Overview of Systemic Therapy for Lung Cancer

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Medical Oncologist
Western Health
Peter Mac
Talk Summary

• Small cell lung cancer
• Non-small cell lung cancer
  – Adjuvant
  – Metastatic
    • Targeted therapy
    • Immunotherapy
    • Patient subsets
The Problem
Lung Cancer Survival

5-year relative survival (%)

Year

1984–1988
1989–1993
1994–1998
1999–2003
2004–2008
2009–2013

Males
Females
Persons

Australian Institute of Health and Welfare Data
Small Cell Lung Cancer
Small Cell Lung Cancer

• Limited Stage
  – Chemotherapy and chest radiation
  – Standard 1\textsuperscript{st} line therapy:
    • Cisplatin and Etoposide
    • Carboplatin and Etoposide
  – Consider prophylactic cranial irradiation
    • Absolute survival benefit of 5% at 3 years
Small Cell Lung Cancer

- Extensive Stage
  - Chemotherapy
  - Standard 1st line therapy:
    - Carboplatin and Etoposide
  - Consider prophylactic cranial irradiation
  - Consider consolidation radiation to chest
    - 2 year survival 13 vs 3%*

Small Cell Lung Cancer

- Relapsed disease > 6 months
  - Retreat with carboplatin and etoposide
- Relapsed disease < 6 months
  - CAV (OCA): Cyclophosphamide, Doxorubicin, Vincristine
  - Topotecan
  - Irinotecan
  - Paclitaxel
  - etc
The Notch Signalling Pathway: Target in Small Cell Lung Cancer
Rovalpituzumab Tesirine (Rova-T™, SC16LD6.5)
A delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC)

Cathepsin B - cleavable linker

Anti-DLL3 mAb (SC16)

Drug-to-antibody ratio = 2

Pyrrolobenzodiazepine (PBD) dimer toxin (D6.5 / SC-DR002)
**Rovalpituzumab Tesirine in R/R SCLC: Phase I Study**

**Design**

- **First-in-human study**

- **Dose Escalation**
  
  - SCLC, PD after 1 or 2 prior lines of therapy; ECOG PS 0-2 (N = 74)
  
  - **Rovalpituzumab tesirine**
    - 0.05, 0.1, 0.2, * 0.4, † or 0.8 ‡ mg/kg Q3W
    - 0.3, * or 0.4 mg Q6W

- **RP2D established at 0.3 mg/kg Q6W x 2, with retreatment at progressive disease**

- **0.2-0.4 mg/kg active doses pooled for current analysis**

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*Expansion cohorts. †Cumulative toxicity (serosal effusions). ‡2 DLT observed.


Slide credit: clinicaloptions.com
**Rovalpituzumab Tesirine in R/R SCLC: Treatment-Emergent AEs**

<table>
<thead>
<tr>
<th>Treatment-Emergent AE, %</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual treatment-emergent AE in ≥ 15% of pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>88</td>
<td>38</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>4</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Group events with highest grade 3 incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Serosal effusions*</td>
<td>35</td>
<td>11</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>49</td>
<td>8</td>
</tr>
</tbody>
</table>

*Included pleural or pericardial effusion, ascites, or “capillary leak syndrome” (serosal effusions, peripheral edema, and/or hypoalbuminemia).
Rovalpituzumab Tesirine in R/R SCLC: Response Rates per Investigator*

*Evaluable pts receiving active doses of rovalpituzumab tesirine (0.2-0.4 mg/kg).


Slide credit: clinicaloptions.com
Rovalpituzumab Tesirine in R/R SCLC: Response Rates in 2nd and 3rd Lines

Second Line

- N Evaluable DLL3: 32 All, 14 ≥ 50%
- ORR: 13%, 29%
- CBR: 72%, 86%

Third Line

- N Evaluable DLL3: 28 All, 12 ≥ 50%
- ORR: 25%, 50%
- CBR: 64%, 92%


Slide credit: clinicaloptions.com
**Rovalpituzumab Tesirine in R/R SCLC: OS**

![Graph showing OS (OS %) vs. Mos (months) with Censored data points.](image)

- **0.2-0.4 mg/kg**
- **Censored**
- **DLL3 ≥ 50%**
- **All**

**Table: DLL3 Status vs. OS**

<table>
<thead>
<tr>
<th>DLL3 Status</th>
<th>Median, Mos</th>
<th>1 Yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50%</td>
<td>5.8</td>
<td>32</td>
</tr>
<tr>
<td>All</td>
<td>4.6</td>
<td>18</td>
</tr>
</tbody>
</table>

*Pts receiving active doses of rovalpituzumab tesirine (0.2-0.4 mg/kg).


Slide credit: clinicaloptions.com
Small Cell: Rova-T Phase I

• Conclusions
  – Early results are promising, but phase I only
  – Further studies are ongoing
  – DLL3 expression appears to be the first predictive biomarker in small cell lung cancer
Immunotherapy for Small Cell

• Will be discussed in the immunotherapy section
Non-Small Cell Lung Cancer
Adjuvant Therapy
Adjuvant Chemotherapy for NSCLC

• A number of trials and the LACE meta-analysis have shown a benefit of adjuvant chemotherapy in NSCLC
• Benefit is greater for higher stage patients (stage III vs II)
JBR-10 Study: Overall survival comparisons by treatment arm: (A) for all randomly assigned patients; (B) for patients with stage II disease; (C) for patients with stage IB (T2N0) disease.

Butts C A et al. JCO 2010;28:29-34
Adjuvant Chemotherapy: Choice of Regimen

- Cisplatin and vinorelbine doublet
  - Standard regimen at my institutions
  - Incorporates a 3rd generation drug (vinorelbine)
  - Used in large studies in Western populations:
    - JBR 10
    - ANITA
Adjuvant Therapy: EGFR TKIs
EGFR TKIs: Adjuvant Therapy

• No phase III adjuvant studies with large numbers of EGFR mutation positive patients
• BR19 adjuvant gefitinib study closed early
  ▪ Mutation positive subgroup too small to draw meaningful conclusions
• RADIANT adjuvant erlotinib study was negative for its primary endpoint
BR19: (A) Disease-free survival.  (B) Overall survival.

Goss G D et al. JCO 2013;31:3320-3326
RADIANT: Adjuvant Erlotinib
Adjuvant Therapy: Conclusion

• There is no evidence to support the use of adjuvant EGFR TKIs outside the setting of a clinical trial

• Adjuvant chemotherapy should be offered to:
  ▪ Fit patients (ECOG 0 or 1)
  ▪ Stage II or III resected NSCLC
  ▪ Regardless of mutation status
Metastatic NSCLC
Kaplan–Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

Strategies to Improve Outcomes

• Treat based on histology (adenocarcinoma)
• Maintenance Therapy
• Molecular targets (EGFR, ALK etc)
• Immunotherapy
• Anti-angiogenesis
• Strategies for ECOG PS 2 patients
• Strategies for elderly patients
Strategies to Improve Outcomes

• Treat based on histology (adenocarcinoma)
• Maintenance Therapy
• Molecular targets (EGFR, ALK etc)
• Immunotherapy
• Anti-angiogenesis
• Strategies for ECOG PS 2 patients
• Strategies for elderly patients
Overall Survival of ALIMTA/cisplatin vs. GEMZAR/cisplatin – Overall Population

<table>
<thead>
<tr>
<th></th>
<th>ALIMTA + Cisplatin (N=862)</th>
<th>GEMZAR + Cisplatin (N=863)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>10.3 mos (9.8, 11.2)</td>
<td>10.3 mos (9.6, 10.9)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>0.94 (0.84, 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

p<0.001*

*Noninferiority p-value; Clinical Trials Registry available at www.clinicalstudyresults.org (accessed April 27, 2008).
Survival Advantage for ALIMTA/cisplatin for Patients with Adenocarcinoma

ALIMTA + Cisplatin (N=436)

GEMZAR + Cisplatin (N=411)

Median OS (95% CI)

12.6 mos

10.9 mos

Adjusted HR (95% CI)

0.84 (0.71, 0.99)

p=0.033*
Survival Advantage for GEMZAR/cisplatin in Patients with Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>ALIMTA + Cisplatin (N=244)</th>
<th>GEMZAR + Cisplatin (N=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI)</td>
<td>9.4 mos</td>
<td>10.8 mos</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>1.23 (1.00, 1.51)</td>
<td></td>
</tr>
<tr>
<td><strong>p=0.050</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Superiority p-value; ALIMTA [Summary of Product Characteristics]. Eli Lilly and Co; approved April 8, 2008.

Pemetrexed Mechanism of Action

**Diagram:**
- Pemetrexed inhibits
- **TS**, DHFR, GARFT
- Synthesis of pyrimidine nucleotides
- Synthesis of purine nucleotides
- Biosynthesis of DNA
- Biosynthesis of DNA and RNA
Response by TS Expression

A

B

C

P = 0.038

P = 0.014

Time after initiation of permetrexed (months)
Response by TS Expression

• As a group, Squamous carcinomas are more likely to over-express TS
• This likely explains the lack of response to pemetrexed in squamous carcinoma
1st Line Therapy in Australia

- Platinum-Pemetrexed is not PBS listed
  - Not expensive since Pemetrexed out of patent
- Good choices for doublets include:
  - Carboplatin-Gemcitabine
  - Cisplatin-Gemcitabine
  - Carboplatin-Paclitaxel
Strategies to Improve Outcomes

- Treat based on histology (adenocarcinoma)
- Maintenance Therapy
- Molecular targets (EGFR, ALK etc)
- Immunotherapy
- Anti-angiogenesis
- Strategies for ECOG PS 2 patients
- Strategies for elderly patients
Maintenance Therapy

• Defined as therapy continued beyond first line therapy in the absence of progression

• Both “switch” and “continuation” maintenance strategies have been used
Maintenance Therapy: Pemetrexed

• Both the JMEN ("switch") and PARAMOUNT ("continuation") studies showed an overall survival benefit for maintenance pemetrexed in non-squamous NSCLC

• Other benefit of pemetrexed is favourable toxicity profile
Maintenance Therapy

• Other studies have demonstrated a PFS benefit from maintenance therapy:
  ▪ Docetaxel (Fidias, JCO 2009)
  ▪ Gemcitabine or erlotinib (IFCT-GFPC 0502)
  ▪ Erlotinib (SATURN)
    • Overall survival benefit also seen
Maintenance Therapy

• Pemetrexed is the most commonly used maintenance therapy based on:
  ▪ Results in adenocarcinoma patients
  ▪ Toxicity profile

• EGFR TKIs are not PBS listed for maintenance therapy in Australia
Strategies to Improve Outcomes

- Treat based on histology (adenocarcinoma)
- Maintenance Therapy
- Molecular targets (EGFR, ALK etc)
- Immunotherapy
- Anti-angiogenesis
- Strategies for ECOG PS 2 patients
- Strategies for elderly patients
Actionable Targets in Lung Adenocarcinomas

1999: Unknown 75%

2004: Unknown 60%

2005-2012: Unknown 35%

KRAS, EGFR, RET, ROS1, MEK, HER2, MET, BRAF, ALK, PIK3CA

Kris M et al. IASLC 2012 Targeted Therapies Conference
Survival of Patients with Drivers: Targeted Therapy vs No Targeted Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver, no targeted therapy (A)</td>
<td>313</td>
<td>2.4 years (1.8 to 2.9)</td>
</tr>
<tr>
<td>No driver (B)</td>
<td>361</td>
<td>2.1 years (1.8 to 2.5)</td>
</tr>
<tr>
<td>Driver, targeted therapy (C)</td>
<td>264</td>
<td>3.5 years (3.2 to 4.6)</td>
</tr>
</tbody>
</table>

Kris JAMA 2014
EGFR
Molecular anatomy of EGFR-driven cellular signaling.

IPASS: Progression-free survival in EGFR-mutation + vs - patients

**EGFR mutation-positive**
- **Gefitinib** (n=132) vs **Carboplatin/paclitaxel** (n=129)
  - HR (95% CI) = 0.48 (0.36, 0.64)
  - p<0.0001
  - No. events gefitinib, 97 (73.5%)
  - No. events CIP, 111 (88.0%)

**EGFR mutation-negative**
- **Gefitinib** (n=91) vs **Carboplatin/paclitaxel** (n=86)
  - HR (95% CI) = 2.85 (2.05, 3.98)
  - p<0.0001
  - No. events gefitinib, 88 (96.7%)
  - No. events CIP, 70 (82.4%)

**Treatment by subgroup interaction test, p<0.0001**

Incidence of EGFR mutation: 261/437 = 59.7%  
Mok et al 2008
# First-line trials of EGFR tyrosine kinase inhibitors vs. chemotherapy in pts with EGFR mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>EGFR TKI</th>
<th>Comparator</th>
<th>N (Total)</th>
<th>EGFR mut-positive</th>
<th>Response rate (%)</th>
<th>Progression-free survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS¹,²</td>
<td>Gefitinib</td>
<td>Carboplatin/ paclitaxel</td>
<td>1217</td>
<td>261</td>
<td>71 vs 47 p=0.0001</td>
<td>9.5 vs 6.3 HR 0.48 (0.36–0.64)</td>
</tr>
<tr>
<td>First-SIGNAL³</td>
<td>Gefitinib</td>
<td>Gemcitabine/ cisplatin</td>
<td>309</td>
<td>42</td>
<td>85 vs 38 p=0.002</td>
<td>8.0 vs 6.3 HR 0.54 (0.27-1.10)</td>
</tr>
<tr>
<td>NEJ002⁴</td>
<td>Gefitinib</td>
<td>Carboplatin/ paclitaxel</td>
<td>224</td>
<td>224</td>
<td>74 vs 31 p&lt;0.001</td>
<td>10.8 vs 5.4 HR 0.30 (0.22–0.41)</td>
</tr>
<tr>
<td>WJTOG-3405⁵</td>
<td>Gefitinib</td>
<td>Cisplatin/ docetaxel</td>
<td>172</td>
<td>172</td>
<td>62 vs 32 p&lt;0.0001</td>
<td>9.2 vs 6.3 HR 0.5 (0.34–0.71)</td>
</tr>
<tr>
<td>OPTIMAL⁶</td>
<td>Erlotinib</td>
<td>Gemcitabine/ carboplatin</td>
<td>154</td>
<td>154</td>
<td>83 vs 36 p&lt;0.0001</td>
<td>13.1 vs 4.6 HR 0.16 (0.10–0.26)</td>
</tr>
<tr>
<td>EURTAC⁷</td>
<td>Erlotinib</td>
<td>Chemotherapy</td>
<td>173</td>
<td>173</td>
<td>58 vs 16</td>
<td>9.7 vs 5.2 HR 0.37 (0.25–0.54)</td>
</tr>
<tr>
<td>LUX-LUNG 3⁸</td>
<td>Afatinib</td>
<td>Pemetrexed/ cisplatin</td>
<td>345</td>
<td>345</td>
<td>56 vs 23 p&lt;0.0001</td>
<td>11.1 vs 6.9 HR 0.58 (0.43–0.78)</td>
</tr>
<tr>
<td>LUX-LUNG 6⁹</td>
<td>Afatinib</td>
<td>Carboplatin/ cisplatin</td>
<td>364</td>
<td>364</td>
<td>67 vs 23 p&lt;0.0001</td>
<td>11.0 vs 5.6 HR 0.28 (0.20–0.39)</td>
</tr>
</tbody>
</table>

Mechanisms of resistance to 1\textsuperscript{st} and 2\textsuperscript{nd} Generation EGFR TKIs
The relative frequencies of the various mechanisms of acquired resistance.

- **MET amplification**: 3%
- **Small cell + MET**: 1%
- **Small cell**: 1%
- **Small cell + T790M**: 2%
- **MET + T790M**: 3%
- **HER2**: 8%
- **HER2 + T790M**: 4%
- **Unknown**: 18%
- **T790M**: 60%

Third Generation EGFR TKIs with activity against T790M

<table>
<thead>
<tr>
<th>Third generation EGFR TKIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib (AZD9291)</td>
</tr>
<tr>
<td>Rociletinib (CO-1686)</td>
</tr>
<tr>
<td>HM61713</td>
</tr>
<tr>
<td>EGF816</td>
</tr>
<tr>
<td>ASP8273</td>
</tr>
</tbody>
</table>

Covalent inhibitors

- Inhibit T790M and activating mutations
- Variable activity against wild type EGFR
Randomised Phase III study of osimertinib vs platinum-pemetrexed for \textit{EGFR T790M}-positive advanced NSCLC (AURA3)

The \textit{NEW ENGLAND JOURNAL of MEDICINE}

\textbf{Original Article}

Osimertinib or Platinum–Pemetrexed in \textit{EGFR T790M}–Positive Lung Cancer

AURA3 study design

Key eligibility criteria
• ≥18 years (≥20 years in Japan)
• Locally advanced or metastatic NSCLC
• Evidence of disease progression following first-line EGFR-TKI therapy
• Documented EGFRm and central confirmation of tumour EGFR T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
• WHO performance status of 0 or 1
• No more than one prior line of treatment for advanced NSCLC
• No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
• Stable asymptomatic CNS metastases allowed

N = 419

Endpoints
Primary:
• PFS by investigator assessment (RECISTv1.1)
Secondary and exploratory:
• Overall survival
• Objective response rate
• Duration of response
• Disease control rate
• Tumour shrinkage
• BICR-assessed PFS
• Patient reported outcomes
• Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

Osimertinib (n=279)
80 mg orally QD

Platinum-pemetrexed (n=140)
Pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² Q3W for up to 6 cycles + optional maintenance pemetrexed#
• Analysis of PFS by BICR was consistent with the investigator-based analysis: HR **0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

• The objective response rate: **osimertinib** 71% vs. **platinum therapy plus pemetrexed** 31%; (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; P<0.001).
PFS benefit in AURA3 patients with CNS metastases at baseline.

With CNS metastases

- **Osimertinib (n=93)**
  - Median PFS, months (95% CI): 8.5 (6.8, 12.3)
- **Platinum-pemetrexed (n=51)**
  - Median PFS, months (95% CI): 4.2 (4.1, 5.4)

**HR 0.32**
(95% CI 0.21, 0.49)

Without CNS metastases

- **Osimertinib (n=186)**
  - Median PFS, months (95% CI): 10.8 (8.3, 12.5)
- **Platinum-pemetrexed (n=89)**
  - Median PFS, months (95% CI): 5.6 (4.2, 6.8)

**HR 0.40**
(95% CI 0.29, 0.55)

**No. at risk**

- **Osimertinib**: 93, 80, 46, 27, 14, 4, 0, 0
- **Platinum-pemetrexed**: 51, 32, 9, 4, 2, 0, 0

**Months**

- **Osimertinib**: 186, 160, 116, 61, 36, 9, 0
- **Platinum-pemetrexed**: 89, 61, 35, 13, 5, 1, 0
Tumour or Plasma cfDNA positivity for T790M is predictive of tumour response to osimertinib

Tumour T790M positive (n=173)

ORR (95% CI): 62% (54, 70)

Plasma T790M positive (n=164)

ORR (95% CI): 63% (55, 70)

New paradigm

Acquired resistance to EGFR-TKI

- T790M positive
- T790M negative
- T790M unknown

Tumour T790M positive

- ORR (95% CI): 62% (54, 70)

Plasma T790M positive

- ORR (95% CI): 63% (55, 70)

Data cut-off: 1 May 2015

AURA3: T790M mutation is detected in plasma of ~50% of patients with T790M in tumour tissue

- Patients with tissue sample available at screening (n=756)

<table>
<thead>
<tr>
<th>Plasma ctDNA test results, n</th>
<th>Tissue T790M positive (n=399)</th>
<th>Tissue Ex19del positive (n=427)</th>
<th>Tissue L858R positive (n=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma positive</td>
<td>184</td>
<td>273</td>
<td>139</td>
</tr>
<tr>
<td>Plasma negative</td>
<td>175</td>
<td>60</td>
<td>67</td>
</tr>
<tr>
<td>No plasma test / invalid</td>
<td>37 / 3</td>
<td>91 / 3</td>
<td>47 / 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent agreement using tissue test as reference, % (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive percent agreement (sensitivity)</td>
</tr>
<tr>
<td>T790M</td>
</tr>
<tr>
<td>Ex19del</td>
</tr>
<tr>
<td>L858R</td>
</tr>
<tr>
<td>Negative percent agreement (specificity)</td>
</tr>
<tr>
<td>T790M</td>
</tr>
<tr>
<td>Ex19del</td>
</tr>
<tr>
<td>L858R</td>
</tr>
<tr>
<td>Overall concordance</td>
</tr>
<tr>
<td>T790M</td>
</tr>
<tr>
<td>Ex19del</td>
</tr>
<tr>
<td>L858R</td>
</tr>
</tbody>
</table>

- 51% sensitivity and 77% specificity for T790M detection using cobas tissue test as reference
- High sensitivity and specificity is observed for Exon 19 deletion and L858R

*Percent agreement of the cobas® plasma test with the cobas® tissue test. Positive percent agreement and negative percent agreement are used here as measures of test sensitivity and specificity, respectively, and calculated with invalid results excluded.

CI, confidence interval; Ex19del, Exon 19 deletion.
AURA-3 Conclusions

- Osimertinib now “officially” becomes the standard of care for patients with acquired resistance through T790M
- mPFS of 10.1m compared with 4.4m by platinum/PEM with hazard ratio of 0.30. ORR 71% vs 31% (P<0.001)
- Active in patients with brain metastases
- Low toxicity profile compared with platinum/PEM or 1-2Gen EGFR-TKI
- Rebiopsy (+/- liquid) increasingly important
- Future issues include;
  - Optimal sequence of different EGFR-TKIs (including 1st line osimertinib)
  - Strategy to cope with acquired resistance against osimertinib
ALK
FISH Assay for ALK Rearrangement*

*Assay is positive if rearrangements can be detected in ≥15% of cells
FISH = fluorescence in situ hybridization

1Shaw AT et al. J Clin Oncol 2009;27:4247-4253
**ALK Gene Rearrangements**

- Most common in younger nonsmokers with adenocarcinoma, adenosquamous carcinoma, and rarely SCC
- Frequency: 4% overall, 33% in EGFR-negative never-smokers
- Several ALK variants identified in NSCLC
- Testing
  - Vysis break apart FISH (> 15% cells with split signal in 50 nuclei scored); ALK IHC also approved
  - ALK next generation sequencing
- 3 agents now approved for ALK-positive NSCLC (first line and/or after progression)


Slide credit: clinicaloptions.com
PROFILE 1014: First-line Crizotinib vs Pemetrexed/Platinum* in Advanced NSCLC

- Phase III trial (N = 343) ALK-positive pts with nonsquamous NSCLC and no prior systemic treatment for advanced disease

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (n = 172)</th>
<th>Chemotherapy (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>10.9</td>
<td>7.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.35-0.60)</td>
<td></td>
</tr>
<tr>
<td><em>P value</em></td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>74</td>
<td>45</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>&lt; .001</td>
<td></td>
</tr>
</tbody>
</table>

*Carboplatin or cisplatin.

## PROFILE 1014: Select AEs of Any Cause With ≥ 5% Difference Between Treatment Groups

<table>
<thead>
<tr>
<th>AEs (≥ 20%, Either Arm), n (%)</th>
<th>Crizotinib (n = 171)</th>
<th>Chemotherapy (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Higher frequency (≥ 5% absolute difference) in crizotinib arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Vision disorder</td>
<td>122 (71)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>▪ Diarrhea</td>
<td>105 (61)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>▪ Edema&lt;sup&gt;c&lt;/sup&gt;</td>
<td>83 (49)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>▪ Vomiting</td>
<td>78 (46)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>▪ Constipation</td>
<td>74 (43)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>▪ Elevated transaminases</td>
<td>61 (36)</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Higher frequency (≥ 5% absolute difference) in chemotherapy arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Fatigue</td>
<td>49 (29)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>36 (21)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>▪ Stomatitis</td>
<td>24 (14)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>▪ Asthenia</td>
<td>22 (13)</td>
<td>0</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>15 (9)</td>
<td>0</td>
</tr>
</tbody>
</table>


Slide credit: [clinicaloptions.com](https://clinicaloptions.com)
J-ALEX: Alectinib vs Crizotinib as First-line Therapy for ALK-Positive NSCLC


Slide credit: clinicaloptions.com
## J-ALEX: Safety

<table>
<thead>
<tr>
<th>AEs (≥ 20%, Either Arm), n (%)</th>
<th>Alectinib (n = 103)</th>
<th>Crizotinib (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Constipation</td>
<td>36 (35.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (10.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (5.8)</td>
<td>0</td>
</tr>
<tr>
<td>AST increase</td>
<td>11 (10.7)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>9 (8.7)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (20.4)</td>
<td>0</td>
</tr>
<tr>
<td>Dyseusia</td>
<td>19 (18.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10 (9.7)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

- 8.7% alectinib discontinuations due to AE vs 20.2% for crizotinib
- 29.1% alectinib dose interruptions due to AE vs 74.0% for crizotinib


Slide credit: clinicaloptions.com
ASCEND-4: First-line Ceritinib Vs Chemotherapy for ALK-Positive NSCLC

- Randomized, global, open-label phase III study
- Primary endpoint: PFS

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>Ceritinib (n = 189)</th>
<th>Chemotherapy (n = 187)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>16.6</td>
<td>8.1</td>
<td>0.55</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>72.5</td>
<td>26.7</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>OIRR, %</td>
<td>72.7 (n = 22)</td>
<td>27.3 (n = 22)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

- Median DoR of 23.9 mos for pts treated with ceritinib
- Median PFS of 26.3 mos for pts without brain metastases at screening treated with ceritinib

Response to Ceritinib or Alectinib in Previously Treated ALK-Positive NSCLC

- Ceritinib (2014) and alectinib (2015) approved for pts with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib

Second-Generation ALK Inhibitor CNS Activity

*No previous ALK inhibitor.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brain ORR (%)</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib (750 mg/day)</td>
<td>63.0%*</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>36.0%</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>39.4%</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>58.8%*</td>
<td>17</td>
</tr>
<tr>
<td>Alectinib (600 mg BID)</td>
<td>75.0%</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>57.0%</td>
<td>35</td>
</tr>
<tr>
<td>Brigatinib (90 or 180 mg QD)</td>
<td>36.0%</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>67.0%</td>
<td>18</td>
</tr>
<tr>
<td>Lorlatinib (Various)</td>
<td>39.0%</td>
<td>18</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
Resistance to Second-Generation ALK TKIs

Ceritinib (N = 24)
- WT
- L1196M
- G1269A
- C1156Y
- G1202R
- I1171T/N/S
- S1206Y
- E1210K
- F1174C
- V1180L
- ≥ 2 ALK mutations
- ALK WT

Alectinib (N = 17)
- WT
- L1196M
- G1269A
- I1171T/N/S
- S1206Y
- E1210K
- F1174C
- V1180L
- G1202del
- ≥ 2 ALK mutations
- ALK WT

Brigatinib (N = 6)
- WT
- L1196M
- G1269A
- C1156Y
- G1202del
- ≥ 2 ALK mutations
- ALK WT

Lorlatinib Inhibits All Known Crizotinib-Resistance Mutations, Including ALK G1202R

Pt 1: ALK+ NSCLC
- Previously treated with crizotinib and ceritinib
- Local molecular testing after ceritinib with ALK G1202R
- Started lorlatinib at 75 mg QD
- Dose reduced to 50 mg QD
- Ongoing at > 16 mos

Pt 2: ALK+ NSCLC
- Previously treated with crizotinib and brigatinib
- Local molecular testing after brigatinib with ALK G1202R
- Started lorlatinib at 200 mg QD
- Dose reduced to 100 mg QD
- Ongoing at > 12 mos


Slide credit: clinicaloptions.com
Summary: ALK Driven NSCLC

- ALK testing by IHC should be standard for metastatic non-squamous, NSCLC
- Ceritinib and Crizotinib approved for 1\textsuperscript{st} line therapy in Australia
- Second-generation ALK inhibitors are active in CNS disease
- Sequential ALK inhibitors should be used if possible:
  - Always consider clinical trials in ALK positive patients
ROS1

- ROS1 is a tyrosine kinase
- Can fuse with various “partners”
- Fusion partners induce dimerisation and constitutive activation
**ROS1 Fusion**

- Most common in younger pts, never-smokers, adenocarcinoma, high-grade histology[^1]

- Frequency: 1.2% to 1.7% overall[^2]

- Several variants identified; clinical significance unknown[^3]
  - FIG-, CD74-, SCL34A2-, TPM3-, SDC4-, EZR-, LRIG3, KDEL2-, and CCDC6-

- Testing: Vysis break apart FISH (> 15% cells with split signal in 50 nuclei scored)[^4-^6]
  - ROS1 NGS, PCR, IHC (not validated)

- Crizotinib highly active; FDA approved in March 2016 for ROS1-positive NSCLC[^7]


Slide credit: clinicaloptions.com
Activity of Crizotinib in Pts With \textit{ROS1} Fusions: Best Overall Response

Pts With NSCLC Who Tested Positive for \textit{ROS1} Fusion (N = 50)

- 72\% ORR
- Median PFS: 19.2 mos (95\% CI: 14.4-NR)


Slide credit: clinicaloptions.com
Prolonged PFS With Crizotinib in ROS1-Positive NSCLC

Median PFS: 19.2 mos

FDA approved in 2016 for ROS1-positive NSCLC


Slide credit: clinicaloptions.com
All nonsquamous NSCLC should be tested for *ROS1* mutations

Crizotinib is highly active in patients with ROS1-positive NSCLC
  - ORR of approximately 70%
  - Prolonged PFS

Crizotinib is approved by the FDA for pts with ROS1-positive NSCLC and is the guideline recommended first-line therapy option in this setting
MET Exon 14 Skipping
The MET Pathway

- **MET** is a known proto-oncogene
  - activation can occur via a diverse set of mechanisms
- **MET** exon 14
  - encodes a juxtamembrane domain involved in receptor degradation
  - introns flanking exon 14 are removed via normal splicing mechanisms
**MET Exon 14 Alterations**

- MET mutations that lead to decreased MET degradation
  - deletions, insertions, or base substitutions
  - many disrupt splice sites flanking MET exon 14 → exon 14 skipping
  - increased MET receptor on the tumor cell surface


Presented by: Alexander Drilon MD
A, baseline and 4-week PET scan from patient 2 (MET c.3028G>C exon 14 splice variant) following treatment with cabozantinib.

Table 1: Selected rare molecular subgroups of lung adenocarcinoma

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Prevalence</th>
<th>Clinico-pathological characteristics</th>
<th>Targeted therapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Approved</td>
</tr>
<tr>
<td>ALK rearrangements</td>
<td>2-7%</td>
<td>Younger age</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-smokers</td>
<td>Ceritinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>1-2%</td>
<td>Younger age</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-smokers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RET rearrangements</td>
<td>1-2%</td>
<td>Non-smokers</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>2-4%</td>
<td>Non-smokers</td>
<td>Irreversible pan-HER2 inhibitors Hep30 inhibitors mTOR inhibitors</td>
</tr>
</tbody>
</table>
| BRAF mutations        | 3-5%       | Former or current smokers             | Vermutena 
|                       |            |                                      | Drakeninib    | MEK inhibitors |


Conclusions

• “Oncogene-addicted” tumours are likely fundamentally different to tumours without driver mutations

• Targeted therapies are available on PBS for:
  – EGFR mutations
  – ALK translocations

• Clinical trials and access programs are available for some of the other mutations
Strategies to Improve Outcomes

- Treat based on histology (adenocarcinoma)
- Maintenance Therapy
- Molecular targets (EGFR, ALK etc)
- Immunotherapy
- Anti-angiogenesis
- Strategies for ECOG PS 2 patients
- Strategies for elderly patients
Immune Therapy: Mechanism of Action
Two Principal Means to Promote Immune-Mediated Tumor Destruction: Cytolytic T Lymphocytes and Antibodies

A: Antigen-specific Cytolysis

B: Antibody-dependent Cytotoxicity

NK = natural killer.
check point inhibition
WAKING UP THE BODY’S DEFENCES

Tumour cells can inhibit the body’s immune response by binding to proteins, such as PD-1, on the surface of T cells. Antibody therapies that block this binding reactivate the immune response.
PD1/PDL1:
Multiple agents in Development

• Nivolumab (BMS)
  – PD1 inhibitor
• Pembrolizumab “Keytruda” (Merck)
  – PD1 inhibitor
• Atezolizumab/MPDL3280A (Roche)
  – PDL1 inhibitor
• Durvalumab (MedImmune)
  – PDL1 inhibitor
Is there a Biomarker?

- Perhaps
- PDL1 expression by IHC
  - parallel development with each drug
  - not standardized across different laboratories or drugs (yet)
  - Standardization work is ongoing
PD-1/PD-L1 Therapy: Toxicity
Toxicity

• Topalian et al
  – Serious drug related adverse events 11%
  – No association with dose or tumour type
  – Events of special interest:
    • Colitis, vitiligo, hypophysitis, pneumonitis, thyroiditis

3 deaths due to pneumonitis despite immunosuppression with steroid, infliximab, mycophenolate

2 NSCLC pts
1 CRC pt
TOXICITY - Brahmer et al.
Inflammatory colitis after five doses of anti–programmed death-1 monoclonal antibody (MDX-1106) at 1 mg/kg.

management:
steroids
infliximab

Julie R. Brahmer et al. JCO 2010;28:3167-3175

©2010 by American Society of Clinical Oncology
Toxicity: Diarrhoea & Colitis

<table>
<thead>
<tr>
<th>trial</th>
<th>Diarrhoea (any grade)</th>
<th>G3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topalian et al</td>
<td>11%</td>
<td>1%</td>
</tr>
<tr>
<td>CheckMate 063</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>CheckMate 017</td>
<td>1%</td>
<td>0.07%</td>
</tr>
<tr>
<td>CheckMate 057</td>
<td>8%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Median time to onset 2.5months (1-6months)
High dose steroid (~40mg/day prednisolone) for >1month

**Recommendation:**
G2 diarrhoea >5/7 duration: 0.5-1mg/kg prednisolone daily
G3/4 diarrhoea: 1-2mg/kg prednisolone daily (or equivalent)
Toxicity: Endocrinopathies

• Thyroid dysfunction
  – 8% hypothyroidism & 3% hyperthyroidism
  – Median time to onset 2.5 months & 1.6 months
  – Manage medically & continue drug

• <1% patients
  – Hypophysitis
  – Hypopituitarism
  – Adrenal insufficiency
Other Toxicities of Interest

- Nephritis
- Rash
- Neuropathies
  - Guillain Barre, ‘myasthenia syndrome’, peripheral nerve palsies
- Hepatitis
Other Toxicities of Interest

• stop drug & give steroids

ALL TRIALS HAVE EXCLUDED PATIENTS WITH PRE-EXISTING AUTO IMMUNE DISORDERS
Pembrolizumab has Activity in Multiple Tumor Types

Rationale

Alley et al. AACR Annual Meeting 2015; Abstract CT 103
Nivolumumab
Nivolumab

• Fully human IgG4 monoclonal antibody directed against PD-1 on T cells
Nivolumab for
Squamous Lung Cancer
2\textsuperscript{nd} Line
CheckMate 017 (NCT01642004) - Study Design

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0–1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis
  N = 272

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
n = 135

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
n = 137

Patients stratified by region and prior paclitaxel use

- Primary Endpoint:
  - OS
- Additional Endpoints:
  - Investigator-assessed CRR
  - Investigator-assessed PFS
  - Correlation between PD-L1 expression and efficacy
  - Safety
  - Quality of life (LCSS)

- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was P <0.03

LCSS = Lung cancer symptom scale
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Presented By David Spigel at 2015 ASCO Annual Meeting
Overall Survival

Nivolumab
- mOS mo.: 9.2 (95% CI: 7.3, 13.3)
- # events: 86
- 1-yr OS rate: 42%

Docetaxel
- mOS mo.: 6.0 (95% CI: 5.1, 7.3)
- # events: 113
- 1-yr OS rate: 24%

HR = 0.59 (95% CI: 0.44, 0.79), P = 0.00025

Prescribed By David Spigel at 2015 ASCO Annual Meeting
OS by PD-L1 Expression

1% PD-L1 Expression level

- PD-L1 ≥1%
  - Nivolumab: 9.3
  - Docetaxel: 7.2
- PD-L1 <1%
  - Nivolumab: 8.7
  - Docetaxel: 5.9

5% PD-L1 Expression level

- PD-L1 ≥5%
  - Nivolumab: 10
  - Docetaxel: 6.4
- PD-L1 <5%
  - Nivolumab: 8.5
  - Docetaxel: 6.1

10% PD-L1 Expression level

- PD-L1 ≥10%
  - Nivolumab: 11
  - Docetaxel: 7.1
- PD-L1 <10%
  - Nivolumab: 8.2
  - Docetaxel: 6.1

Presented By David Spigel at 2015 ASCO Annual Meeting
Nivolumab for
Non-Squamous NSCLC
2\textsuperscript{nd} Line
CheckMate 057 (NCT01673867) Study Design

- Stage IIIB/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed\(^a\)
- Prior TKI therapy allowed for known ALK translocation or EGFR mutation
  \(N = 582\)
- Nivolumab
  3 mg/kg IV q2W until PD, or unacceptable toxicity
  \(n = 292\)
- Docetaxel
  75 mg/m\(^2\) IV q3W until PD, or unacceptable toxicity
  \(n = 290\)
- Primary Endpoint
  - OS
- Additional Endpoints
  - ORR\(^b\)
  - PFS\(^b\)
  - Safety
  - Efficacy by tumor PD-L1 expression
  - Quality of life (LCSS)

Patients stratified by prior maintenance therapy
and line of therapy (second- vs third-line)

- PD-L1 expression measured using the Dako/BMS automated IHC assay\(^{14,15}\)
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness.

\(^a\)Maintenance therapy included bevacizumab, oxaliplatin, or erlotinib (not considered a separate line of therapy).

\(^b\)Per RECIST v1.1 criteria as determined by the investigator.
Overall Survival

Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting
OS by PD-L1 Expression

- ≥1% PD-L1 expression level
  - HR (95% CI) = 0.59 (0.43, 0.82)
  - mOS (mo) = 17.2

- ≥5% PD-L1 expression level
  - HR (95% CI) = 0.43 (0.30, 0.63)
  - mOS (mo) = 13.2

- ≥10% PD-L1 expression level
  - HR (95% CI) = 0.40 (0.26, 0.59)
  - mOS (mo) = 13.1

Symbols represent censored observations.

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Presented By Luis Paz-Ares at 2015 ASCO Annual Meeting
Difference in Survival by PD-L1 Expression

- PD-L1 expression seemed to be predictive in Non-Squamous carcinoma, but not for Squamous
  - Squamous carcinoma more often related to smoking
  - Higher mutational load
  - Potentially expresses more antigens
  - May be more immunogenic
**OAK: Overall Survival**


<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab (n = 425)</th>
<th>Docetaxel (n = 425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>13.8</td>
<td>9.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.73 (0.62-0.87)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>.0003</td>
<td></td>
</tr>
</tbody>
</table>

**OS (%)**

- 0 - 100
- 10 - 90
- 20 - 80
- 30 - 70
- 40 - 60
- 50 - 50
- 60 - 40
- 70 - 30
- 80 - 20
- 90 - 10
- 100 - 0

**Mos**

- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27

Slide credit: clinicaloptions.com
Keynote 24 Study: First Line Pembrolizumab
Keynote 24 Study

- Recently presented at ESMO conference and published in NEJM
- 305 patients
- Untreated advanced NSCLC
- PD-L1 expression on > 50% of tumour cells
- Negative for EGFR or ALK mutations
Keynote 24 Study

- Randomised to:
  - Platinum based chemotherapy
  - Pembrolizumab 200mg every 3 weeks
- Crossover permitted
- Primary endpoint of progression free survival
Progression-free Survival in the Intention-to-Treat Population.
Overall Survival in the Intention-to-Treat Population.

Hazard ratio for death, 0.60 (95% CI, 0.41–0.89)
P = 0.005

<table>
<thead>
<tr>
<th>Month</th>
<th>Pembrolizumab</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>151</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>123</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>106</td>
</tr>
<tr>
<td>9</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>15</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Adverse Events in the As-Treated Population.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Panentherapy Group (N = 184)</th>
<th>Chemotherapy Group (N = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>133 (72.4)</td>
<td>133 (72.4)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>57 (30.6)</td>
<td>53 (28.7)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Events occurring in any of the described categories:

- Neutropenia
- Anaemia
- Fatigue
- Decreased appetite
- Diarrhea
- Hemorrhage
- Vomiting
- Perforation
- Constipation
- Nausea
- Abnormal liver function tests
- Neurotoxicity
- Decreased white blood count
- Increased bilirubin level
- Decreased platelet count
- Increased creatinine level
- Increased transaminase level
- At the time of the data cut-off

The as-treated population included all patients who received at least one dose of a trial treatment. For the patients in the chemotherapies group who crossed over to the panentherapy group after disease progression, only events that occurred during treatment with the assigned chemotherapies are included.

Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case report form. Events listed here are not considered drug-related unless they are specifically related to the drug or treatment regimen and are not related to death or hospitalization. The investigator had the option to list events as drug-related or not drug-related. Events are listed in descending order of frequency for the total population. The table includes events that were not specifically related to death or hospitalization and were not considered drug-related.

The data cut-off was 1 March 2016.

PCPA 2017 Dish Herath

Keynote 24

• Shows superiority of Pembrolizumab compared to chemotherapy in 30% of NSCLC patients
• Less toxic than chemotherapy
• This is a very important study
Immunotherapy: Small Cell Lung Cancer
KEYNOTE-028: Pembrolizumab in Advanced SCLC

- Multicohort, open-label phase Ib trial

**SCLC Cohort**
- Pts with PD-L1–positive SCLC and failure or inability to receive standard therapy; ECOG PS 0-1; ≥ 1 measurable lesion; no autoimmune disease or interstitial lung disease (n = 20)

**Primary Endpoint:** ORR (per RECIST v. 1.1), safety

**Secondary Endpoints:** PFS, OS, duration of response

**PD-L1 expression assessed by centrally reviewed IHC (22C3 antibody)**

**Pembrolizumab 10 mg/kg IV q2w for 24 mos or until progression or intolerable toxicity**

- **CR, PR, or SD**
- **Progressive disease or unacceptable toxicity**
- **Discontinue treatment**

KEYNOTE-028: Tumor Response

- Pembrolizumab therapy associated with partial response in 7 pts
  - 5/7 responders with tumor reduction > 50% in size
  - 6/7 responders with reduction in tumor size by Wk 8

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>35 (15-59)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>5 (0-25)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9</td>
<td>45 (23-69)</td>
</tr>
<tr>
<td>No assessment</td>
<td>3</td>
<td>15 (3-38)</td>
</tr>
</tbody>
</table>

CheckMate 032: Nivolumab ± Ipilimumab in Previously Treated SCLC

4 cycles

- Nivolumab 3 mg/kg IV q2w (n = 40)
- Nivolumab 1 mg/kg + Ipilimumab 1 mg/kg IV q3w (n = 3)
- Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV q3w (n = 47)
- Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV q3w (n = 38)

Pts with recurrent SCLC + prior platinum-based treatment (N = 128)

Endpoints
- Primary: ORR
- Secondary: safety
- Exploratory: PFS, OS, biomarker analysis

Nivolumab 3 mg/kg IV q2w

Analyzed separately

CheckMate 032: Efficacy Outcomes

<table>
<thead>
<tr>
<th>Response</th>
<th>Nivolumab (n = 40)</th>
<th>Nivolumab + Ipilimumab (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>18</td>
<td>17*</td>
</tr>
<tr>
<td>CR, %</td>
<td>0</td>
<td>2.2</td>
</tr>
<tr>
<td>PR, %</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>SD, %</td>
<td>20</td>
<td>37</td>
</tr>
<tr>
<td>PD, %</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>Median time to response, mo</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median DoR, mos (range)</td>
<td>NR (4.1 to &gt; 11)</td>
<td>6.9 (1.5 to &gt; 11.1)</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>4.4</td>
<td>8.2</td>
</tr>
</tbody>
</table>

*7 additional PRs after database lock increased ORR to 32.6% in combination arm.

## CheckMate 032: Safety

<table>
<thead>
<tr>
<th>Safety Outcome, %</th>
<th>Nivolumab (n = 40)</th>
<th>Nivolumab + Ipilimumab (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related deaths</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td>Treatment-related discontinuation</td>
<td>7.5</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Any Grade</th>
<th>Grade 3/4</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AE</td>
<td>53</td>
<td>15</td>
<td>77</td>
<td>34</td>
</tr>
</tbody>
</table>

- Safety profiles of both treatments consistent with other tumor types
  - Paraneoplastic syndromes and autoimmune diseases require close monitoring

Immunotherapy for Small Cell

- PD-1/PD-L1 antibodies have activity
- Further trials are awaited
Immune Therapy: Cost ($$)
Cancer Drugs Hit Market at Ever-Higher Prices

U.S. prices for new cancer drugs have soared since the 1970s despite an increasing number of available brands.

Median monthly cost for new cancer drugs during the five-year period

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975-79</td>
<td>$129</td>
</tr>
<tr>
<td>1980-84</td>
<td>$430</td>
</tr>
<tr>
<td>1980-89</td>
<td>$1,097</td>
</tr>
<tr>
<td>1985-89</td>
<td>$1,199</td>
</tr>
<tr>
<td>1990-94</td>
<td>$1,770</td>
</tr>
<tr>
<td>2000-04</td>
<td>$4,716</td>
</tr>
<tr>
<td>2005-09</td>
<td>$7,000</td>
</tr>
<tr>
<td>2010-14</td>
<td>$9,905</td>
</tr>
</tbody>
</table>

Number of new drugs introduced:
- 1975-79: 5
- 1980-84: 3
- 1980-89: 6
- 1985-89: 14
- 1990-94: 30
- 2000-04: 18
- 2005-09: 21
- 2010-14: 33

Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.
Source: Peter Bach and Geoffrey Schnorr at Memorial Sloan Kettering Cancer Center

Bloomberg Graphics ©
Cancer Drugs Hit Market at Ever-Higher Prices

U.S. prices for new cancer drugs have soared since the 1970s despite an increasing number of available brands.

Median monthly cost for new cancer drugs during the five-year period

$10K

0 2 4 6 8 10

$129 $430 $1,097 $1,199 $1,770 $4,716 $7,000 $9,905

Number of new drugs introduced


5 3 6 14 30 18 21 33

Note: Costs are monthly Medicare prices for each drug the year it was introduced, adjusted for inflation.
Source: Peter Bach and Geoffrey Schnorr at Memorial Sloan Kettering Cancer Center

Bloomberg Graphics

Pembrolizumab
2 mg/kg

$14,500
US – FDA
  – Cost : benefit not considered
  – Approved on efficacy alone
  – Companies don’t have to compete on price

Australia – PBS
  – Recommendation from PBAC
  – Slow process (years)
  – Drug must meet cost : benefit analysis
  – Small market
    • Does not influence international price
    • Companies may not bother to market drugs if cost offered by PBS is too low
• Should we discuss un-funded drugs with our patients?

**YES**

– 89% patients wanted a discussion about expensive anti cancer drugs (Mileshkin et al. COSA 2014)

– Patients would consider paying if treatment curative, PFS gain >24 months or if could easily afford it
Strategies to Improve Outcomes

• Treat based on histology (adenocarcinoma)
• Maintenance Therapy
• Molecular targets (EGFR, ALK etc)
• Immunotherapy
• Anti-angiogenesis
• Strategies for ECOG PS 2 patients
• Strategies for elderly patients
Bevacizumab

- Monoclonal antibody
- Anti-angiogenic agent
- Binds Vascular Endothelial Growth Factor (VEGF)
ECOG 4599: Phase III Trial of Carboplatin/Taxol +/- Avastin

First-line Adv. NSCLC nonsquamous cell (N = 878)
Stratified by:
- Disease stage
- Prior weight loss
- Prior XRT
- Measurable dzs Y/N

Randomized

Carboplatin/taxol cycles $\times 6^*$
*No crossover allowed

Carboplatin/taxol $\times 6$ + Avastin
15 mg/kg q3wk, then bevacizumab alone

Primary endpoint: Survival

Carbo/Taxol +/- Avastin: Key Clinical Outcomes

- Response rate: 15% for carbo/taxol vs. 35% for same chemo + avastin

PFS

- Carbo/taxol
- Carbo/taxol + avastin

$P<0.001; \; HR=0.66$
- Median PFS: 6.2 months vs. 4.5 months
- 6-Month PFS: 55% vs. 33%
- 1-Year PFS: 15% vs. 6%

OS

- Carbo/taxol
- Carbo/taxol + avastin

$P=0.003; \; HR=0.79$
- Median OS: 12.3 months vs. 10.3 months
- 1-Year OS: 51% vs. 44%
- 2-Year OS: 23% vs. 16%

HR=hazard ratio; OS=overall survival; PFS=progression-free survival.
Bevacizumab

• In the US, used in conjunction with platinum doublet chemotherapy
• Usually continued as maintenance therapy
  ▪ Despite lack of evidence supporting this
• Increased risk of bleeding – not used in:
  ▪ Squamous carcinoma
  ▪ Patients with brain metastases
  ▪ Patients with haemoptysis
Role of Bevacizumab

• Not PBS listed for NSCLC
Angiogenesis: 2\textsuperscript{nd} line therapy
# Second-Line Therapy: Options & Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Median OS (mos)</th>
<th>1-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAX 317[^a]</td>
<td>Docetaxel (N = 103)</td>
<td>7.0</td>
<td>37.0%</td>
</tr>
<tr>
<td></td>
<td>Best supportive care (N = 100)</td>
<td>4.6</td>
<td>12.0%</td>
</tr>
<tr>
<td>Hanna et al. 2004[^b]</td>
<td>Pemetrexed (N = 283)</td>
<td>8.3</td>
<td>29.7%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (N = 288)</td>
<td>7.9</td>
<td>29.7%</td>
</tr>
<tr>
<td>INTEREST[^c]</td>
<td>Gefitinib (N = 723)</td>
<td>7.6</td>
<td>32.0%</td>
</tr>
<tr>
<td></td>
<td>Docetaxel (N = 710)</td>
<td>8.0</td>
<td>34.0%</td>
</tr>
<tr>
<td>TITAN[^d]</td>
<td>Erlotinib (N = 203)</td>
<td>5.3</td>
<td>26.0%</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy (N = 221: 116 docetaxel, 105 pemetrexed)</td>
<td>5.5</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

REVEL: Docetaxel +/- Ramucirumab as Second Line Therapy for Adv NSCLC

- Ramucirumab (RAM) is a human IgG1 monoclonal antibody, specifically binding to the extracellular domain of VEGFR-2
- Approved in previously treated gastric cancer

Primary endpoint: OS

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Docetaxel 75 mg/m2 + Ramucirumab 10 mg/kg IV Q21 days</td>
</tr>
<tr>
<td>B</td>
<td>Docetaxel 75 mg/m2 + Placebo IV Q21 days</td>
</tr>
</tbody>
</table>

Treat until PD or prohibitive toxicity

- Adv NSCLC (any histology)
- Prior platinum-based chemo
- Prior bev allowed
- N = 1253

Perol, A#LBA-8006
REVEL: Efficacy of Ramucirumab

<table>
<thead>
<tr>
<th>RAM + DOC (N = 628)</th>
<th>PL + DOC (N = 625)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>22.9%</td>
<td>13.6%</td>
</tr>
<tr>
<td>DCR (CR + PR +SD)</td>
<td>64.0%</td>
<td>52.6%</td>
</tr>
</tbody>
</table>

**Overall Survival (ITT)**

**Progression-Free Survival (ITT)**

Stratified HR (95% CI) = 0.782 (0.677-0.859)
Stratified log-rank P < .0001
Patients with NSCLC who have failed first-line chemotherapy

Randomization

Oral nintedanib + Chemotherapy (docetaxel)

Second-line treatment

Placebo + Chemotherapy (docetaxel)

Number of docetaxel cycles not restricted
Monotherapy with nintedanib/placebo allowed after ≥ 4 cycles

Primary endpoint: PFS
Key secondary endpoint: OS

Results presented at ASCO 2013

LUME-Lung 1: OS (All Patients)


Nintedanib + docetaxel (n = 655)
Placebo + docetaxel (n = 659)

<table>
<thead>
<tr>
<th></th>
<th>Nintedanib + docetaxel</th>
<th>Placebo + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>10.1</td>
<td>9.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.94 (0.83 to 1.05)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>.2720</td>
<td></td>
</tr>
</tbody>
</table>
LUME-Lung 1: OS (Adenocarcinoma Patients)

Nintedanib + docetaxel (n = 322) vs Placebo + docetaxel (n = 336)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Prob. of Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>52.7%</td>
</tr>
<tr>
<td>24</td>
<td>25.7%</td>
</tr>
</tbody>
</table>

Median, mo:
- Nintedanib + docetaxel: 12.6
- Placebo + docetaxel: 10.3

HR (95% CI): 0.83 (0.70 to 0.99)

P = 0.0359

LUME-Lung 1: Summary

- Met primary endpoint of delaying tumour growth following failure of first-line therapy
- Showed a significant survival benefit in patients with adenocarcinoma compared with an active comparator
- Well tolerated with manageable safety profile
Angiogenesis: Conclusions

- 1\textsuperscript{st} line agents not used much in Australia due to cost
- 2\textsuperscript{nd} line agents have a small amount of activity, but difficult to know when to use in the setting of PD-1 antibody results
Strategies to Improve Outcomes

- Treat based on histology (adenocarcinoma)
- Maintenance Therapy
- Molecular targets (EGFR, ALK etc)
- Immunotherapy
- Anti-angiogenesis
- Strategies for ECOG PS 2 patients
- Strategies for elderly patients
ECOG PS 2 Patients

• Many studies in metastatic disease had low numbers of ECOG PS 2 patients or excluded ECOG PS 2 patients.
• Previously single agent chemotherapy was thought to be a good approach in this group
• A more recent study compared Pemetrexed alone to Carboplatin-Pemetrexed
(A) Progression-free and (B) overall survival for patients randomly assigned to pemetrexed (P) or combination of carboplatin and pemetrexed (CP).

Zukin M et al. JCO 2013;31:2849-2853
ECOG PS2: Conclusion

- Platinum doublet therapy is the standard of care
- Be aware of risks of increased toxicity in this patient group
  - Less physiological reserve
Strategies to Improve Outcomes

• Treat based on histology (adenocarcinoma)
• Maintenance Therapy
• Molecular targets (EGFR, ALK etc)
• Immunotherapy
• Anti-angiogenesis
• Strategies for ECOG PS 2 patients
• Strategies for elderly patients
Elderly Patients

- Study of carboplatin-paclitaxel vs vinorelbine or gemcitabine monotherapy

- Median age 77

- Well tolerated (febrile neutropenia 4% in combination arm)

Elderly Patients

- Platinum doublet chemotherapy is effective in elderly patients
- Activity of immunotherapy increases available option
  - PBS funding uncertain
Final Conclusions

• Survival results in lung cancer are poor
• However, many exciting therapies are being developed
  – Immunotherapy
  – Targeted therapies
  – DLL3/Notch pathway inhibitors in small cell lung cancer