Combined modality treatment for NSCLC with N2 disease

Gerry Hanna
Senior Lecturer and Consultant in Clinical Oncology

Centre for Cancer Research and Cell Biology

@gerryhanna  g.hanna@qub.ac.uk
**DISCLOSURE OF INTEREST**

**Honoraria:** AstraZeneca, Roche, Pfizer, Bristol-Myers Squibb, Novartis

**Consulting or Advisory Role:** Pfizer

**Speakers’ Bureau:** AstraZeneca, Roche, Pfizer, Bristol-Myers Squibb

**Research Funding:** Dermal Laboratories, AstraZeneca

**Travel, Accommodations, Expenses:** Roche, Boehringer Ingelheim
Talk Outline

• Challenges in the management of stage III NSCLC

• Unresectable: What is the evidence for CRT in stage III disease?

• Optimal Radiotherapy?

• Role of Immunotherapy?

• Future directions?
1. Challenges in the management of stage III NSCLC
Patient Heterogeneity

Need to consider:
Performance status
Co-morbidities
Cardio-pulmonary reserve
Stage Migration Over Time

When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.
Heterogeneity in Pathology

Squamous Cell Carcinoma

Adenocarcinoma
Heterogeneity in Resources/Expertise
Heterogeneity in Disease Location & Extension

Decaluwe et al EJ Cardiothorac Sx 2009; 36: 433-9
De Leyn et al JTO 2009; 4: 62-8
IASLC: Outcome by cN Category

Asamura et al JTO 2015; 10(12): 1675-84
Is all N2 NSCLC the same?

III A<sub>1</sub> Incidental nodal metastases found on final pathologic examination of the resection specimen

III A<sub>2</sub> Nodal (single station) metastases recognized intraoperatively

III A<sub>3</sub> Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)

III A<sub>4</sub> Bulky or fixed multistation N2 disease

IASLC: More Complex N2 Staging

- Overall Survival

60 Month

N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

60 Month

58%
50%
52%
41%
36%

Overall Survival

Years

N1a vs N1b vs N2a1 vs N2a2 vs N2b Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+, R0 Resection, and Region.
(Cox PH regression on All cases)

<table>
<thead>
<tr>
<th>comparison</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1b vs N1a</td>
<td>1.36</td>
<td>0.005</td>
</tr>
<tr>
<td>N2a1 (skip) vs N1b</td>
<td>0.92</td>
<td>0.433</td>
</tr>
<tr>
<td>N2a2 vs N2a1 (skip)</td>
<td>1.37</td>
<td>0.0002</td>
</tr>
<tr>
<td>N2b vs N2a2</td>
<td>1.21</td>
<td>0.0117</td>
</tr>
<tr>
<td>N2a2 vs N1b</td>
<td>1.26</td>
<td>0.0197</td>
</tr>
</tbody>
</table>

Asamura et al JTO 2015; 10(12): 1675-84
Management Challenges in unresectable stage III NSCLC

Loco-regional Control

Distant Control
Management Challenges in unresectable stage III NSCLC

Loco-regional Control

Distant Control

Sanctuary Site
Brain Metastases
ESMO Consensus Guidelines: Decision Making in NSCLC Stage III

Optimal diagnostic work-up:
- PET-CT within 4 weeks of treatment
- MRI Brain
- (Minimally) invasive mediastinal staging

Assessment of fitness:
- Cardio-pulmonary reserve
- Cisplatin-based chemotherapy tolerability
- Charlson co-morbidity index
- Comprehensive geriatric assessment

Resectable

Potentially Resectable

Unresectable

‘Complete resection is an outcome parameter with major impact on overall prognosis’

‘Evaluating and predicting such parameters upfront is key for adequate planning of definitive local treatment without treatment interruptions’

Eberhardt et al Ann Oncol 2015; 26: 1573-88
ESMO Consensus Guidelines: Algorithm

Eberhardt et al Ann Oncol 2015; 26: 1573-88
ESMO Consensus Guidelines: Algorithm

Eberhardt et al Ann Oncol 2015; 26: 1573-88
2. Unresectable: What is the evidence for CRT in stage III disease?
Addition of Induction Chemotherapy to RT

N=155 Stage III NSCLC

Sequential #2 cisplatin & vinblastine and 60 Gy RT:
- Median OS 13.8 months

60 Gy RT alone:
- Median OS 9.7 months

P=0.0066

Dillman et al NEJM 1990; 323: 940-5
Meta-analysis: Concurrent Compared to Sequential CRT

- Overall Survival
  - 3 yr OS benefit 5.7%
  - 3 yr LR PFS benefit 6%
  - Increased ≥G3 oesophageal toxicity 4 to 18%

Auperin et al JCO 2010; 28: 2181
RTOG 9410: Concurrent Compared to Sequential CRT

N=407 Stage III NSCLC

Arm 2: Concurrent #2 cisplatin & vinblastine 63 Gy RT
- Median OS 17 months

Arm 1: Sequential #2 cisplatin & vinblastine 63 Gy RT
- Median OS 14.6 months

Curran et al J Natl Cancer Inst 2011; 103: 1452–60
Optimal CT for Concurrent?

3 Year OS

Toxicities (≥G3)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CE</th>
<th>CP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>9%</td>
<td>7%</td>
<td>0.17</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>20%</td>
<td>15%</td>
<td>0.18</td>
</tr>
<tr>
<td>N/V</td>
<td>20%</td>
<td>9%</td>
<td>0.018</td>
</tr>
<tr>
<td>Anemia</td>
<td>16%</td>
<td>8%</td>
<td>0.06</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14%</td>
<td>6%</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>54%</td>
<td>23%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Cisplatin - etoposide
- Cisplatin - vinorelbine
- Carboplatin - paclitaxel (US)
- Cisplatin daily (NKI)

Stauer JAMA Oncol 2016
PROCLAIM: Pemetrexed in Non-Squamous Stage III NSCLC

- 555 patients treated
- No difference OS median 27 vs 25 mths
- Trend towards OS for IIIB & PTV >700 ml
- Trend towards PFS
- Significantly fewer ≥G3 drug-related AE

Senan et al JCO 2016; 34: 953
Cetuximab in RTOG 0617

All Patients
One-sided log-rank, p=0.2938
Cetuximab in RTOG 0617

O.S. in high EGFR expression (H score ≥200)
Two-sided log-rank, p=0.0325

All Patients
One-sided log-rank, p=0.2938
### Induction Chemotherapy Prior to Definitive CRT

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chemotherapy better tolerated</td>
<td>• Delays definitive concurrent CRT</td>
</tr>
<tr>
<td>• Disease sensitivity can be assessed</td>
<td>• Accelerated repopulation may occur if CRT is delayed</td>
</tr>
<tr>
<td>• Volume reduction may occur allowing smaller RT fields</td>
<td>• Toxicity from induction may cause delay in CRT</td>
</tr>
<tr>
<td>• Smaller volumes may be more likely cured</td>
<td>• Tumour progression during induction making CRT not possible</td>
</tr>
</tbody>
</table>
CALGB 39801: Induction CT prior to cCRT?

Stage III NSCLC

- 182 Carboplatin Paclitaxel weekly for 7 weeks with 66 Gy 33#
- 184 Carboplatin Paclitaxel 2 cycles then weekly for 7 weeks with 66 Gy 33#

Overall Survival

Median OS:
- CRT 12 months
- CT & CRT 14 months
- P=0.3

Vokes et al JCO 2007; 25:1698-1704
## Consolidation chemotherapy post cCRT?

<table>
<thead>
<tr>
<th>Phase</th>
<th>Schedule</th>
<th>Regimen</th>
<th>Median survival (months)</th>
<th>Survival (%)</th>
<th>Grade 3–5 acute toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oesophagitis</td>
</tr>
<tr>
<td>CALGB 39,801 [61]</td>
<td>III</td>
<td>Induction → concurrent</td>
<td>Carboplatin/paclitaxel × 2 → weekly Carboplatin/paclitaxel + 66 Gy</td>
<td>14</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent</td>
<td>Weekly carboplatin/paclitaxel + 66 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOG LUN 01-24 [63]</td>
<td>III</td>
<td>Concurrent</td>
<td>Cisplatin/etoposide × 2 + 59.4 Gy</td>
<td>12</td>
<td>29 (2 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent → consolidation</td>
<td>Cisplatin/etoposide × 2 + 59.4 Gy → docetaxel × 3</td>
<td>21.2</td>
<td>0.88</td>
</tr>
<tr>
<td>SWOG 0023 [69]</td>
<td>III</td>
<td>Concurrent → consolidation → maintenance</td>
<td>Cisplatin/etoposide × 2 + 61 Gy → docetaxel × 3</td>
<td>35</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent → consolidation</td>
<td>Cisplatin/etoposide × 2 + 61 Gy → docetaxel × 3 → gefitinib maintenance</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Belani [66]</td>
<td>II</td>
<td>Induction → concurrent</td>
<td>Carboplatin/paclitaxel × 2 → weekly</td>
<td>12.7</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent</td>
<td>carboplatin/paclitaxel + 61 Gy × 2</td>
<td>16.3</td>
<td>17 (3 years)</td>
</tr>
<tr>
<td>Berghmans [65]</td>
<td>II</td>
<td>Induction → concurrent</td>
<td>Cisplatin/Vinorelbine/Gemcitabine × 2 → Cisplatin/Vinorelbine/Gemcitabine + 66 Gy</td>
<td>17.0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent → consolidation</td>
<td>Cisplatin/Vinorelbine/Gemcitabine × 2 + 66 Gy → Cisplatin/Vinorelbine/Gemcitabine × 2</td>
<td>23.9</td>
<td></td>
</tr>
<tr>
<td>Senan [62]</td>
<td>II</td>
<td>Induction → concurrent</td>
<td>Cisplatin/docetaxel × 2 → weekly</td>
<td>17.5</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent → consolidation</td>
<td>cisplatin/docetaxel + 66 Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garrido [64]</td>
<td>II</td>
<td>Induction → concurrent</td>
<td>Gemcitabine/docetaxel × 2 → weekly</td>
<td>13.8</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Concurrent → consolidation</td>
<td>Weekly carboplatin/docetaxel + 60 Gy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bayman et al Lung Cancer 2014; 83:117–125
3. Potentially Resectable: Is surgery better than RT for local control in pN2 disease?
3. Potentially Resectable: Is surgery better than RT for local control in pN2 disease?
EORTC 08941: Sequential Surgery vs RT

N2 Stage III NSCLC

579 Registered

3# Platinum based CT

332 Response

No Response Off Study

RT 60-62.5 Gy

Surgery

RT 60-62.5 Gy

50% R0
36% R1
14% R2
40% PORT

Van Meerbeeck et al JNCI 2007; 99: 442–50
EORTC 08941: Outcomes

Van Meerbeeck et al JNCI 2007; 99: 442–50

- Median OS:
  - RT 11.3 months
  - Sx 9.0 months
  - p=0.605

- Median OS:
  - RT 17.5 months
  - Sx 16.4 months
  - p=0.596
EORTC 08941: Adverse Events & Relapse

Adverse Events

Radiotherapy
- Grade 3/4 Oesophageal: 4%
- Grade 3/4 Pulmonary: 7%
- Grade 5 Pneumonitis: 1%

Surgery
- Grade 3 Oesophageal (PORT): 1%
- Grade 4 Pneumonitis (PORT): 1%
- 30 d mortality: 4%
- 90 d mortality: 9%

Patterns of Relapse

Van Schil et al ERJ 2005; 26: 192–197
Van Meerbeeck et al JNCI 2007; 99: 442–50
**EORTC 08941: Exploratory Analyses in Sx Arm**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Median OS, months (95% CI)</th>
<th>5-year OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bi-)lobectomy</td>
<td>58</td>
<td>25.4 (17.7 to 48.9)</td>
<td>27</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>72</td>
<td>13.4 (11.1 to 19.5)</td>
<td>12</td>
</tr>
<tr>
<td>Mediastinal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypNo-1</td>
<td>64</td>
<td>22.7 (17.6 to 42.7)</td>
<td>29</td>
</tr>
<tr>
<td>ypN2</td>
<td>86</td>
<td>14.9 (11.2 to 18.5)</td>
<td>7</td>
</tr>
<tr>
<td>Type of resection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>77</td>
<td>24.1 (16.7 to 42.4)</td>
<td>27</td>
</tr>
<tr>
<td>Incomplete</td>
<td>76</td>
<td>12.1 (9.5 to 17.1)</td>
<td>7</td>
</tr>
<tr>
<td>No PORT</td>
<td>92</td>
<td>14.1 (11.2 to 19.9)</td>
<td>19</td>
</tr>
<tr>
<td>PORT</td>
<td>62</td>
<td>18.0 (15.0 to 25.9)</td>
<td>13</td>
</tr>
</tbody>
</table>

Van Meerbeeck et al JNCI 2007; 99: 442–50
4. Potentially Resectable: What about tri-modality treatment in pN2 disease?
4. Potentially Resectable: What about tri-modality treatment in pN2 disease?
Intergroup 0139/RTOG 9309: cCRT with or without Sx

T-stage | CRT (24.8%) | Sx (24.2%)
---|---|---
T1 | 50 | 47
T2 | 120 (64.4%) | 121 (62.4%)
T3 | 22 (10.9%) | 26 (13.4%)

Number of positive nodal stations:
- 1: 135 (73.7%) | 146 (75.3%)
- 2: 39 (19.3%) | 39 (20.1%)
- 3: 4 (2.0%) | 4 (2.1%)
- Unknown: 6 (3.0%) | 5 (2.6%)

pN2 Stage III NSCLC: Considered ‘Resectable’

216 2# CT cCRT 45 Gy – Sx – 2# CT
- 164 Sx
- 111 Consolidation CT

213 2# CT cCRT 61 Gy – 2# CT
- 179 61 Gy cCRT
- 144 Consolidation CT

Intergroup 0139/RTOG 9309: Outcomes

Median PFS:
RT 10.5 months
Sx 12.8 months
p=0.017

Median OS:
RT 22.2 months
Sx 23.6 months
p=0.24

Intergroup 0139/RTOG 9309: Adverse Events & Relapse

Adverse Events

Radiotherapy
• Grade 3/4 Neutropenia 41%
• Grade 3/4 Oesophageal: 23%
• Grade 3/4 Pulmonary: 14%
• No Grade 5

Radiotherapy & Surgery
• Grade 3/4 Neutropenia 38%
• Grade 3 Oesophageal: 10%
• Grade 4 Pneumonitis: 9%
• 30 d mortality: 5%
• 90 d mortality: 8%
• Mortality post pneumonectomy 26%

Patterns of Relapse

No differences in sites for first progression

Intergroup 0139/RTOG 9309: Exploratory Analyses in Sx Arm

Matched pair analysis of lobectomy patients

Median OS:
RT 22 months
RT & Lobectomy 34 months
p=0.002

pN2 Stage III NSCLC: Considered ‘Resectable’

**3# Cisplatin Paclitaxel**
1# Cisplatin Vinorelbine +
45 Gy 1.5 Gy/# bd

**Resectable?**

- Yes: 81% R0
- No: Treat as cCRT arm

**81 Surgery**

**80 1# Cisplatin Vinorelbine + 10-13 Gy 2 Gy/# od**

Eberhardt et al JCO 2015; 33:4194-201
ESPATUE: Outcomes

5 yr PFS: CRT 35%
Sx 32%
p = 0.21

5 yr OS: CRT 40%
Sx 44%
p = 0.34

Eberhardt et al. JCO 2015; 33:4194-201
### ESPATUE: Adverse Events

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definitive cCRT</th>
<th></th>
<th>cCRT Sx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 5</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Number (No.)</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>35</td>
<td>44</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>21</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other GI or renal</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>infection</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>16</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Eberhardt et al JCO 2015; 33:4194-201
SAKK 16/00: CT with or without RT prior to Sx

pN2 Stage III NSCLC: Considered ‘Resectable’

- CRT CT
  - 115 3# CT
    - Sx
      - 81% R0
      - 12% R1
      - 8% R2
      - 16% PORT

- 117 3# CT & seq RT 44 Gy 22# 3 w
  - Sx
    - 91% R0
    - 6% R1
    - 3% R2

Pless et al Lancet 2015; 386: 1049–56
SAKK 16/00: Outcomes

Median PFS:
CRT 12.8 months
CT 11.6 months
p=0.67

Median OS:
CRT 37.1 months
CT 26.2 months

Pless et al Lancet 2015; 386: 1049–56
SAKK 16/00: RT Related Adverse Events

<table>
<thead>
<tr>
<th>Non-haematological</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphagia</td>
<td>70 (71%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>40 (41%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (37%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Skin toxic effects</td>
<td>24 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>20 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxic effects</td>
<td>18 (18%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>14 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>9 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>5 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>98 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>98 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>98 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>98 (100%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Pless et al Lancet 2015; 386: 1049–56
5. Optimal Radiotherapy in Stage III (N2)
RTOG 0617: Optimal RT 60-66 Gy with cCRT

Median OS
20 vs 29 months

Isotoxic Intensity Modulated Radiotherapy (IMRT) in Stage III Non Small Cell Lung Cancer (NSCLC): A feasibility study

Kate Haslett¹, Neil Bayman¹, Kevin N. Franks², Nichola Groom³, Gerard G. Hanna⁴, Susan V. Harden⁵, Catherine Harris¹, Stephen Harrow⁶, Matthew Hatton⁷, Paula McCloskey⁸, Fiona McDonald⁹, Linda Ashcroft¹, W. David Ryder¹, Corinne Faivre-Finn¹⁰

¹The Christie NHS Foundation Trust, Manchester, ²Leeds Cancer Centre/University of Leeds, Leeds, ³Mount Vernon Hospital, London, ⁴Belfast City Hospital, Belfast, ⁵Addenbrookes Hospital, Cambridge, ⁶Beatson West of Scotland Cancer Centre, Glasgow, ⁷Weston Park Hospital, Sheffield, ⁸Northern Ireland Cancer Centre, Belfast, ⁹Institute of Cancer Research & Royal Marsden Hospital, London, ¹⁰The University of Manchester and The Christie NHS Foundation Trust, Manchester
Why Isotoxic Intensity Modulated Radiotherapy in NSCLC?

Poor local control and survival in stage III NSCLC
Concurrent CTRT is not suitable for all patients
Need to optimise sequential CTRT

Combination of strategies
• Dose escalation
• Individualisation
• Acceleration
• Facilitated by the use of IMRT

Single arm prospective multicentre (7 UK centres) feasibility study
Primary endpoint: Delivery of isotoxic IMRT to dose >60 Gy EQD2 (total biologically equivalent in 2 Gy fraction)
Summary

- Current RT standard of care is delivered in a one size fits all manner
- Unmet need to intensify and individualise RT treatment
- Isotoxic IMRT is a feasible and well tolerated method of treatment intensification
- Improved survival compared to standard sequential CRT
- Future
  - Informed by clinical trials
    - UK led study comparing dose escalation to standard RT
  - Biomarkers = predict response/toxicity = individualise

ADSCAN trial

- Control Arm
  - 55Gy in 20 fractions over 28 days
- CHART-ED
  - 54Gy in 36 fractions, & 10.8Gy in 6 fractions
- IDEAL
  - Isotoxic RT 30 fractions 5 weeks
- I-START
  - Isotoxic RT, 20 fractions/4 weeks, 55-63 Gy
- Isotoxic IMRT
  - Max dose 79.2 Gy in 1.8Gy bd fractions
55 Gy in 20 #

Altered Fractionation - SOCCAR

55 Gy in 20 #

Meta-Analysis: Sequential RT Conventional vs Accelerated Fractionation

5 yr O.S. benefit = 2.5%

Mauguen et al JCO 2012; 30: 2788
Protons for stage III?

Adaptive Planning

Concurrent CRT with Protons

Protons vs IMRT

Protons vs IMRT

6. Immunotherapy – a new Pardigm?
PACIFIC: Adjuvant IO post cCRT

Stage III NSCLC Concomitant CRT with at least 2 cycles of platinum based systemic therapy

- Maintenance Anti PD-1 Duvalumab up to 12 mths
- Maintenance Placebo up to 12 mths

Disease stage:
- IIIA: 252 (52.9) vs 125 (52.7)
- IIIB: 212 (44.5) vs 107 (45.1)
- Other: 12 (2.5) vs 5 (2.1)

Antonia et al NEJM 2017; 377(20): 1919-29
## PACIFIC: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N=475)</th>
<th>Placebo (N = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade%^</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>460 (96.8)</td>
<td>222 (94.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (35.4)</td>
<td>59 (23.2)</td>
</tr>
<tr>
<td>Pneumonitis or radiation pneumonitis†</td>
<td>161 (33.9)</td>
<td>58 (24.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (23.8)</td>
<td>48 (20.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (22.3)</td>
<td>56 (23.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (18.3)</td>
<td>44 (18.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (14.7)</td>
<td>21 (9.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>30 (12.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (13.9)</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (13.1)</td>
<td>18 (7.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>59 (12.4)</td>
<td>26 (11.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>58 (12.2)</td>
<td>11 (4.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (12.2)</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>58 (12.2)</td>
<td>23 (9.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>56 (11.8)</td>
<td>20 (8.5)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>55 (11.6)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>52 (10.9)</td>
<td>21 (9.0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>51 (10.7)</td>
<td>31 (13.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (10.5)</td>
<td>27 (11.5)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39 (8.2)</td>
<td>24 (10.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>36 (7.6)</td>
<td>25 (10.7)</td>
</tr>
</tbody>
</table>
7. Novel Agents with RT in Stage III
The CONCORDE Study

Platform study of novel agents in COmbination with COnditional Radiotherapy in locally advanced disease

Gerry Hanna, Alastair Greystoke, Sarah Brown
on behalf of the CONCORDE study team

Clinical development of new drug–radiotherapy combinations

Ricky A. Sharma¹, Ruth Plummer², Julie K. Stock³, Tessa A. Greenhalgh⁴, Ozlem Ataman⁵, Stephen Kelly⁶, Robert Clay⁷, Richard A. Adams⁸, Richard D. Baird⁹, Lucinda Billingham⁴⁰, Sarah R. Brown¹¹, Sean Buckland¹², Helen Bulbeck¹³, Anthony J. Chalmers¹⁴, Glen Clack¹⁴, Aaron N. Cranston¹⁵, Lars Damstrup¹⁶, Roberta Ferraldeschi¹⁷, Martin D. Forster¹, Julian Golec¹⁸, Russell M. Hagan¹⁹, Emma Hall²⁰, Axel-R. Hanuske²¹, Kevin J. Harrington²⁰, Tom Haswell²², Maria A. Hawkins², Tim Illidge²³, Hazel Jones², Andrew S. Kennedy²³, Fiona McDonald²⁰, Thorsten Melcher²⁴, James P. B. O’Connor²², John R. Pollard²⁵, Mark P. Saunders²², David Sebag-Montefiore²¹, Melanie Smith²⁵, John Staffurth², Ian J. Stratford²² and Stephen R. Wedge² on behalf of the NCRI CTRad Academia-Pharma Joint Working Group

Clinical Development of Drug-Radiotherapy Combinations
February 22-23, 2018
Hyatt Regency Bethesda Hotel, Bethesda, MD
UK Consensus Workshop on Drug-RT Combination Platform Studies
Potential Candidates for CONCORDE

AZD6738 (ATRi) + Radiotherapy in Murine H460 (NSCLC) Model

Clear enhancement in NSCLC lung model

CONCORDE – Study Aim and Patient Pathway

• The overall aim is to determine RP2Ds of DDRi when given in combination with radical RT, in patients with stage II or III NSCLC.

- **Registration**
- **Chemotherapy (if given)**
- **Main Consent**
- **Treatment Period**
  - Week* 1, 7
- **Formal DLT Window**
  - Week 19
- **Safety Efficacy F/U**
  - Week 52

*Timings taken from day 1 of Radiotherapy
# RT to be given as 66Gy in 2Gy Fractions

• The RP2D for each combination will be determined using the time to event continuous reassessment method (TiTE-CRM).
Primary endpoint:
• DLTs within 3 months of RT

Secondary endpoints:
• Toxicity (acute and late)
• Treatment compliance
• Best overall response
• PFS
• OS
Combined modality therapy in N2 disease

- Stage III NSCLC is a heterogeneous disease and will get more heterogeneous
- Concurrent CRT remains the gold standard in Stage IIIa NSCLC
- Standard RT dose remains 60-66 Gy or 55Gy/20#
- Sequential chemotherapy can be considered for down-staging
- Immunotherapy post CRT emerging SOC
- Novel agents may have a role in addition to CRT