survival

Mok et al., ESMO 2008
**EGFR Mutation - Conclusions**

- *EGFR* mutations are a *predictive* marker of response and improved PFS with EGFR TKIs in first-line treatment.

- Clinical characteristics are NOT sufficient to predict benefit from TKIs in the absence of mutation, so *mutation testing* for patients with a high clinical suspicion of mutation should be a standard practice.
Testing for *EGFR* Mutations

- **Sequencing the DNA** – requires a substantial amount of tumor tissue. Currently patented by Genzyme (Cambridge, MA).

- Turnaround time: 3-4 weeks
Testing for *EGFR* Mutations

- **Allele specific PCR-based assays** – i.e. Scorpion ARMS. Detects only the most common known mutations.
- Requires less tissue and has turnaround time of < 1 week.

www.dxsdiagnostics.com/Site/Content/Dxs/US-EGFR29MutationTestKit
Increased *EGFR* gene copy by FISH

Cappuzzo, JNCI 97:643, 2005
EGFR Gene Copy number in BR.21 Trial

Tsao et al, NEJM 353:133, 2005
EGFR Copy Number vs EGFR Mutations in IPASS trial

- *EGFR* mutation positive tumors are also usually FISH positive

- In the absence of mutation, FISH-positivity did *not* predict improved outcome on IPASS

- For now, *EGFR* gene copy number by FISH *should not* be used routinely to guide treatment with EGFR TKIs

Mok, ASCO 2009
Serum Proteomic Signatures

- MALDI (Matrix-assisted laser desorption/ionization mass spectrometry)
- No need for tumor tissue!
- Can identify proteins in fmol/pmol concentrations

Carbone et al., JTO 2007 – Serum from pts with NSCLC compared to control serum
Serum Proteomic Signature as a Predictor of Benefit from EGFR TKIs?

- Used serum from several groups of patients treated with EGFR TKIs
- Created “good” vs. “poor” prognosis groups
- Not predictive of survival in pts not treated with TKIs

Taguchi et al., JNCI 2007
Phase III PROSE Study

275 patients with have prospective serum profiling (VeriStrat; Biodesix, Inc.)

- Metastatic NSCLC
- Second-line treatment
- Stratified by proteomic profile score

Primary Endpoint: Overall survival

1. Erlotinib
2. Chemo
**KRAS Mutation**

- Present in 20% of NSCLC (typically adenocarcinoma and typically in smokers)
- Meta analysis has shown that presence of a KRAS mutation is a poor prognostic factor
- Could KRAS predict a poor response to EGFR TKIs?

Mascoux, British Journal of Cancer (2005) *92*, 131–139
KRAS and Resistance to EGFR TKIs

- Numerous studies have shown that *EGFR* mutation and *KRAS* mutation are almost mutually exclusive.

**TABLE 1. ANALYSES OF KRAS MUTATIONS AND EFFICACY OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS IN NON–SMALL CELL LUNG CANCER**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>Patients Tested for KRAS Mutations (Total Number Mutant)</th>
<th>Response Rate in KRAS Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao (2)</td>
<td>Gefitinib/erlotinib</td>
<td>59 (9)</td>
<td>0%</td>
</tr>
<tr>
<td>Jackman (47)</td>
<td>Erlotinib</td>
<td>41 (6)</td>
<td>0%</td>
</tr>
<tr>
<td>Zhu (48)</td>
<td>Erlotinib</td>
<td>206 (30)</td>
<td>5%</td>
</tr>
<tr>
<td>Miller (49)</td>
<td>Erlotinib</td>
<td>80 (18)</td>
<td>0%</td>
</tr>
<tr>
<td>Massarelli (50)</td>
<td>Gefitinib/erlotinib</td>
<td>70 (16)</td>
<td>0%</td>
</tr>
<tr>
<td>Hirsch (51)</td>
<td>Gefitinib</td>
<td>138 (36)</td>
<td>1%</td>
</tr>
<tr>
<td>Hirsch (52)</td>
<td>Gefitinib</td>
<td>152 (12)</td>
<td>0%</td>
</tr>
<tr>
<td>Han (53)</td>
<td>Gefitinib</td>
<td>69 (9)</td>
<td>0%</td>
</tr>
<tr>
<td>Van Zandwijk (54)</td>
<td>Gefitinib</td>
<td>15 (3)</td>
<td>0%</td>
</tr>
<tr>
<td>Fujimoto (55)</td>
<td>Gefitinib</td>
<td>31 (7)</td>
<td>0%</td>
</tr>
<tr>
<td>Felip (56)</td>
<td>Erlotinib</td>
<td>39 (7)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Reilly et al., 2009 Proc Am Thor Surg
As RAS is downstream of EGFR, activating RAS mutations take EGFR “out of the loop”

- Invasion
- Metastasis
- Survival
- Angiogenesis (new blood vessels)
- Proliferation (cell growth)
- Apoptosis

MAPK = mitogen-activated protein kinase.

PFS on SATURN in patients with KRAS wild-type tumours

HR = 0.70 (0.57–0.87)
Log-rank p = 0.0009

Tarceva (n=205)
Placebo (n=198)
PFS on SATURN in patients with KRAS mutation-positive tumours

HR=0.77 (0.50–1.19)
Log-rank p=0.2246
Maybe not…

• For now, the presence of a KRAS mutation should not be a contraindication for the use of EGFR TKIs in 2\textsuperscript{nd}-3\textsuperscript{rd} line.

• In standard clinical practice, there is no need to determine KRAS mutation status outside of a clinical trial, although it can serve as indirect evidence of the absence of EGFR mutation.
Conclusions: Markers for 2010

- **EGFR** mutation testing should be done **routinely** on patients with high probability of having mutations (ideally everybody if cost was not an issue), and + pts treated with EGFR TKIs preferentially.

- **EGFR** gene copy number by FISH and **KRAS** mutation testing should **not be used** to guide treatment of NSCLC in 2010.
Markers for the next decade?

- ALK translocation
- Excision repair cross complementation group 1 (ERCC1)
- Ribonucleotide reductase M1 (RRM1)
**ALK Translocation**

- Anaplastic lymphoma kinase (ALK) gene rearranged in 4% of NSCLC patients
- EML4 most common partner
- Up to 20% of non-smokers (perhaps 1 in 3 never smokers who are EGFR wild-type)
- No overlap with EGFR mutations
- More common in men, younger age, adenocarcinoma, signet ring histology
- Preclinically responds to ALK inhibition
Diagnostic features of EML4-ALK-positive non-small-cell lung cancer (NSCLC)
ALK Inhibitor PF-02341066 in NSCLC Patients with ALK Translocations

- 32 pts enrolled to date, 28 evaluable for response
- Overall Response Rate (ORR) = 59% (17/29 pts)
- Disease Control Rate (PR+SD) = 83% (24/29 pts)
- Phase III trial is enrolling now!

Shaw et al., WCLC 2009
Excision repair cross complementation group 1 (ERCC1)

- Critical protein in the DNA repair pathway
- Excision repair pathway is responsible for the repair of damage caused by platinum chemotherapy
- Low levels of ERCC1 expression are associated with poor prognosis, but may make cancer more sensitive to platinum-chemo.
Ribonucleotide reductase M1 (RRM1)

• Key protein in producing deoxyribonucleotides (building blocks for DNA).
• RRM1 is a target of the chemotherapy drug gemcitabine (Gemzar).
• Low levels of RRM1 may increase cancer’s sensitivity to Gemzar.
International Adjuvant Lung trial (IALT)

Stage I-III completed resected NSCLC
N=1867

Cisplatin + Vinca alkaloid or Etoposide
N=932

Observation
N=935

- First randomized trial to show survival benefit from adjuvant chemotherapy.
- Tested ERCC1 expression by immunohistochemistry in banked tumor samples and compared survival based on high vs. low expression

Olaussen et al., NEJM 355 (10); 2006
DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

Olaussen et al., NEJM 355 (10); 2006

4% improvement in 5-year survival

No. at Risk
Chemotherapy: 319, 341, 282, 206, 143, 81
Control: 312, 247, 187, 128, 68

No. at Risk
Chemotherapy: 224, 194, 161, 121, 81, 47
Control: 202, 163, 120, 91, 59, 35

No. at Risk
Chemotherapy: 214, 178, 141, 106, 75, 42
Control: 202, 142, 104, 78, 48, 26

No. at Risk
Chemotherapy: 165, 147, 121, 85, 62, 34
Control: 170, 149, 127, 96, 69, 33
DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

Olaussen et al., NEJM 355 (10); 2006

Survival with chemo 56 mos vs 42 without

No. at Risk
Chemotherapy 349 341 282 206 143 81
Control 372 312 247 187 128 68

No. at Risk
Chemotherapy 224 304 161 121 81 47
Control 202 303 120 81 55 35

No. at Risk
Chemotherapy 214 178 141 106 75 42
Control 202 142 104 78 48 26

No. at Risk
Chemotherapy 165 147 121 83 62 34
Control 170 149 127 96 65 33
DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

Survival with chemo 50 mos vs 55 without

Olaussen et al., NEJM 355 (10); 2006
Individualizing Therapy in Early-stage NSCLC by RRM1 and ERCC1 Status: SWOG 0720

Registration: stage IA ≥2 cm and IB

RRM1 and ERCC1 determination

RRM1 and ERCC1 high: no adjuvant therapy

RRM1 and ERCC1 low: adjuvant gemcitabine/cisplatin

SWOG=Southwest Oncology Group.

Platinum/Gemcitabine in Advanced NSCLC: ERCC1 and RRM1 Levels and Survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>OS, All Pts</th>
<th>ERCC1 Level, OS</th>
<th>RRM1 Level, OS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lord, 2002</td>
<td>56</td>
<td>8.6 mos</td>
<td>14.4 mos</td>
<td>4.7 mos</td>
<td>0.009</td>
</tr>
<tr>
<td>Rosell, 2004</td>
<td>81</td>
<td>12.8 mos</td>
<td>13.7 mos</td>
<td>9.5 mos</td>
<td>0.190</td>
</tr>
<tr>
<td>Ceppi, 2006</td>
<td>43</td>
<td>13.3 mos</td>
<td>17.3 mos</td>
<td>10.9 mos</td>
<td>0.003</td>
</tr>
<tr>
<td>Bepler, 2008</td>
<td>87</td>
<td>5.8 mos</td>
<td>6.8 mos</td>
<td>3.4 mos</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Multivariate analysis.*

Spanish Lung Trial

## Results by Treatment Arm


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n = 141)</th>
<th>Genotypic Group (n = 225)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Partial response</td>
<td>33.3</td>
<td>44.4</td>
</tr>
<tr>
<td>Stable disease</td>
<td>40.4</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>17.7</td>
<td>18.2</td>
</tr>
<tr>
<td>Could not be determined</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Overall response rate</strong></td>
<td></td>
<td><strong>39.3</strong></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>9.92</td>
<td>9.6</td>
</tr>
<tr>
<td>1 year</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>2 years</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>3 years</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>5.19</td>
<td>6.1</td>
</tr>
</tbody>
</table>

*Abbreviation: PFS, progression-free survival.*

*Control vs genotypic (P = .02).*

†Control vs low genotypic (P = .03).
Molecular Analyses-Directed Individualized Therapy (MADeIT)

• Phase II trial of tailored chemotherapy, guided by ERCC1 and RRM1 expression levels as assessed by mRNA (PCR test).

• 85 previously untreated NSCLC patients entered, 53 were able to start treatment.
The Algorithm

ERCC 1 Expression

(ERCC1 mRNA)

Platinum withheld

RRM1 Expression

High

Docetaxel

Gemcitabine

Navelbine

Docetaxel

Low

Treatment with Platinum

RRM1 Expression

High

Carboplatin

Docetaxel

Low

Carboplatin

Gemcitabine

Simon, ASCO 2007
MADeIT Trial Results…

- Response rate: 44%
- Median PFS: 6.6 mos
- Median OS: 13.3 mos
- Being tested in a phase III trial (MADeIT II)

Simon et al., J Clin Oncol 25:2741-2746
Conclusions: ERCC1 & RRM1

• These markers may be predictive of benefit from adjuvant treatment in early stage (I-III) disease, and trials are ongoing to verify this.

• The markers appear to be less clearly predictive in the metastatic setting, and the testing is more complicated.

• This may be due to differential expression of markers between primary tumors and mets*.

Conclusions

- Molecular markers have the potential to guide treatments by **aiming us at the underlying cause** of the malignancy.

- More targets and more effective treatments will be needed before this can be applied to a large number of people.

- For now, **EGFR mutation** is the only validated molecular marker that guides treatment of NSCLC.

- Within 5 years, EML4-ALK, ERCC1, and others may be in routine practice.
Classifying NSCLC: 2010 and 2020

2010
- EGFR mutant: 4%
- ALK trans+: 10%
- KRAS Mutant: 20%
- Bevacizumab Eligible: 0%
- NSCLC NOS: 6%

2020
- EGFR mutant: 4%
- ALK trans+: 20%
- KRAS Mutant: 10%
- Bevacizumab Eligible: 4%
- NSCLC NOS: 6%

Legend:
- EGFR mut+
- EGFR wt
- EGFR T790M
- ERCC1+ RRM1-
- ERCC1+RRM1+
- ERCC1-RRM1+
- ERCC1-RRM1-
- HER2 amplified
- LKB1 mut+
- PTEN inactive
- MET amplified
- RAS mut+
- ALK transl+
- Cetuximab elig
- Bev eligible