Combined Modality Therapy in Non-Small Cell Lung Cancer: Radiation Oncologist’s Dilemmas

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Stage III NSCLC

Stage T1bN2M0/IIIA

Stage T2aN3M0/IIIB
What Do We Know?

• Concurrent chemoradiotherapy is accepted as standard
• Involved field RT; CT-based simulation; 3D conformal or IMRT techniques; once daily fractionation; are all standard
• Proton radiotherapy is investigated
Concurrent Chemotherapy and Thoracic RT: Overall Survival

HR = 0.84 [0.74;0.95], p = 0.004

Absolute benefit in OS with concomitant CT:
At 2 years: 5.3%
At 3 years: 5.7%
At 5 years: 4.5%

RT + conc CT
RT + seq CT

LePechoux et al, IASLC 2007
Treatment Algorithm
For Locally Advanced NSCLC: 2012

Locally Advanced NSCLC & PS 0-1

Induction Chemotherapy → Chemoradiation Therapy → Consolidation Chemotherapy
Phase III Trial of Extended (ENI) vs. Involved Field RT (IF RT)

Stage III NSCLC: Chemo→Chemo/RT
200 patients randomized

<table>
<thead>
<tr>
<th></th>
<th>ENI</th>
<th>IFRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Yr LF</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>1yr OS</td>
<td>59.7%</td>
<td>67.2%</td>
</tr>
<tr>
<td>2yr OS</td>
<td>25.6%</td>
<td>38.7%</td>
</tr>
<tr>
<td>3 yr OS</td>
<td>19.2%</td>
<td>27.3%</td>
</tr>
</tbody>
</table>

p = 0.048

Yuan S et al, Am J Clin Oncol 2007
Three-dimensional conformal radiation therapy (3D-CRT) uses CT or MRI scans, creating a 3-D picture of the tumor. Improved precision minimizes normal tissue damage.
CT simulation improves tumor definition (=no miss);

3D radiation planning allows RT of the entire tumor volume to the full uniform dose.
What is Image Guided Radiation Therapy (IGRT)?

- External beam radiation therapy with positional verification using imaging prior to each fraction (2D or 3D).

- The treatment unit must have software that allows registration of the images and calculates required shifts.

- It is a complete process that extends from the step of imaging a patient at the time of CT simulation through the step of imaging the patient again at the treatment unit.

AAPM QA Subcommittee Report  2009
IGRT

• The images used for IGRT are critical to the process, therefore IGRT is only as good as the initial image and target definition!

• “Uncertainties in target definition and microscopic spread are quickly becoming the weakest link of RT in lung cancer.”

(Sonke JJ 2010)
CT Simulation

Automated CT Segmentation

Planning

Delivery/Daily Verification

Anatomy Map ("find tumor" "find organs at risk")

Planning

Treatment Delivery ("hit tumor" "omit organs at risk")
4D CT Scan Measures Lung Cancer Motion
4D CT-scan (4D Imaging)

End-inspiration

Full respiratory cycle
4 sec

End-expiration

CT Image Sorting Program

Mid-exhale  End-exhale  Mid-inhale  End-inhale
Tumor contoured on 10 Phases of 4D CT

Phase 10

ITV

PTV
Blurry tumor halo outside CT image
CT Simulation

- Anatomy Map
  - “find tumor”
  - “find organs at risk”

Automated CT Segmentation

Planning

Delivery/Daily Verification

- Treatment Delivery
  - “hit tumor”
  - “omit organs at risk”
ExacTrac (2D Imaging)
Cone Beam CT (3D Volumetric Imaging)

CT mounted on the linear accelerator allows real-time volumetric imaging.
4D CB CT (Cone Beam CT on the Linear Accelerator)
3D? IMRT? Protons?
Proton Unit
What is the advantage, if any, of IMRT compared with 3DCRT in treating early stage or locally advanced lung cancer?

- No published randomized trials comparing IMRT with 3DCRT in lung cancer.
- IMRT Experts Consensus Panel (2012):

  “IMRT may provide dosimetric and possibly clinical advantages in radiotherapy treatment to some (possibly most or even all) patients with NSCLC being considered for high-dose, potentially curative radiotherapy. Current data are insufficient to fully determine the clinical, or even the dosimetric, advantage of IMRT versus traditional 3D conformal RT”.

Bezjak A et al, 2012
**IMRT vs. 3DRT: MD Anderson Retrospective Comparison**

3DRT (n=318); IMRT (n=91) with 4D CT planning

87% pts PET-staged in IMRT group vs. 49% in 3D group

MST
16.8 vs. 10.2 mo

Liao ZH, 2010
MDACC Phase II Trial of Proton Thoracic RT and Concurrent Carboplatin/Paclitaxel in Stage III NSCLC

- 44 pts, KPS≥70, weight loss<10%, PET-staged
- RT technique (74 Gy):
  - 4D CT simulation
  - Passively scattered proton beam RT
  - Adaptive replanning during RT (in 25% pts)
  - Median V20 was 25%
- Isolated failures:
  - Local 9%
  - Nodal 2.3%
  - No Grade 4/5 events

MST 29.4 mo
PFS 63% @ 1 yr

Chang J et al, 2012
MDACC Phase II Randomized Trial, Ongoing

Pts with Stage III NSCLC

- IMRT 74 Gy Concurrent weekly carboplatin/paclitaxel
- Protons 74 Gy (RBE) Concurrent weekly carboplatin/paclitaxel
... and Do Not Know?

• Why has the survival of patients with Stage III improved?
• What is the optimal RT dose?
• Can we boost only a portion of the tumor to high RT doses?
• Can we predict those who will fail loco-regionally?
• How to incorporate biological agents?
Concurrent ChemoRT Trials (Phase II/III, Multi-institutional)

Mediation Survival (months)

1994-98
1998-2001
2002-04
2005-08

WJLCG
RTG 94-10
CALGB 9431
SMOG 9504
NPC 95-01
Czech
LAMP
LAMP
CTRT 99/97
CALGB 39801
CALGB 39801
CALGB 30105
RTG 0117
HOG
HOG
RTG 0324
CALGB 30407
CALGB 30407
RTG 0617
RTG 0617

Courtesy: Nitin Ohri MD
Concurrent ChemoRT Trials (Phase II/III, Multi-institutional)

- Phase II PET Staging: 59%
- Phase III PET Staging: 70%, 84%, 100%

Courtesy: Nitin Ohri MD
PET Staging Causes Stage Migration

[Graph showing the percentage of patients in different stages of cancer over time, with a legend indicating PET use and stages.]
Concurrent ChemoRT Trials
(Phase II/III, Multi-institutional)

**Phase II**
- FEV1 requirement (L): 0.8, 0.8, 0.8
- PET Staging: 59%

**Phase III**
- FEV1 requirement (L): 2.0, 0.8, 1.5
- PET Staging: 70%, 84%, 100%

**Median Survival (months)**

- WuCG
- CALGB 9431
- SWOG S9504
- NPC 95-01
- Czech
- LAMP
- LAMP CTRT99/07
- CALGB 39801
- CALGB 39801
- CALGB 30105
- RTOG 0117
- HOG
- HOG RTOG 0324
- CALGB 30407
- CALGB 30407
- RTOG 0617
- RTOG 0617

*Courtesy: Nitin Ohri MD*
## RT Dose in Concurrent Chemoradiotherapy Cooperative Group Trials for NSCLC

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>RT Dose (Gy)</th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 94-31</td>
<td>66</td>
<td>17.7</td>
</tr>
<tr>
<td>GLOT</td>
<td>66</td>
<td>15.6</td>
</tr>
<tr>
<td>LAMP</td>
<td>63</td>
<td>16.1</td>
</tr>
<tr>
<td>RTOG 94-10</td>
<td>63</td>
<td>17.1</td>
</tr>
<tr>
<td>SWOG 95-04</td>
<td>61</td>
<td>26</td>
</tr>
<tr>
<td>INT O139</td>
<td>61</td>
<td>21.7</td>
</tr>
<tr>
<td>Czech</td>
<td>60</td>
<td>20.2</td>
</tr>
<tr>
<td>Study</td>
<td>Chemotherapy</td>
<td>MTD (Gy)</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>CALGB arm 1</td>
<td>Carboplatin paclitaxel</td>
<td>74</td>
</tr>
<tr>
<td>ASTRO 05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALGB arm 2</td>
<td>Gemcitabine carboplatin</td>
<td>74</td>
</tr>
<tr>
<td>ASTRO 05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCCTG</td>
<td>Carboplatin paclitaxel</td>
<td>74</td>
</tr>
<tr>
<td>ASTRO 05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNC</td>
<td>Carboplatin paclitaxel</td>
<td>74</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RTOG 0617:
Phase III Trial of Standard-Dose (60 Gy) Versus High-Dose (74 Gy) Conformal RT with Concurrent and Consolidation Chemotherapy and +/- Cetuximab in Stage III NSCLC

**Primary Endpoint** – Survival (n=512) (2 X 2 design evaluating dose and cetuximab independently)

Stratified by stage (A vs B), type of RT (3-D vs IMRT) and PS (0 vs 1)
### Pretreatment Characteristics

<table>
<thead>
<tr>
<th>Pretreatment Characteristics</th>
<th>60 Gy (n=216)</th>
<th>74 Gy (n=208)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>127 (58.8%)</td>
<td>119 (57.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>89 (41.2%)</td>
<td>89 (42.8%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>27 (12.5%)</td>
<td>30 (14.4%)</td>
</tr>
<tr>
<td>White</td>
<td>189 (87.5%)</td>
<td>178 (85.6%)</td>
</tr>
<tr>
<td>RT Technique</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3DCRT</td>
<td>116 (57.3%)</td>
<td>113 (54.3%)</td>
</tr>
<tr>
<td>IMRT</td>
<td>100 (46.3%)</td>
<td>95 (45.7%)</td>
</tr>
<tr>
<td>PET Staging</td>
<td>91.2%</td>
<td>88.9%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>86 (39.8%)</td>
<td>73 (35.1%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>86 (39.8%)</td>
<td>96 (46.2%)</td>
</tr>
<tr>
<td>NSCLC NOS</td>
<td>39 (18.1%)</td>
<td>33 (15.9%)</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>138 (65.7%)</td>
<td>131 (63.6%)</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>72 (34.3%)</td>
<td>75 (36.4%)</td>
</tr>
</tbody>
</table>

Bradley J, 2012
# RTOG 0617

## Toxicity Definitely, Probably, or Possibly Related to Treatment (Using CTCAE Version 3.0)

**September 2011**

<table>
<thead>
<tr>
<th></th>
<th>Arm A: 60 Gy +/- Cetuximab (n=192)</th>
<th>Arm B: 74 Gy +/- Cetuximab (n=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Worst non-hematologic</td>
<td>79 (41.1%)</td>
<td>14 (7.3%)</td>
</tr>
<tr>
<td>Worst overall</td>
<td>84 (43.8%)</td>
<td>45 (23.4%)</td>
</tr>
</tbody>
</table>

### Grade 5 Events

- As scored by institution:
  - 2 Pulmonary
  - 1 Thrombosis
  - 1 Death NOS
- No significant difference:
  - 2 Pulmonary
  - 1 Thrombosis
  - 1 Upper Gl Hemorrhage
  - 1 Pulmonary Hemorrhage
  - 1 Pneumonia NOS
  - 1 Esophageal
  - 1 Death NOS
Overall Survival – Comparison of 60 Gy vs. 74 Gy Arms

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard Dose: 60 Gy</th>
<th></th>
<th>High Dose: 74 Gy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Alive</td>
<td># at Risk</td>
<td>% Alive</td>
<td># at Risk</td>
</tr>
<tr>
<td>0</td>
<td>100.0%</td>
<td>213</td>
<td>100.0%</td>
<td>204</td>
</tr>
<tr>
<td>3</td>
<td>98.5%</td>
<td>190</td>
<td>95.4%</td>
<td>175</td>
</tr>
<tr>
<td>6</td>
<td>91.2%</td>
<td>149</td>
<td>87.7%</td>
<td>137</td>
</tr>
<tr>
<td>9</td>
<td>84.7%</td>
<td>124</td>
<td>78.4%</td>
<td>116</td>
</tr>
<tr>
<td>12</td>
<td>81%</td>
<td>104</td>
<td>70.4%</td>
<td>93</td>
</tr>
<tr>
<td>Dead/Total</td>
<td>58/213</td>
<td></td>
<td>70/204</td>
<td></td>
</tr>
</tbody>
</table>

MST (mo) | 21.7 | 20.7

p = 0.02 (one-sided p-value, left tail)

(9410 CON-QD one-year survival = 62.1%, MST = 17.0 months)
RTOG 0617: Overall Survival by RT Dose

Overall Survival (%)

Patients at Risk

<table>
<thead>
<tr>
<th>RT Dose</th>
<th>Patients at Risk</th>
<th>Months since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy</td>
<td>213</td>
<td>190 149 124 104</td>
</tr>
<tr>
<td>74 Gy</td>
<td>204</td>
<td>175 137 116  93</td>
</tr>
</tbody>
</table>

*One-sided p-value, left tail

HR = 1.45 (1.02, 2.05)  p* = 0.02
Multivariate Cox Model Backwards Selection

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>60Gy v 74 Gy</td>
<td>1.55 (1.07, 2.23)</td>
<td>0.020</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-squam v Squam</td>
<td>1.37 (0.94, 1.98)</td>
<td>0.097</td>
</tr>
<tr>
<td>Gross Tumor Volume</td>
<td>Continuous</td>
<td>1.002 (1.000, 1.003)</td>
<td>0.034</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>1.010 (1.004, 1.017)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Exit criteria = p>0.10; radiation dose and histology forced to remain.
Covariates dropped from the model were: gender, age, lung V5.

RTOG will undertake a careful re-analysis of all heart contours and doses received by the heart.
Conclusions

- The high dose (74 Gy) arms were closed for futility (cannot show a survival benefit with further follow up)
- The trial continued accrual to 60 Gy +/- Cetuximab and closed in May 2012
- Toxicity was similar between arms
- Factors associated with improved overall survival are lower radiation dose (60 Gy), non-squamous histology, smaller gross tumor volume and heart V5
- At this point, no clear reason for the lack of benefit on the high dose arm has emerged
“Dose-painting” Based on FDG-PET Scan

• A new paradigm of “biologic conformality” where variable doses are delivered to portions of tumor (rather than current emphasis on the homogenous dose).

• Target volumes for prescription of additional dose can be defined based on individual voxels (“paint-by-number” approach), or the tumor can be segmented into one or more subvolumes (compartments).

• Assumption that regions with high tracer uptake can be interpreted as target for RT dose escalation (rather than hypometabolic, hypoxic areas) will have to be proven true.
Mid-course FDG-PET (40-50 Gy) & Post-RT PET

Kong F et al, JCO 2007
Mid-course FDG-PET & Outcome

Kong F et al, JCO 2007
Lung Cancer Response During RT (days: 0, 7, 14) as Prognostic Variable

- 55% had a metab resp at 70 days; 45% were NON-RESPONDERS (and responders lived longer).
- Non-responders had significantly higher max SUVs at all time points investigated (in addition to different time trends)

van Baardwijk A et al, 2007
A large heterogeneity in changes in SUV max were observed during thoracic RT, possibly stratifying patients into prognostic groups before they complete treatment.
Primary endpoint:
local progression-free survival at 1 yr

66 Gy given in 24 fractions of 2.75 Gy with an integrated boost to the primary tumor as a whole to 81.6 Gy. MLD 19 Gy

66 Gy given in 24 fractions of 2.75 Gy with an integrated boost to the 50% SUVmax area to 93.6 Gy. MLD 19.9 Gy
Concurrent chemo-radiotherapy. T2-4N0-3M0. Primary tumor diameter 4 cm or more. MaxSUV > 5. Eligible for radical treatment.

Register

Dose calculation

Dose escalation not possible

Chemo-radiotherapy to tolerance

Dose escalation possible

RANDOMIZE

Homogeneous boost

Inhomogeneous boost

De Ruysscher D, Belderbos J et al 2010
RTOG 1106: Randomized Phase II Trial of Individualized Adaptive Radiation Dose Escalation Using During-Treatment FDG-PET in Locally Advanced NSCLC

**SCREENING PLAN**
to determine Mean Lung Dose & Tx Dose Bin (74 Gy to 95% PTV)

**STRATIFIED RANDOMIZATION (MEAN LUNG DOSE & TUMOR VOLUME)**

**ARM 1: CONCURRENT CHEMO-RT**
RT to 50 Gy (2 Gy/Fx)
Carboplatin/Paclitaxel Weekly

**ARM 2: CONCURRENT CHEMO-RT**
RT to 47.5-49.5 Gy (variable Gy/Fx)
Carboplatin/Paclitaxel Weekly

**DURING-TX FDG-PET/CT IMAGING**

**ARM 1: CONTINUE RT**
Same RT plan to 60 Gy total (30 Fx)

**ARM 2: ADAPTIVE RT**
Based on during-tx FDG-PET
RT up to 85.5 Gy individualized by MLD

**CONSOLIDATIVE CHEMOTHERAPY**
Dry Run Credentialing

- Provided Pre & During-Tx 4DCT & PET/CT to 11 pilot sites to perform:
  - Registration
  - Contouring
  - Screening Plan
  - Initial Plan
  - Adaptive Plan
  - Electronic Data Submission including protocol datasheet
## Results: Screening Plan

<table>
<thead>
<tr>
<th>Metric</th>
<th>Per Protocol - Acceptable</th>
<th>Dry Run (mean ± σ for 11 institutions)</th>
<th># Institutions Per Protocol or Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of PTV covered by 74 Gy</td>
<td>95% - 90%</td>
<td>94.2 ± 2.9 %</td>
<td>10/11</td>
</tr>
<tr>
<td>Mean Lung Dose</td>
<td>NA</td>
<td>18.3 ± 1.5 Gy</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Results: Initial Plan

<table>
<thead>
<tr>
<th>Metric</th>
<th>Per Protocol - Acceptable</th>
<th>Dry Run</th>
<th># Institutions Per Protocol or Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of PTV covered by Rx Dose</td>
<td>95 % - 90 %</td>
<td>92.3 ± 3.1 %</td>
<td>9/11</td>
</tr>
</tbody>
</table>

![Diagram showing radiation dose distribution](image-url)
Contour Variations

PreGTV

Heart

Brachial Plexus

Courtesy of Yunfeng Cui
# Results: Adaptive Plan

<table>
<thead>
<tr>
<th>Metric</th>
<th>Per Protocol - Acceptable</th>
<th>Dry Run</th>
<th># Institutions Per Protocol or Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Dose Rx</td>
<td>NA</td>
<td>$3.61 \pm 0.63 \text{ Gy/Fx}$</td>
<td>NA</td>
</tr>
<tr>
<td>% of PTV covered by Rx Dose</td>
<td>95 % - 90 %</td>
<td>$81.9 \pm 22.2 %$</td>
<td>6/11</td>
</tr>
</tbody>
</table>

**DurPTV (Adaptive Rx)**
## Results: Composite Plan

<table>
<thead>
<tr>
<th>Metric</th>
<th>Per Protocol - Acceptable</th>
<th>Dry Run</th>
<th># Institutions Per Protocol or Acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of PTV covered by Rx Dose</td>
<td>95 % - 90 %</td>
<td>92.0 ± 8.6 %</td>
<td>7/11</td>
</tr>
</tbody>
</table>
Conclusions

• Most centers can follow process for creating plans & accumulating dose for adaptive lung therapy with multiple datasets
• Clarifications needed regarding contouring atlas for heart, brachial plexus, and nodal targets
• More education required on planning priorities in areas of PTV/OAR overlap
Half of NSCLCs have an identifiable driver mutation.

In 2012, it is important to know whether the patient has EGFR and ALK in 2012 genetic aberrations.

How to incorporate these findings into combined modality therapy?
Treatment Algorithm For Advanced NSCLC: First Line Therapy 2012

Advanced Stage NSCLC & PS 0-1

- **EGFR mutation positive**
  - Erlotinib or Gefitinib 1\(^{st}\) line

- **ELM4-ALK positive**
  - Consider Crizotinib 1\(^{st}\) or 2\(^{nd}\) line

- **EFGR mutation & ALK negative & Nonsquamous histology**
  - Consider
    - Carboplatin-Paclitaxel + Bevacizumab or Cisplatin-Pemetrexed +/- Bevacizumab

- **EFGR mutation/ALK negative & Squamous histology**
  - Consider
    - Cisplatin or Carboplatin combined with Pemetrexed, Docetaxel or Gemcitabine or Paclitaxel or Cisplatin-Vinorelbine ± Cetuximab

**Updated from Gandara, Herbst et al: Clin Lung Cancer 2009**
Comparison of Responses: *EGFR* mutations with erlotinib vs *EML4-ALK* translocations with Crizotinib in Advanced NSCLC

70% partial response rate

Jackman CCR 2009, Bang ASCO 2010
EGFR +
EML4-ALK +

70% partial response
Individualized Combined Modality Therapy for Stage III Non-small Cell Lung Cancer (NSCLC)

RTOG 1210/Alliance 31101

Stratification

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Weight Loss (in prior 6 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EGFR</td>
<td>1. ≤ 5%</td>
</tr>
<tr>
<td>2. ALK</td>
<td>2. &gt; 5%</td>
</tr>
</tbody>
</table>

EGFR TK Mutation Cohort

**Arm 1:** Erlotinib, 150 mg/day for 12 weeks

**Arm 2:** Concurrent Chemotherapy and radiation, 64 Gy

Concurrent chemotherapy and radiation, 64 Gy
Individualized Combined Modality Therapy for Stage III Non-small Cell Lung Cancer (NSCLC) 
RTOG 1210/Alliance 31101

**Stratification**

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Weight Loss (in prior 6 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. EGFR</td>
<td>1. ≤ 5%</td>
</tr>
<tr>
<td>2. ALK</td>
<td>2. &gt; 5%</td>
</tr>
</tbody>
</table>

**ALK Tran L Cohort**

**Arm 1**: Crizotinib, 250 mg/bid for 12 weeks

**Arm 2**: Concurrent chemotherapy and radiation, 64 Gy

Concurrent chemotherapy and radiation, 64 Gy
“When meditating over the disease, I never think of finding a remedy for it, but instead, a means of preventing it.”

Louis Pasteur (1822-1895)