Combining Lurbinectedin and Doxorubicin
The UCLH Experience in Small Cell Lung Cancer

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Small Cell Lung Cancer (SCLC)

- Lung Cancer is the most common cancer across men and women globally and the highest cause of cancer mortality
- SCLC accounts for 10-15% of all lung cancer
- Strong association with tobacco use and associated co-morbidities
- ~30% present with ‘limited stage’ disease with only a proportion eligible for ‘radical intent’ treatment, chemo-radiation, associated with ~18 month survival
- >80% treated with palliative chemotherapy with median survival 9-11 months

Jackman and Johnson, 2005
Extensive Stage SCLC: First-line therapy

- Combination chemotherapy with cisplatin / carboplatin and etoposide is the mainstay of first-line treatment
  - Response rates 60-70%
  - 4 to 6 cycles
  - Median progression free survival 2-3 months
  - 2-year overall survival < 5%
- Minimal improvement in first line therapy in decades
  - Cisplatin / Irinotecan demonstrated to be superior in Japanese population; not seen in study in Western population
  - Consolidation Thoracic Radiotherapy
  - Prophylactic Cranial Irradiation

Noda et al., NEJM 2002; Hanna et al., JCO 2006; Rossi et al., JCO 2012; Slotman et al., Lancet Onc 2015
Management of Recurrent Disease

- Recurrence $\leq$ 90 days: “Resistant” or “Refractory” disease
- Recurrence $> 90$ days: “Relapsed” or “Sensitive” disease

Topotecan as second-line therapy in SCLC

- Three open-label single-arm studies of IV topotecan days 1-5 q3 weekly showed response rates ranging 11% to 31% for ‘sensitive’ disease and 2% to 7% for ‘resistant’ disease
- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival.

Ardizzoni et al., 1997; Von Pawel et al., 1999; NCCN guidelines v2.2017
Topotecan vs CAV in second-line setting

- Randomized study in patients with relapse >60 days after completion of first-line therapy
  - Topotecan: 1.5 mg/m² IV daily days 1-5 Q21d vs CAV: Cyclophosphamide 1000 mg/m², Doxorubicin 45 mg/m², Vincristine 2 mg IV day 1 Q21d
- ORR: 24 vs 18%
- mTTP: 13.3 vs 12.3 wks
- mOS: 25.0 vs 24.7 wks

Von Pawel et al., JCO 1999
Management of Recurrent Disease

Topotecan is the only FDA- and EMA-approved second-line therapy in SCLC

- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival
- Oral topotecan also improved survival compared to BSC

Oral and IV formulations approved by FDA and EMA

Ardizzoni et al., 1997; Von Pawel et al., 1999; O'Brien et al., 2006; NCCN guidelines v2.2017
Upcoming Interests – Immunotherapy

- Phase 3 Cisplatin & Etoposide +/- Ipilimumab

- Checkmate 032 - Phase 2 Nivolumab monotherapy vs Nivolumab plus Ipilimumab

<table>
<thead>
<tr>
<th>Objective response rate, % (n/N)</th>
<th>Nivolumab-3 (n = 98)</th>
<th>Nivolumab-1 + Ipilimumab-3 (n = 61)</th>
<th>Nivolumab-3 + Ipilimumab-1 (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10 (10/98)</td>
<td>23 (14/61)</td>
<td>19 (10/54)</td>
</tr>
<tr>
<td>Platinum-sensitive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 (6/55)</td>
<td>28 (7/25)</td>
<td>19 (4/21)</td>
</tr>
<tr>
<td>Platinum-resistant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (3/30)</td>
<td>17 (4/23)</td>
<td>10 (2/21)</td>
</tr>
</tbody>
</table>

Antonia et al., Lancet Onc 2016; Reck et al.; JCO 2016
Upcoming Interests – DLL3 inhibitors

- Rovalpituzumab tesirine (Rova-T) – A delta-like protein 3 Antibody-Drug Conjugate
  - Phase 1 dose escalation study in SCLC (2nd or 3rd line therapy)
    - Maximum tolerated dose 0.4 mg/kg 3 weekly
    - Recommended phase II dose and schedule 0.3 mg/kg 6 weekly
    - ‘Active’ dose levels: 0.2 mg/kg or 0.4 mg/kg every 3 weeks or 0.3 mg/kg or 0.4 mg/kg every 6 weeks

<table>
<thead>
<tr>
<th></th>
<th>ORR (all patients) N=60</th>
<th>ORR (DLL3 +ve pts) N=26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rova-T ‘Active’ dose levels</td>
<td>18% (11/60) PFS 2.8m OS 4.6m</td>
<td>38% (10/26) PFS 4.3m OS 5.8m</td>
</tr>
</tbody>
</table>

Rudin et al., Lancet Oncology 2016
Upcoming Interests – Lurbinectedin & Doxorubicin
Lurbinectedin (PM1183) & Doxorubicin (DOX), as a possible new second-line therapy in Small Cell Lung Cancer (SCLC)

- Dose finding part of a Phase Ib study defined a recommended phase II dose of lurbinectedin 4.0 mg flat dose (FD) or 2.0 mg/m$^2$ + DOX 50 mg/m$^2$ both on day (D)1 every three weeks (q3w)
- Myelosuppression was dose-limiting regardless of colony stimulating factor (CSF) prophylaxis use
- After DOX withdrawal, treatment could continue with lurbinectedin alone, if clinically appropriate
- Compelling activity was observed during escalation phase with 5 of 7 evaluable 2nd line in SCLC pts (71%) having objective partial response (PR) as per RECIST v.1.1
- Thus, an expansion cohort of 20 2nd line SCLC pts was evaluated

Forster et al., ASCO 2015
Safety (n=21)

Hematology

- Neutropenia
- Thrombocytopenia
- Anemia

Laboratory

- ALT
- AST
- T. Bil
- AP
- Creatinine
- Alopecia
- Fatigue
- Anorexia
- Nausea/Vomiting
- Diarrhea/Const.
- Dysgeusia
- Myalgia
- Dizziness
- Pneumonia
- FN
- NT Infection

Clinical AEs

- Alopecia
- Anorexia
- Fatigue
- Mucositis
- Nausea/Vomiting
- Diarrhea/Const.
- Dysgeusia
- Myalgia
- Dizziness
- Pneumonia
- FN
- NT Infection

Neutropenia time course according to CSF prophylactic use or not (n=109 cycles)

<table>
<thead>
<tr>
<th></th>
<th>CSF (n=52)</th>
<th>No CSF (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 neutropenia</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>Median day of grade 4 nadir (range)</td>
<td>8 (7-11)</td>
<td>14 (10-16)</td>
</tr>
<tr>
<td>Time to recovery to rechallenge, in days</td>
<td>4 (2-21)</td>
<td>4 (1-13)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.7%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>None</td>
<td>3.5%</td>
</tr>
<tr>
<td>Grade 4 thrombocytopenia</td>
<td>7.7%</td>
<td>None</td>
</tr>
</tbody>
</table>

AEs, Adverse events; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; Const, constipation; FN, febrile neutropenia; NT, neutropenic; T Bil, Total bilirubin.

CSF, colony stimulating factor.
Efficacy

1\textsuperscript{st} line Platinum-based combination

\[\text{N=} 21\]

- \text{PR} 76\%
- \text{PD} 14\%
- \text{SD} 5\%
- \text{CR} 5\%

ORR 81%
95% CI: 58-95%

2\textsuperscript{nd} line Lurbinectedin /DOX

\[\text{N=} 21\]

- \text{PR} 57%
- \text{CR} 10\%
- \text{PD} 19\%
- \text{SD} 14\%

median CTFI 3.1 months

ORR 67%
95% CI: 43-85%

CI, confidence interval; CR, complete response; CTFI, chemotherapy-free interval; DOX, doxorubicin; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Forster et al., ASCO 2015
Best RECIST v.1.1 response according to chemotherapy free interval (CTFI)

Exceptional activity with significant but manageable toxicity led to a further expansion cohort of Lurbinectedin (2mg/m²) and Doxorubicin (40mg/m²) and plans for a randomised study

Forster et al., ASCO 2015
Patient Characteristics

- Dose escalating phase I study in patients with different tumour types
- 9 patients with metastatic small cell lung cancer treated at UCLH

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>9</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Median Age</td>
<td>63 (58-78)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Lurbinectedin combination dose (mg)</th>
<th>Dox (mg/m²)</th>
<th># patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>2mg/m²</td>
<td>40</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th># Lines prior systemic therapy</th>
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</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platinum Sensitivity</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Sensitive</td>
<td>6</td>
</tr>
<tr>
<td>Resistant</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Platinum Free interval (weeks)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>17</td>
</tr>
<tr>
<td>Range</td>
<td>8 to 55</td>
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</table>
## Toxicity

<table>
<thead>
<tr>
<th>Patient #</th>
<th>PM Dose (mg)</th>
<th>Dox Dose (mg/m²)</th>
<th>#Dox/PM combo</th>
<th>#PM single agent</th>
<th>DR in combo</th>
<th>DR single agent</th>
<th>Reason for DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>3 mg</td>
<td>50</td>
<td>4</td>
<td>0</td>
<td>no</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.5 mg</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>no</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.75 mg</td>
<td>40</td>
<td>6</td>
<td>2</td>
<td>no</td>
<td>yes</td>
<td>G4 neut/ G3 plts</td>
</tr>
<tr>
<td>4</td>
<td>3.75 mg</td>
<td>40</td>
<td>10</td>
<td>4</td>
<td>no</td>
<td>yes</td>
<td>G4 neut/ G3 plts</td>
</tr>
<tr>
<td>5</td>
<td>4 mg</td>
<td>50</td>
<td>8</td>
<td>4</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4 mg</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>no</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4 mg</td>
<td>50</td>
<td>8</td>
<td>7</td>
<td>yes</td>
<td>yes</td>
<td>G4 neut</td>
</tr>
<tr>
<td>8*</td>
<td>4 mg</td>
<td>50</td>
<td>4</td>
<td>0</td>
<td>no</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>9**</td>
<td>5 mg</td>
<td>50</td>
<td>3</td>
<td>1</td>
<td>yes</td>
<td>yes</td>
<td>G4 neut</td>
</tr>
</tbody>
</table>

* Discontinued treatment due to fatigue / decline in PS without evidence of PD
** Discontinued treatment due to persistent pancytopenia despite dose reductions
Best Imaging Response

![Bar chart showing the number of patients in each RECIST response category: CR (Complete Response), PR (Partial Response), SD (Stable Disease), and PD (Progressive Disease). The chart indicates a higher number of patients with PR compared to the others.](chart.png)
Median # cycles of Dox/Lurbinectedin = 4, range 2-10
Five patients on single agent lurbinectedin, median 4, range 1-7
Median # total cycles 4, mean 7.2, range 2-15
* Platinum refractory patients
## Treatment Duration

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Dose PM</th>
<th>Dose Dox</th>
<th>#Dox/PM</th>
<th>#PM single agent</th>
<th>Best response</th>
<th>Reason for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 mg</td>
<td>50 mg/m²</td>
<td>4</td>
<td>0</td>
<td>PR</td>
<td>Pneumonia and decline in PS*</td>
</tr>
<tr>
<td>2</td>
<td>3.5 mg</td>
<td>40 mg/m²</td>
<td>2</td>
<td>0</td>
<td>PD</td>
<td>Disease Progression</td>
</tr>
<tr>
<td>3</td>
<td>3.75 mg</td>
<td>40 mg/m²</td>
<td>6</td>
<td>2</td>
<td>PR</td>
<td>Disease Progression (Brain)</td>
</tr>
<tr>
<td>4</td>
<td>3.75 mg</td>
<td>40 mg/m²</td>
<td>10</td>
<td>4</td>
<td>PR</td>
<td>Disease Progression (Brain)</td>
</tr>
<tr>
<td>5</td>
<td>4 mg</td>
<td>50 mg/m²</td>
<td>8</td>
<td>4</td>
<td>PR</td>
<td>Disease Progression</td>
</tr>
<tr>
<td>6</td>
<td>4 mg</td>
<td>40 mg/m²</td>
<td>2</td>
<td>0</td>
<td>PD</td>
<td>Disease Progression</td>
</tr>
<tr>
<td>7</td>
<td>4 mg</td>
<td>50 mg/m²</td>
<td>8</td>
<td>7</td>
<td>PR</td>
<td>Disease Progression</td>
</tr>
<tr>
<td>8</td>
<td>4 mg</td>
<td>50 mg/m²</td>
<td>4</td>
<td>0</td>
<td>PR</td>
<td>Toxicity, fatigue and decline in PS**</td>
</tr>
<tr>
<td>9</td>
<td>5 mg</td>
<td>50 mg/m²</td>
<td>3</td>
<td>1</td>
<td>PR</td>
<td>Persistent pancytopenia despite DR***</td>
</tr>
</tbody>
</table>

* PD 4 months after trial discontinuation
** Death 2 months after trial discontinuation
*** New brain mets 2 months after trial discontinuation
Duration on study drug

Median duration on IMP 99 days (35-341)
Patient JB

- 71 year old male
  - Ex smoker
  - COPD; CVD (TIAs); Depression
- April 2014 – T4N2M1b Extensive Stage Small Cell Lung Cancer with left suprhapilar mass invading mediastinum, mediastinal LNs and a liver metastasis
- October 2014 – completed 6 cycles of carboplatin and etoposide with partial response
  - Had persisting respiratory symptoms and declined PCI but received palliative RT to left lung and mediastinum (20Gy in 5#) in Feb 2015
- March 2015 (~4 months PFI) developed disease progression in lungs and bone
• Referred to UCLH
  – Grade 1 cough; grade 1 SOB; grade 1 lethargy
  – ‘PS 1’
  – Intrathoracic disease (47mm mediastinal mass)
• May 2015 – commenced lurbinectedin 2mg/m² (3.75 mg) and doxorubicin 40mg/m²
  – Minimal toxicity (G1 lethargy)
  – Partial response in June 2015 post 2 cycles (40% reduction in target lesions; 28mm)
• Incremental response until complete response of target lesion (post 4 cycles) and very good partial response of non target disease
• January 2016 – completed 10 cycles combination chemotherapy
Baseline

Post 2 cycles

6 months
• Jan 2016 started onto single agent lurbinectedin (4mg/m²; 7mg)
  – Dose reduced to 3mg/m² (5.25mg) due to pancytopenia after cycle 2
  – maintained PR on CT after 2 cycles
• April 2016 – complaining of blurred vision and unsteadiness
  – CT brain – multiple brain metastases
  – No extra-cranial progression
  – Off study
• April 2016 - RIP
Summary

• Tolerability across multiple dose levels driven by myelosuppression
  – Much better tolerated on expansion ‘phase III’ schedule
  – Side effects are manageable, with option for dose delays or modification if required
  – Maintenance monotherapy also feasible
• Very impressive responses
  – Some longer duration than with 1st line therapy!
• Phase III registration study ongoing with hopes to define a new standard second line SCLC treatment and improves outcomes for this patient population
Thanks

• UCLH CRF staff
  – Rebecca Kristeleit
  – Michael Flynn and other Clinical Fellows
  – David Leader and other research nurses
  – Aaron Clarke and other data managers
• NIHR UCH Clinical Research Facility

• Patients and their families

Any Questions?