Novel therapies for advanced squamous-cell carcinoma

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15-18 April 2015, Geneva, Switzerland
Disclosure Statement

• **Education-Advisory**: Genesis Hellas, Janssen Hellas, Amgen Hellas

• **Honoraria**: Roche Hellas, AstraZeneca Hellas
Squamous-cell carcinoma (SqCC)

- Although declining proportion of NSCLC, still accounts for 30% of new cases
- Distinct epidemiological, clinicopathological and molecular characteristics (i.e. stronger association with smoking, rarity of EGFR and KRAS mutations or ALK rearrangements)
- Limited treatment options: Platinum-based therapy in 1st-line, Docetaxel-based treatment or erlotinib in 2nd line and beyond\(^1\).
- Advanced SqCC has enjoyed little of the benefit from new therapeutic options seen in ADC of the lung.

Vincent DM Front. Oncol Dec 2014
Anything new in chemotherapy?

- Cisplatin-gemcitabine still offers the best PFS (4.3 months) and OS (9.4 months), (ECOG1594)
- Pemetrexed has been shown inferior and contra-indicated
- Bevacizumab contra-indicated due to safety concerns
- Nab-paclitaxel with carboplatin appears to be superior to paclitaxel-carboplatin in SqCC with 41% ORR and less grade 3/4 neuropathy and arthralgia
- Japan: Carboplatin/S-1 superior to carboplatin-paclitaxel in SqCC (OS: 14.0 vs 10.6 months), (LETS study).

Comprehensive genomic characterization of squamous cell lung cancers

The Cancer Genome Atlas Research Network

- 178 SqCC samples profiled as part of the TCGA project
- Complex genomic alterations
- A mean of 360 exonic mutations, 165 genomic rearrangements and 323 Copy number alterations per tumor
- Statistically recurrent mutations in 18 genes

Hammerman et al, Nature 2012
Mutational Landscape in Advanced SqCC

- Nearly universal presence of TP53 mutations (81%)
- Cell cycle regulation genes altered in 72%
- Squamous differentiation genes in 44%
- RTKs - PI3K/AKT and MAPK-mediated pathways in 69%, of tumors

Hammerman et al, Nature 2012
Table 1 | Selected genomic alterations in SqCC.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation rate</th>
<th>Normal function</th>
<th>Consequence of alteration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) KEAP1</td>
<td>12%</td>
<td>Oxidative stress response</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(a) NFE2L2</td>
<td>19%</td>
<td>Oxidative stress response</td>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>(a) CUL3</td>
<td>7%</td>
<td>Oxidative stress response</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(b) SOX2</td>
<td>Zero</td>
<td>Squamous differentiation</td>
<td>Activation</td>
<td>Amplified in 21%</td>
</tr>
<tr>
<td>(b) NOTCH1</td>
<td>8%</td>
<td>Squamous differentiation</td>
<td>Mostly loss-of-function</td>
<td>Mutually exclusive with TP63 or SOX2 alterations</td>
</tr>
<tr>
<td>(b) TP63 (p40 isoform)</td>
<td>16%</td>
<td>Squamous differentiation</td>
<td>Activation, oncogene</td>
<td>Disabled in ~90% SqCC</td>
</tr>
<tr>
<td>(c) TP53</td>
<td>&gt;81%</td>
<td>Genomic integrity, apoptosis</td>
<td>Loss-of-function</td>
<td>Inactivated in 72% by several mechanisms</td>
</tr>
<tr>
<td>(d) CDKN2A</td>
<td>15%</td>
<td>Cell cycle control</td>
<td>Loss-of-function</td>
<td>Mutually exclusive with CDKN2A alterations</td>
</tr>
<tr>
<td>(d) RB1</td>
<td>7%</td>
<td>Cell cycle control</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(e) NF1</td>
<td>11%</td>
<td>RAS inhibitor</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(e) BRAF</td>
<td>4%</td>
<td>Signal transduction</td>
<td>Activation</td>
<td></td>
</tr>
<tr>
<td>(e) RASA1</td>
<td>4%</td>
<td>RAS inhibitor</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(e) KRAS</td>
<td>&lt;1%</td>
<td>Signal transduction</td>
<td>Activation</td>
<td>Very uncommon in SqCC</td>
</tr>
<tr>
<td>(f) HLA-A</td>
<td>3%</td>
<td>Antigen display</td>
<td>Loss-of-function</td>
<td>May permit avoidance of immune destruction</td>
</tr>
<tr>
<td>(g) PTEN</td>
<td>8%</td>
<td>PI3K/Akt pathway inhibitor</td>
<td>Loss-of-function</td>
<td></td>
</tr>
<tr>
<td>(g) PIK3CA</td>
<td>16%</td>
<td>PI3K/Akt pathway growth and survival</td>
<td>Activation</td>
<td>AKT3 also activated in 16%</td>
</tr>
<tr>
<td>(h) FGFR1</td>
<td>Few</td>
<td>RTK growth/survival</td>
<td>Activation</td>
<td>Amplified in 21%</td>
</tr>
<tr>
<td>(h) EGFR</td>
<td>±1% L861Q mutation rate</td>
<td>RTK in growth/survival growth function</td>
<td>Activation</td>
<td>Amplified in 9%, rarely mutated</td>
</tr>
<tr>
<td>(i) MLL2</td>
<td>20%</td>
<td>Chromatin regulation</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

Vincent DM Front. Oncol Dec 2014
Many of these mutations are inactivations of tumor suppressor genes!

Targetable genetic alterations

Hammerman et al., Nature 2012

15-18 April 2015, Geneva, Switzerland
**A. RTKs: ErbB family and Squamous-cell Lung Cancer**

**Afatinib: an irreversible ErbB Family Blocker**

- Afatinib is an orally available, irreversible ErbB Family Blocker, with high efficacy potential
  - Inhibition of ErbB Family receptor heterodimerization
  - *In vitro* activity against EGFR-resistant T790M mutation

LUX-Lung 8: Study Design

Primary endpoint – Progression-free survival by central independent radiology review (RECIST 1.1)

Advanced NSCLC (Stage IIIB/IV)\textsuperscript{a}

- Squamous histology\textsuperscript{b}
- \(\geq 4\) cycles of a first-line platinum doublet\textsuperscript{c}
- ECOG PS 0–1
- Adequate organ function

Excluded:
- Patients without PD
- Prior EGFR TKI or antibody
- Active brain metastases, Interstitial lung disease

Randomisation 1:1

- Afatinib 40 mg QD\textsuperscript{d}

- Erlotinib 150 mg QD

Treatment until disease progression or unacceptable AEs

Stratification: East Asian versus Non-East Asian

Tumour tissue collected for correlative science

Radiographic tumour assessment at baseline, Weeks 8, 12, 16; every 8 weeks thereafter


15-18 April 2015, Geneva, Switzerland
LUX-Lung 8: PFS (Independent Review)

LUX-Lung 8: Objective Response (Independent Review)


15-18 April 2015, Geneva, Switzerland
# LUX-Lung 8: Drug-Related AEs (>5%)  
Grouped categories by CTCAE grades

<table>
<thead>
<tr>
<th>AE category</th>
<th>Afatinib (N=329) n, (%)</th>
<th>Erlotinib (N=332) n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Total with related AEs</td>
<td>298 (91)</td>
<td>75 (23)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>218 (66)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Rash/acne*</td>
<td>208 (63)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>90 (27)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>44 (13)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>38 (12)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (12)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Paronychia*</td>
<td>35 (11)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>29 (9)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>27 (8)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (8)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>2 (&lt;1)</td>
</tr>
</tbody>
</table>
## Overview of Second-Line Trials testing EGFR-TKIs and MoAbs in patient cohorts including SqCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Median PFS (mo)</th>
<th>HR for PFS</th>
<th>Median OS (mo)</th>
<th>HR for OS</th>
<th>ORR (%)</th>
<th>Safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR.21</td>
<td>Erlotinib vs placebo (n=727) Squamous (n=222)</td>
<td>2.2 vs 1.8</td>
<td>0.61</td>
<td>6.7 vs 4.7</td>
<td>0.70</td>
<td>9 vs 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Squamous (n=222)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZEST</td>
<td>Vandetanib vs erlotinib (n=1240) Squamous (n=272)</td>
<td>2.6 vs 2.0</td>
<td>0.98</td>
<td>6.9 vs 7.8</td>
<td>1.01</td>
<td>12 vs 12</td>
<td>50% grade ≥ 3 AEs</td>
</tr>
<tr>
<td>BETA</td>
<td>Erlotinib + bev vs erlotinib (n=636) Squamous (n=28)</td>
<td>3.4 vs 1.7</td>
<td>0.62</td>
<td>9.3 vs 9.2</td>
<td>0.97</td>
<td>13 vs 6</td>
<td>60% grade ≥ 3 AEs</td>
</tr>
<tr>
<td>TITAN</td>
<td>Doce/pem vs erlotinib, (n=304) Squamous (n=154)</td>
<td>2.2 vs 1.6</td>
<td>1.19</td>
<td>5.5 vs 5.3</td>
<td>0.96</td>
<td>8 vs 6</td>
<td>31% grade ≥ 3 AEs</td>
</tr>
<tr>
<td>SUN1087</td>
<td>Sunitinib + erlotinib vs erlotinib (n=960) Squamous (n=270)</td>
<td>3.6 vs 2.0</td>
<td>0.81</td>
<td>9.0 vs 8.5</td>
<td>0.92</td>
<td>11 vs 7</td>
<td></td>
</tr>
<tr>
<td>TAILOR</td>
<td>Doce vs erlotinib, EGFR wt (n=222) Squamous (n=54)</td>
<td>2.9 vs 2.4</td>
<td>0.72</td>
<td>8.2 vs 5.4</td>
<td>0.78</td>
<td>15 vs 3</td>
<td>5% FN</td>
</tr>
<tr>
<td>Thatcher et al. JCO 2014 (Suppl)</td>
<td>Cisplatin-Gemcitabine ± Necitumumab (Mab Against EGFR) N=545, ALL SQUAMOUS!</td>
<td>11.5 vs 9.9</td>
<td><strong>0.84 (P=0.012)</strong></td>
<td></td>
<td></td>
<td>11% ° 3 diarrhoea</td>
<td></td>
</tr>
</tbody>
</table>

HR for PFS: Hazard Ratio for Progression-Free Survival
HR for OS: Hazard Ratio for Overall Survival
ORR: Objective Response Rate
Safety profile: Grade ≥ 3 AEs

**BR.21**
- Erlotinib vs placebo (n=727)
- Squamous (n=222)

**ZEST**
- Vandetanib vs erlotinib (n=1240)
- Squamous (n=272)

**BETA**
- Erlotinib + bev vs erlotinib (n=636)
- Squamous (n=28)

**TITAN**
- Doce/pem vs erlotinib (n=304)
- Squamous (n=154)

**SUN1087**
- Sunitinib + erlotinib vs erlotinib (n=960)
- Squamous (n=270)

**TAILOR**
- Doce vs erlotinib, EGFR wt (n=222)
- Squamous (n=54)

**Thatcher et al. JCO 2014 (Suppl)**
- Cisplatin-Gemcitabine ± Necitumumab (Mab Against EGFR)
- N=545, ALL SQUAMOUS!
## Second-line trials with FGFR, RET and VEGFR TKIs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target</th>
<th>Treatment</th>
<th>Median PFS (mo)</th>
<th>HR for PFS</th>
<th>Median OS (mo)</th>
<th>HR for OS</th>
<th>ORR (%)</th>
<th>Safety profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZODIAC</td>
<td>RET VEGFR</td>
<td>Vandetanib + docetaxel vs docetaxel(n=727)</td>
<td>4.0 vs 3.2</td>
<td>0.79</td>
<td>10.6 vs 10.0</td>
<td>0.91</td>
<td>17 vs 10</td>
<td>9% FN</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>Squamous (n=344)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZEAL</td>
<td>RET VEGFR</td>
<td>Vandetanib + pem vs pem (n=1391)</td>
<td>4.1 vs 2.8</td>
<td>0.86</td>
<td>10.5 vs 9.2</td>
<td>0.86</td>
<td>19 vs 8</td>
<td>52% grade ≥ 3 AEs</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>Squamous (n=114)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LUME-</td>
<td>FGFR VEGFR</td>
<td>Nintedanib + doce vs doce (n=1314)</td>
<td>3.4 vs 2.7</td>
<td>0.79</td>
<td>10.1 vs 9.1</td>
<td>0.94</td>
<td>4.4 vs. 3.3</td>
<td>&gt;70% grade ≥ 3 AEs; 7% FN</td>
</tr>
<tr>
<td>Lung 1</td>
<td>PDGFR</td>
<td>Squamous (n=487)</td>
<td>2.9 vs 2.6</td>
<td>0.77</td>
<td>8.6 vs 8.7</td>
<td>1.01</td>
<td>4.7 vs. 2.2</td>
<td></td>
</tr>
<tr>
<td>REVEL</td>
<td>VEGFR</td>
<td>Ramucimurab + doce vs doce (n=1253)</td>
<td>4.5 vs 3.0</td>
<td>0.76</td>
<td>10.5 vs 9.1</td>
<td>0.86</td>
<td>23.0 vs 13.6</td>
<td>&gt;70% grade ≥ 3 AEs; 16% FN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous (n=328)</td>
<td>4.2 vs 2.7</td>
<td>0.76</td>
<td>9.5 vs 8.2</td>
<td>0.88</td>
<td>26.7 vs 10.5</td>
<td></td>
</tr>
</tbody>
</table>

Herbst RS et al. The Lancet Oncology (2010); 11(7):619-626
Garon E et al Lancet Oncology (2014):epub

FN: febrile neutropenia
The FGFR-mediated pathway in SqCC

- Amplified in 12% of SqCC cases (TCGA data)
- Preclinical efficacy evidence for cediranib, nintedanib, pazopanib and ponatinib
- LUME-LUNG-1 study (phase III in 2nd line: 42.1% with SqCC): Docetaxel+nintedanib vs Docetaxel plus placebo
- Disease control rate superior to SqCC compared to ADC: 49.3% vs 35.5% (p<0.001)
- HR for PFS identical in both groups (HR=0.77)
- Surprisingly, OS favored the ADC group...
- Ponatinib (NCT01761747) and Pazopanib (NCT01208064) in phase II ongoing

Other molecular targeted agents under investigation in advanced SqCC

<table>
<thead>
<tr>
<th>Target</th>
<th>Frequency</th>
<th>Drug</th>
<th>Phase</th>
<th>RESULTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF1R</td>
<td>Mutated 4-6%</td>
<td>Figitumumab</td>
<td>II-III</td>
<td>Phase III</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>MET</td>
<td>Amplified 6%</td>
<td>Onartuzumab + Erlotinib</td>
<td>II-III</td>
<td>Phase III</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Randomized</td>
<td>phase II Pacltaxel-Carbo ± Onartuzumab Ongoing (NCT01519804)</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplified 8-10%</td>
<td>Sunitinib</td>
<td>I-II</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>CDK4/6</td>
<td>Mutated 15%</td>
<td>Palbociclib</td>
<td>II</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>PARP</td>
<td></td>
<td>Veliparib</td>
<td>II Randomized</td>
<td>HR=0.72 for OS Ramalingam et al, ESMO 2014</td>
<td>Phase III Pacltaxel-Carbo ± Veliparib Ongoing (NCT01560104)</td>
</tr>
</tbody>
</table>

Modified from Beck JT et al Cancer Treatment Reviews 2014
B. MAPK-MEK-mediated pathway and SCC

- Most patients with SqCC are current or ex-smokers
- **KRAS** mutations associated with tobacco use
- Inhibition of signaling by downstream MEK inhibition can reverse resistance in KRAS mutant cells

**BUT:** **KRAS** mutations are rare in SqCC! (6% in the west, 1.8% in Asia)

*Califano et al. Cancer Treatment Reviews 2015 (in press)*
## C: PI3K-Akt-mTOR pathway and SCC

<table>
<thead>
<tr>
<th>Molecule Mutated/</th>
<th>Frequency</th>
<th>Drug</th>
<th>Phase</th>
<th>RESULTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI3KCA</td>
<td>Mut 6.5%</td>
<td>Buparsilib GDC-0032</td>
<td>II</td>
<td>II</td>
<td>Pending</td>
</tr>
<tr>
<td></td>
<td>Copy No gain &gt;20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKT</td>
<td>Mut 5%</td>
<td>Several small molecules in early clinical development</td>
<td>I-II</td>
<td></td>
<td>Pending</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mut 4%</td>
<td>Dasatinib</td>
<td>I</td>
<td></td>
<td>Pending</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mut 15%</td>
<td>PI3KCA inhibitors</td>
<td>II</td>
<td></td>
<td>Pending</td>
</tr>
</tbody>
</table>

*Modified from Beck JT et al Cancer Treatment Reviews 2014*
D. SCC of the lung is a highly mutated tumour: Potentially immunogenic

Mean rate of somatic exonic mutations: 8.1 per Megabase

Nivolumab: CA209-063 (CheckMate 063) Study Design

**Endpoints**

**Primary:**
- Confirmed ORR* (IRC assessed)

**Secondary:**
- Confirmed ORR* (investigator assessed)

**Exploratory:**
- Safety and tolerability
- PFS/OS
- PD-L1 expression and efficacy

**Study Design**

- **Stage IIIB/IV SQ NSCLC**
- ≥2 prior systemic therapies
- ECOG 0–1

(N = 140 screened)

- Planned to treat approximately 100 patients
  - Expected ORR of 10–50%, with 20% maximum width of exact 2-sided 95% confidence interval
- Assessments (RECIST v1.1) performed at week 8 and Q6W

- Nivolumab 3 mg/kg IV Q2W until PD or unacceptable toxicity

(N = 117)

S. Ramalingam et al. ASCO 2014

15-18 April 2015, Geneva, Switzerland

Further checks: DOR = duration of response; IRC = independent radiology review committee; IV = intravenous; ORR = objective response rate; PD = progressive disease.
Median OS, months (95% CI): 8.2 (6, 11)

1-year OS rate, % (95% CI): 41 (32, 50)

Number of events: 72/117

Median follow-up for survival: 8 months (range, 0–17 months)

15-18 April 2015, Geneva, Switzerland
Phase 3, Open-Label Randomized Trial of Nivolumab vs. Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC) (CA209-017)

**Phase 3 Trial**
Stage IIIB/IV or recurrent squamous cell NSCLC
N=264

**Primary Endpoints**
- ORR
- OS

**Secondary Endpoints**
- PFS
- ORR and OS in PD-L1+ vs. PD-L1− subgroups
- DOR (IRC assessed)
- QoL

**Key Eligibility Criteria**
- ≥ 18 years of age
- Stage IIIB/IV squamous cell NSCLC or recurrent disease following RT or surgical resection
- Prior Platinum-containing chemotherapy
- ECOG PS ≤ 1
- Formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation

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**Co-Primary Objective Response Rate (ORR) & Overall Survival (OS)**

**Study Positive:**
mOS 9.2m vs 6m, HR: 0.59
March 2015: FDA Approval for 2nd line Squamous NSCLC
## Immunotherapy in SqCC: Main ongoing trials

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DESIGN</th>
<th>Phase</th>
<th>TRIAL NAME</th>
<th>Clinicaltrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (BMS)</td>
<td>Paclitaxel-Carboplatin ± Ipilimumab</td>
<td>III</td>
<td>NCT01285609</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (MSD) Anti-PD1</td>
<td>Chemo backbone ± Pembrolizumab</td>
<td>II-III</td>
<td>KEYNOTE 010 KEYNOTE 024</td>
<td>NCT01905657 NCT0214738</td>
</tr>
<tr>
<td>MEDI4736 (AZ) Anti-PDL1</td>
<td>Chemo backbone ± MEDI4736</td>
<td>II-III</td>
<td>ATLANTIC PACIFIC</td>
<td>NCT02087423 NCT 02344129</td>
</tr>
<tr>
<td>MPDL3280a (GENETECH)</td>
<td>Docetaxel vs MPDL3280A In 2nd line</td>
<td>III</td>
<td>NCT02008227</td>
<td></td>
</tr>
</tbody>
</table>
Towards the future: The “umbrella” study concept

• **LUNGSCAPE** and **SPECTALUNG** initiatives in Europe (ETOP, ESMO and EORTC)

• **LUNGMAP** initiative in USA (MDACC): The Master-Lung-1 Protocol for 2nd-line treatment of SCC (SWOG S1400)
  - PIK3CA mut ➔ Chemotherapy + PIK3 inhibitor
  - CCND1 mut ➔ CDK4/6 inhibitor
  - FGFR ampl ➔ FGFR inhibitor
  - c-MET ampl ➔ HGF inhibitor + erlotinib
  - PDL1 (+) IHC ➔ MEDI4736 (anti-PDL1 mAb)

*Herbst RS et al Clin Cancer Res 2015*
Conclusions-Future challenges

- Exome sequencing reveals genetic heterogeneity, still discloses recurrent genetic alterations, some of which are targetable.
- Focus on Receptor Tyrosine kinases, cell cycle regulation, the PI3K-Akt pathway and immune checkpoint regulation.
- OS benefit seen with ramucirumab, necitumumab, cetuximab, erlotinib and nivolumab.
- Special emphasis on immune checkpoint inhibition (recent FDA approval of Nivolumab in 2nd-line setting of SCC).
- SCC of the lung may not be looked at as the “neglected sibling” of lung ADC anymore!