SYSTEMIC THERAPY OF NON-SMALL CELL LUNG CANCER: 2017

LUNG CANCER STATISTICS
- 2016
- US 225,200 cases
- 160,000 deaths
- 5 year survival (stage IV) 5%
- Up to 69% of patients with potentially actionable mutation Tsao et al J Thorac Oncol 11;613, 2016

PENINSULA REGIONAL ONCOLOGY AND HEMATOLOGY DATA (STAGE IV)
- 2013 - 2015
- 187 patients
- Adenocarcinoma 87 (46.2%)
- Squamous cell 31 (16.4%)
- Large cell 14 (7.5%)
- Small cell 42 (22.3%)
- Others 14 (7.5%)
NUMBER OF TREATMENT REGIMENS FOR STAGE IV LUNG CANCER AT PRMC

- 0 67 (35.8%)
- 1 81 (43.3%)
- 2 36 (19.3%)
- 3 3 (1.6%)

SELECTION OF TREATMENT

- Efficacy
- Toxicity
- Cost
- Convenience to patient

CASES

- HS
- 45 yo woman non smoker
- Cough x 2 months
- Xray mass in right lung
- CT 10 cm mass – bronch Bx Adenocarcinoma
- Brain MRI – Met
- Stereotactic Radiation to brain
**HS**

- July 2016 starts Carboplatin + Pemetrexed
- Ordered path for EGFR, ALK, ROS1 - insuff
- After 2 cycles growth -
- Started Nivolumab 11/2/16
- Progression after 3 cycles
- Deceased December 28th 2016

**CASE 2**

- RG
- 63 yo woman - former smoker
- Dxed adenocarcinoma lung 2008
- Surgical resection soon after dxed with bone mets
- Started Carboplatin + Pemetrexed + Bev with response
- Maintenance Bev
- Progression
- Pt’s own initiative - discovered EGFR mut
- Started Erlotinib
- Response for about 18 months
- Developed Adrenal met - rads
- Started Afatinib
RG(3)

- Breast mets – s/p mastectomy followed by rads.
- 2nd Breast met. – s/p mastectomy
- No systemic therapy
- Progression of disease
- Started Osimertinib on trial (L858R mut +)

LUNG CANCER TREATMENT

- Surgery
- Radiation Therapy
- Chemotherapy
- Targeted Therapy
- Immunotherapy

SYSTEMIC THERAPY

- 1st line – Platinum doublets
- 2nd line Docetaxel
- 3rd line other single agents
- Comfort care
HEALTH CARE EXPENDITURE IN LUNG CANCER PATIENTS
VERA-LLONCH ET AL, BIOMED CENTRAL 11;305, 2011

- 4068 patients
- Mean age 65 years
- Median f/u 334 days
- Average 1.5 hospital admissions
- 8.9 total admission days
- 69 physician office visits
- Cumulative Health Care Costs $125,849
  - Outpatient 34%
  - Inpatient 20%
  - Chemotherapy 22%
  - Other meds 24%

Pathway alterations in lung adenocarcinoma.

CYTOTOXIC THERAPY

1st line - Platinum based doublets
- platinum/taxane, platinum/gemcitabine
- platinum/pemetrexed + bev, ac
- Platinum/Vinorelbine
- Platinum/etoposide
SCREENING FOR EGFR MUTATIONS IN LUNG CANCER

- Spanish Trial, 2009
- EGFR mutated: 350 out of 2105 (16.6%)
- Women 69.7%
- Never smokers 66.6%
- Adenocarcinoma 80.9%
- Mutations: del in exon 19 (62.2%) and L858R (37.8%)
- Median PFS 14 mths
- OS 27 mths

Rosell et al. NEJM 361; 958-67, 2009
RESISTANCE TO TYROSINE KINASE INHIBITOR
CASE REPORT

- Lorlatinib resistance to Crizotinib in patient with Cysteine to Tyrosine at (C1156Y).
- Later resistance to Lorlatinib created mutation at L1198F which enabled re-sensitization to Crizotinib.

Shaw et al NEJM 374; 54, 2016

OSIMERTINIB AS EGFR INHIBITOR

- AURA3 trial (phase 3)
- 2nd line EGFR tyrosine kinase inhibitor
- Specific for EGFR with T790M mutation
- Osimertinib vs Plat/Pemetrexed
- Osim     Plat/Pem     p
- PFS 10.1 mths  4.4 mths  <0.001
- CNS  8.5 mths  4.2 mths
- ORR  71%     31%     <0.001
- G3/4  23%     47%

Mok et al NEJM

**IMMUNOTHERAPY (1)**

CheckMate 057 phase 3
Previously treated advanced non squamous lung cancer
Nivolumab 3g/kg v Docetaxel 75 mg/m2
Nivolumab every 2 weeks

<table>
<thead>
<tr>
<th></th>
<th>Niv</th>
<th>Doc</th>
<th>p</th>
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<tbody>
<tr>
<td>OS</td>
<td>12.2</td>
<td>9.4</td>
<td>-</td>
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<tr>
<td>OS (1year)</td>
<td>51%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>(18m)</td>
<td>39%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>19%</td>
<td>12%</td>
<td>0.02</td>
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<tr>
<td>PFS</td>
<td>2.3m</td>
<td>4.2 m</td>
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<tr>
<td>G3/4AE</td>
<td>10%</td>
<td>54%</td>
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</table>

Borghaei et al. NEJM, 373;1627, 2015.
IMMUNOTHERAPY (2)

- **OAK trial** phase 2
- Atezolizumab (1200 mg) vs Docetaxel (75 mg/m2)
- Every 3 weeks
- ECOG 0 - 1

<table>
<thead>
<tr>
<th></th>
<th>Atez</th>
<th>Doc</th>
<th>p value</th>
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<tbody>
<tr>
<td>OS</td>
<td>13.8 m</td>
<td>9.6 m</td>
<td>0.0003 (HR 0.73)</td>
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<tr>
<td>TC (i)</td>
<td>15.7</td>
<td>10.3</td>
<td>0.0102 (HR 0.74)</td>
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<tr>
<td>TC (ii)</td>
<td>12.6</td>
<td>8.9</td>
<td>0.75 (HR 0.75)</td>
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<tr>
<td>TC (iii)</td>
<td>20.5</td>
<td>8.9</td>
<td>0.41 (HR 0.41)</td>
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</table>

- Gd3/4AE   15% vs 43%


IMMUNOTHERAPY (3)

- **KEYNOTE-024** phase 3
- 1st line therapy for metastatic NSCLC
- At least 50% exp PD-L1
- No EGFR mut or ALK translocation
- 200 mg/3weeks vs Plt doublet
- Crossover permitted

<table>
<thead>
<tr>
<th></th>
<th>Pemb</th>
<th>Chemo</th>
<th>p (HR)</th>
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<tbody>
<tr>
<td>PFS</td>
<td>10.3 m</td>
<td>6.0 m</td>
<td>0.50</td>
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<tr>
<td>OS (6m)</td>
<td>80.2%</td>
<td>72.4%</td>
<td>0.005 (0.60)</td>
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<tr>
<td>RR</td>
<td>44.8%</td>
<td>27.8</td>
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<tr>
<td>MDR</td>
<td>not reached</td>
<td>6.3 m</td>
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<tr>
<td>G3-5AE</td>
<td>26.6%</td>
<td>53.3%</td>
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IMMUNOTHERAPY IN PREVIOUSLY TREATED PATIENTS WITH NSCLC

- **KEYNOTE 010 trial**
- PD-L1 expression – at least 50%
- Pembrolizumab vs Docetaxel

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<thead>
<tr>
<th></th>
<th>Pemb</th>
<th>Doc</th>
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<tbody>
<tr>
<td>2mg/kg</td>
<td>14.9 vs 8.2 months</td>
<td>HR 0.54, p =0.002</td>
</tr>
<tr>
<td>10mg/kg</td>
<td>17.3 vs 8.2 months</td>
<td>0.5 &lt;0.0001</td>
</tr>
<tr>
<td>3/4AE(2)</td>
<td>13% vs 35%</td>
<td></td>
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<tr>
<td>3/4AE(10)</td>
<td>16 %</td>
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CHEMOTHERAPY + IMMUNOTHERAPY

- KEYNOTE 021 phase 2
- Stage IIIb and IV Adenocarcinoma Lung
- Pembrolizumab + Carbo/Pemetrexed

OR 55% 29%
G 3/4AE 39% 26%

Langer et al. Lancet Oncol 11:1497-1508
Higher toxicity in combination

OTHER DRUGS IN TARGETED THERAPY IN NSCLC

- Crizotinib in ALK+ Lung Ca. NEJM 368; 2385, 2013
- Crizotinib in ROS1. NSCLC. NEJM 371,1963, 2014
- Ceritinib in ALK+ NSCLC. NEJM 370; 1189, 2014

TREATMENT SEQUENCE 2017

- Biomarker testing - EGFR, ALK, ROS1, PD-L1
- Platinum doublet vs Pembrolizumab
- Immunotherapy - Nivolumab
- Docetaxel
- Erlotinib
**TREATMENT SEQUENCE FOR TARGETED THERAPY**

- Biopsy – mutation
- Erlotinib/Afatinib/Gefitinib
- Liquid biopsy for new mutations
- T790M mutation
- Osimertinib

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**Figure 2** Schematic representation of the current paradigm for the pharmacological management of advanced-stage NSCLC

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**Figure 3** Potential algorithm for incorporating chemotherapies, immunotherapy and targeted therapies into the management of NSCLC in the future

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A. overall schema for Lung-MAP.

DATA SHARING
- Cancer LinQ
- Moonshot project
- 3D-tumor atlas

OUTLINE FOR A TREATMENT PATHWAY
- Drug selection
- Patient selection
- Avoid Hospital admission
SUMMARY

- Importance of Biomarkers
- Rapid testing
- Sufficient tissue
- Immuno-competent patient
- Reduce Hospital Admissions
- When not to treat
- When to stop treating

Doctors are men who prescribe medicines of which they know little, to cure disease of which they know less, in human beings of which they know nothing

Voltaire