Current Status of Radiotherapy in Lung Cancer

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• Stage I SBRT:
  – Curative treatment for inoperable patients (LC: 96.5%)
  – May consider as curative treatment for operable patients (Chang et al., Lancet 2015)

• Stage II-IIIA surgical candidate:
  – Neoadjuvant chemoradiation (INT0139)
  – PORT for N2 positive after surgery

• Stage IIIA/IIIB:
  – Combined with chemotherapy for curative treatment if patient not surgical candidate (MST 21-28 mo, Bradley 2015)
  – Co

• Stage IV:
  – Oligomet (Gomez Lancet 2016)
Therapy of Lung Cancer

IV: Systemic therapy + Palliative/consolidative RT

I-III A: Surgery ± adjuvant chemotherapy + PORT

IIIA, IIIB, Combined Chemoradiation

I-III A: Surgery ± adjuvant chemotherapy + PORT

I-III A: Surgery ± adjuvant chemotherapy + PORT

Local

Regional

Distant
Case: Early Stage NSCLC
## Selected SBRT Prospective Reports

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Dose</th>
<th>FU</th>
<th>LC %</th>
<th>OS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyoto</td>
<td>45</td>
<td>12 Gy x 4</td>
<td>32 mo</td>
<td>94</td>
<td>83/72 (3-yr)</td>
</tr>
<tr>
<td>Stanford</td>
<td>20</td>
<td>15-30 x 1</td>
<td>18 mo</td>
<td>----</td>
<td>-------</td>
</tr>
<tr>
<td>Scandinavian</td>
<td>57</td>
<td>15 Gy x 3</td>
<td>35 mo</td>
<td>92 (3-yr)</td>
<td>60 (3-yr)</td>
</tr>
<tr>
<td>Indiana</td>
<td>70</td>
<td>20-22 x 3</td>
<td>50 mo</td>
<td>88 (3y)</td>
<td>43 (3-yr)</td>
</tr>
<tr>
<td>RTOG 0236</td>
<td>55</td>
<td>20 Gy x 3</td>
<td>34 mo</td>
<td>97</td>
<td>56 (3-yr)</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>19-30 x 1</td>
<td>15 mo</td>
<td>68</td>
<td>37 (3-yr)</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>62</td>
<td>15 Gy x 3</td>
<td>28 mo</td>
<td>88</td>
<td>57 (3-yr)</td>
</tr>
<tr>
<td>Tohoku</td>
<td>31</td>
<td>15 x 3, 7.5x8</td>
<td>32 mo</td>
<td>78/40</td>
<td>71 (3-yr)</td>
</tr>
<tr>
<td>VU Univ</td>
<td>206</td>
<td>20 x 3,12 x 5, 7.5 x 8</td>
<td>12 mo</td>
<td>97</td>
<td>64 (2-yr)</td>
</tr>
</tbody>
</table>
RTOG 0236

- Phase II
- T1-3No (up to 5 cm) (except “central lesions”)
- 20 Gy x 3 fractions (with HC is 18 Gy x 3) to PTV
- Each fx separated by at least 40 hrs (completed w/in 14 d)
- 55 patients were evaluable
- Median followup: 34 mos
- 3 yr LC = 98%
  - LC defined: failure within 1cm of treated area
- 3 yr DM = 20%
- Median OS = 48 mos, 2 yr OS=72%, DFS=67%

Timmerman R et al., JAMA 2010
RTOG 0915

- “A randomized phase II study comparing 2 SBRT schedules for medically inoperable patients with stage I peripheral NSCLC”
- T1-T2, < 5cm tumors, no central lesions
  - Arm 1: 34 Gy x 1
  - Arm 2: 12 Gy x 4
- Primary objective: Rate of 1 yr >= grade 3 AE
- Secondary objectives: 1-yr LC, OS, DFS, PET change, PFT change, biomarkers prediction for RP and LC
SBRT dose schemes

**Table 4. SBRT Regimens and Indications for Lung Tumors**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34 Gy x 1</td>
<td>Peripheral small (&lt; 2 cm) tumors, &gt; 1 cm from chest wall</td>
</tr>
<tr>
<td>15-20 Gy x 3</td>
<td>Peripheral &lt; 5 cm tumors, &gt; 1 cm from chest wall</td>
</tr>
<tr>
<td>12-12.5 Gy x 4</td>
<td>Peripheral tumors, particularly those &lt; 1 cm from chest wall</td>
</tr>
<tr>
<td>10-11 Gy x 5</td>
<td>Peripheral tumors, particularly those &lt; 1 cm from chest wall</td>
</tr>
</tbody>
</table>

* 7 Gy x 10   Centralized tumors, apical tumors, around vessels

**All schedules achieve ≥ 100 BED**

* MDACC off protocol consensus

NCCN® Practice Guidelines in Oncology – v.2.2010
Early Stage: Locoregional Failure Depends on BED

<table>
<thead>
<tr>
<th></th>
<th>BED &lt; 100 Gy</th>
<th>BED &gt; 100 Gy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Tumor</td>
<td>43%</td>
<td>8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Regional nodal</td>
<td>21%</td>
<td>9%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>26%</td>
<td>19%</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Onishi et al., JTO 2007
BED for different regimens

\[
\text{BED} = \text{nd} \left\{ [1+\left[ \frac{d}{(\alpha/\beta)} \right] ] \right\}
\]

**BED[(α/β) =10]:**
- 72 Gy: 60 Gy in 30Fx (Conventional RT)
- 84 Gy: 70 Gy in 35Fx
- 88.8 Gy: 74 Gy in 37Fx
- 96 Gy: 60 Gy in 10Fx
- 106 Gy: 48 Gy in 4Fx (Japan Oncology Group)
- 112.5 Gy: 50 Gy in 4Fx (MD Anderson, PTV)
- 119 Gy: 70 Gy in 10Fx (MD Anderson, GTV)
- 151.2 Gy: 54 Gy in 3Fx (RTOG, STAR Trial)
- 180 Gy: 60 Gy in 3Fx (RTOG, 80% Isodose)
SBRT for early stage **OPERABLE** NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>N of pts</th>
<th>Median F/U (mo)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu</td>
<td>50</td>
<td>36</td>
<td>3-yr, 86%</td>
</tr>
<tr>
<td></td>
<td>(29 operable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onishi</td>
<td>257</td>
<td>38</td>
<td>3-yr, 80%</td>
</tr>
<tr>
<td></td>
<td>(99 operable)</td>
<td></td>
<td>5-yr, 71%</td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Adj Chemo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9633</td>
<td>3-yr, 73%</td>
<td>3-yr, 80%</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>5-yr, 58%</td>
<td>5-yr, 60%</td>
<td>0.190</td>
</tr>
</tbody>
</table>

Strauss et al., JCO 26(27):1-12; 2008
Early Stage: SBRT as Curative Treatment

- BED: 112.5 - 151.2 Gy
  - 50Gy/12.5 Gy/fx x 4
  - 54Gy/18 Gy/fx x 3
  - 60Gy/12 Gy/fx x 5
- PTV = GTV + 3mm
- GTV: 110-140% of prescribe dose
- Volumetric IGRT/Motion management

Chang et al., Lancet Oncol. 2015
Increasing Radiation Therapy Dose Is Associated With Improved Survival in Patients Undergoing SBRT for Stage I NSCLC

Overall survival of T2 tumors treated with SBRT stratified by dose; low-dose cohort BED <150 Gy; high-dose BED >150 Gy

SBRT to Central Lesions enhances toxicity using Timmerman regimen

2-year freedom for Grade 3-5 toxicity
- 83% for peripheral lesion
- 54% for central lesions

Current RTOG study: 50 Gy in 5 fraction

Timmerman R et al., J Clin Oncol 2006
Conclusions – Early Stage NSCLC SBRT

- Treatment of choice for inoperable early stage NSCLC
- Improved OS in elderly patients
- Reduce toxicity – respect the dose constraints
- Short term toxicity, OS, and LC outcome comparable to Surgery
- Long term outcome data to be matured, toxicity and LR will increase over time
- Effect of adjuvant chemotherapy – extract from the surgery experience and limited data in SBRT group
Therapy of Lung Cancer

IV: Systemic therapy + Palliative/consolidative RT

I-IIIa: Surgery ± adjuvant chemotherapy + PORT

IIIA, IIIB, Combined Chemoradiation
Lung INT 0139 - Methods

Trial open 1994-2001

396 patients with pT1-3N2M0

and Etoposide 50mg/m² x 2 concurrent 45 Gy/25

Reassess CT scan and repeat PFTs 2-4 wks after RT

Surgery (if response 88%)

61 Gy (no interrupt)

Cis/Etoposide x2

Cis/Etoposide x2

Primary Objective: Overall Survival
Lung INT 0139 - Results

Progression Free Survival

HR = 0.77 95% CL (0.62-0.96) p = 0.017

Overall Survival

HR = 0.87 95% CL (0.70-1.10) p = 0.24
Lung INT 0139 - Results

- Progression but not overall survival (main objective) was improved with trimodality therapy over chemoradiation

- Patients unable to receive surgery do very poorly
**Lung INT 0139 - Results**

**INT 0139 Exploratory Survival Analysis**

- All but 1 postoperative death followed a pneumonectomy

- Hypothesized survival advantage for CT/RT/S if lobectomy performed and for CT/RT if pneumonectomy

- Patients on CT/RT/S were matched with those on CT/RT arm on 4 prestudy factors (KPS, age, sex, T stage); match feasible for 90/98 lobectomies and 51/54 pneumonectomies

![INT 0139 Treatment-Related Deaths on CT/RT/S Arm (n=16) Table](image)
Lung INT 0139 - Results

After lobectomy

- CT/RT/S: 57/90
- CT/RT: 74/90

Logrank p = 0.002

After pneumonectomy

- CT/RT/S: 38/51
- CT/RT: 42/51

Logrank p = NS

Pneumonectomy performed in 13/29 (45%) pT0N0 pts
Postoperative Radiation Therapy (PORT) for NSCLC – who to treat?
PORT: Clinical Scenario

57 y/o male, routine annual chest X-ray showed left upper lobe mass
PET/CT, CT with contrast confirmed left upper lobe 2.5 cm tumor
Bronchoscope and FNA: Squamous cell carcinoma
EBU: negative at station 7, 11R
Underwent LUL sleeve lobectomy and mediastinal nodal dissection
Post op Path: 2.5 cm poorly differentiated SCC, 2/4 of level 5 LN positive
High local recurrence in stage III patients after surgery alone

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Stage</th>
<th>XRT dose</th>
<th>Survival</th>
<th>LRF w/o RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium (van Houtte et al. 1980)</td>
<td>202</td>
<td>I-III</td>
<td>60 Gy</td>
<td>43%</td>
<td>11%</td>
</tr>
<tr>
<td>LCSG (Weisenburger 1986)</td>
<td>230</td>
<td>II-III</td>
<td>50 Gy</td>
<td>40%</td>
<td>21%</td>
</tr>
<tr>
<td>CAMS (Feng et al. 2000)</td>
<td>317</td>
<td>II-III</td>
<td>60 Gy</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>Lille (Lafitte et al., 1996)</td>
<td>163</td>
<td>I</td>
<td>45-60 Gy</td>
<td>52%</td>
<td>17%</td>
</tr>
<tr>
<td>MRC LU11 (Stephens et al 1996)</td>
<td>308</td>
<td>II-III</td>
<td>40 Gy</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>Austria (Mayer et al. 1997)</td>
<td>155</td>
<td>I-III</td>
<td>50-56 Gy</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>GETCB (Dautzenberg et al. 1999)</td>
<td>720</td>
<td>I-III</td>
<td>60 Gy</td>
<td>43%</td>
<td>34%</td>
</tr>
<tr>
<td>Slovenia (Debevec et al. 1996)</td>
<td>74</td>
<td>III</td>
<td>30 Gy</td>
<td>20%</td>
<td>NA</td>
</tr>
<tr>
<td>Italy (Trodella et al. 2002)</td>
<td>104</td>
<td>I</td>
<td>50 Gy</td>
<td>58%</td>
<td>22%</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy improves survival after surgical resection

LACE Meta-analysis (Pignon JCO 2008)
- 5.4% Overall Survival Benefit with adjuvant chemotherapy
- A detrimental effect in patients with:
  1) Stage IA disease
  2) PS 2

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Events / No. Patients</th>
<th>Hazard Ratio</th>
<th>Probability of interaction/trend* test</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IA</td>
<td>104 / 347</td>
<td></td>
<td>.06</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515 / 1,371</td>
<td></td>
<td>.04*</td>
</tr>
<tr>
<td>Stage II</td>
<td>893 / 1,616</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>878 / 1,247</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Postop RT (PORT) improves LC but not overall survival

Table 3.1.2.1. Results of selected randomized trials of postoperative radiotherapy (PORT) for NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Stage</th>
<th>XRT dose (Gy)</th>
<th>Survival with XRT</th>
<th>Survival without XRT</th>
<th>LRF with XRT</th>
<th>LRF without XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium (van Houtte et al. 1980)</td>
<td>202</td>
<td>I--III</td>
<td>60</td>
<td>24%</td>
<td>43%</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>LCSG773 (Weisenburger et al. 1986)</td>
<td>230</td>
<td>II,III</td>
<td>50</td>
<td>40%</td>
<td>40%</td>
<td>3%</td>
<td>21%</td>
</tr>
<tr>
<td>CAMS (Feng et al. 2000)</td>
<td>317</td>
<td>II,III</td>
<td>60</td>
<td>43%</td>
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<td>155</td>
<td>I--III</td>
<td>50-56</td>
<td>30%</td>
<td>20%</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>GETCB (Dautzenberg et al. 1999)</td>
<td>720</td>
<td>I--III</td>
<td>60</td>
<td>30%</td>
<td>43%</td>
<td>28%</td>
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<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Italy (Trodella et al. 2002)</td>
<td>104</td>
<td>I</td>
<td>50</td>
<td>67%</td>
<td>58%</td>
<td>2%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*a Statistically significant difference (p ≤ 0.05)  
*b Data not available.
PORT Meta-Analysis demonstrates PORT is detrimental for <N2 disease

- N=2128, 9 RCTs (1966-1994)
- ≥ Co-60, 30-60 Gy
- OS worse in PORT (HR 1.21), equipoise for N2
- Caveats: Co-60, poor techniques, > 2 Gy per fx, high rates of mortality due to non-cancer deaths (DID)

PORT Meta-analysis Trialist Group, Lancet 1998
PORT Meta-analysis of 9 Trials in 2128 Pts

- Inadequate staging
- Patients with N0 disease in 4 trials
- RT technology (5 yrs: Co-60 8% vs Linear 30%)
- RT techniques (lateral beams in majority of the trials)
- Dose and fractionation (60 Gy, 2.6-3 Gy/fx)
- Trial size imbalance

Lancet 1998; 352:257
SEER PORT study

Stage II/III, lobectomy/penumonectomy, no prior RT, minimal 4 mo survival, cause of death defined

Decrease in use of PORT after 1998

Lally et al., JCO, 2006
Clinical Scenario

Adjuvant chemotherapy CDDP+Docetaxel X 3
Follow-up PET/CT scan one year later, recurrence in the mediastinum
Modern data suggests toxicity from PORT much less than once thought

- **U. Penn** (Machtay et al. JCO 2001)
  - 202 pts at Mayo (1982-98), surgery + PORT
  - All Linac-based, computerized dosimetry, conventional fractionation
  - 4 yr DID for PORT=13.4% vs. matched controls=10%

- **ECOG 3590** reanalysis (Wakelee et al. Lung Cancer 2005)
  - 488 pts randomized to PORT vs PORT + chemo
  - All linac-based, computerized dosimetry, 50.4 Gy
  - 4 yr DID 12.9%, compared to gender matched controls and controlled for smoking is 10.1% (p=0.16)
## SEER PORT study

### Table 4. Comparison of Overall Survival and Disease-Free Survival for Each Nodal Stage

<table>
<thead>
<tr>
<th>Nodal Stage</th>
<th>Overall Survival</th>
<th>Disease-Free Survival</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-Year Rate (%)</td>
<td>5-Year Rate (%)</td>
<td>HR</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>Radiotherapy</td>
<td>31</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>N1</td>
<td>Radiotherapy</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>N2</td>
<td>Radiotherapy</td>
<td>27</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; Ref, reference.

PORT increased DFS, OS and DSS of N2 patients

Lally et al., JCO, 2006
Modern data for PORT suggests survival benefit in select patients

- **ANITA adjuvant chemo trial**
  - PORT was recommended for pN+ disease
  - Retrospective analysis of PORT outcomes
  - 232 of 840 pts received PORT (45-60 Gy)
  - Overall, PORT had deleterious impact on survival
  - PORT improved survival in two groups
    - pN1 patients **without** chemotherapy (MS 50 vs 26 mos)
      - But detrimental for pN1 pts with chemo (MS 47 vs 94 mos)
    - pN2 patients with or without chemotherapy (MS 47 vs 24 mos, and 23 vs 13 mos)

Douillard JY et al., IJROBP 2008
Operable LA-NSCLC: 3 D Era (2003 or later) PORT increase OS

Plot of overall survival for (A) all patients, (B) N0 patients, (C) N1 patients, and (D) N2 patients stratified by postoperative radiotherapy (PORT) use.

Elyn H. Wang et al. JCO 2015;33:2727-2734

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Modern data for PORT suggests survival benefit in select patients

- **Italian PORT** for stage I patients
  - Phase III, 1989-1997, all *pathologic* stage I
  - 104 patients randomized to PORT or no PORT 50.4 Gy
  - Target volume: bronchial stump, ipsi hilum (mean treated area 50 cm²)
  - PORT improved Local control (97.8% vs 77%) and overall survival (67% vs 58%, p=0.048)
  - Toxicity from PORT minimum (6 pts developed Grade 1 lung toxicity)

Trodella L et al., Rad Oncol 2002
# Lung –ART Trial

International phase III trial compare OS of completely resected N2 node after PORT vs. no PORT

**Volume definition:**

---

<table>
<thead>
<tr>
<th>Surgically involved mediastinal nodes</th>
<th>LN stations to be included in the CTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2R</td>
<td>1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>1–2L</td>
<td>1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>3 (Right -sided tumor)</td>
<td>3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>3 (Left-sided tumor)</td>
<td>3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>4R</td>
<td>2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>4L</td>
<td>2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>5</td>
<td>2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>6</td>
<td>2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*</td>
</tr>
<tr>
<td>7 (Right-sided tumor)</td>
<td>4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*</td>
</tr>
<tr>
<td>7 (Left-sided tumor)</td>
<td>4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*</td>
</tr>
<tr>
<td>8 (Right-sided tumor)</td>
<td>4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction</td>
</tr>
<tr>
<td>8 (Left-sided tumor)</td>
<td>4L, 5, 6, 7 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction</td>
</tr>
</tbody>
</table>

*Abbreviations: LN = lymph node; CTV = clinical target volume.*

*Unless other nodes are involved.*
PORT: Indications, Volume, and Dose

- **Indications/dose:**
  - N2 node/50 Gy/25 fractions
  - N2 node with ECE/54Gy/25-30 fractions
  - Positive margin (60-66 Gy/30-33 fractions, NCCN suggest concurrent chemo)
  - Gross residual: treat as unresected NSCLC
  - Surgeon’s concern – always talk to the surgeon to locate the area of concern

- **Volume:** involved nodal station/hilum (always review the preop images to understand where is the high risk area)

- **IMRT/IMRT SIB** (when ECE or positive margin)
Summary: PORT in the modern era

• PORT has a tainted past that is largely due to poor quality radiation and techniques
• Using modern approaches, deaths due to intercurrent disease should be ~2 to 3% (should be better than this since these were 3D CRT)
• PORT should improve survival in the highest risk patients (stage III-N2) with or without adjuvant chemotherapy
• The phase III Lung ART trial should definitively answer this question
Locally Advanced Non-small-cell Lung Cancer
Therapy of Lung Cancer

IV: Systemic therapy + Palliative/consolidative RT

I-III A: Surgery ± adjuvant chemotherapy + PORT

IIIA, IIIB, Combined Chemoradiation

Distant

Local

Regional
Imaging
Imaging
Treatment Recommendation?

- Stage IIIB NSCLC:
  - Multiple LN levels
  - SCV LN
  - Large primary and LNs

- Significant respiratory symptoms

- Concurrent chemoradiation
Modest Improvement in Survival Outcomes over 40 years

Median Survival Time (month)

1980's 1990's 2000's 2010s

Modified from Hak Choy 2003
Auperin Metaanalysis

  - Metanalysis 6 trials
- ChemoRT
  - Improves PFS and OS
  - Reduces LRF: 28% vs. 34%
  - Does not effect DM
  - Increases Grade 3+ esophagitis: 18% vs. 2%

3 yr OS
- ChemoRT: 23.8%
- Chemo → RT: 18.1%

Auperin et al. 2010 JCO 28 (13) 2181-2190
CALGB 39801: Induction chemotherapy → Definitive CRT showed no benefit

- Phase III RCT
- 366 pts unresectable IIIA/B
- Randomized to CRT 66 Gy vs Induction chemo x 2 cycles → CRT 66 Gy
- Higher rates of Grade 3/4 neutropenia with induction chemotherapy
- No difference in OS between arms, even when analyzing good prognostic pts (wt loss <5%)

Vokes EE et al., J Clin Oncol 2007
Consolidation chemotherapy – Meta analysis showed no benefit

- Systematic pooled analysis of the literature
- Phase II/III trials treated with CRT +/- consolidation chemo (CCT+ or CCT-)
- 41 studies were identified, including 7 phase III trials
- 25 trials had consolidation chemo, and 20 did not
- There were no difference in pooled mOS for CCT+ (19 mos) vs CCT- (17.9 mos) (p=0.4)
- No difference in toxicities

Tsujino K et al., JTO 2013
RTOG 0617: higher dose or cetuximab does not benefit unselected patients over std CRT

<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>0</td>
<td>100.0%</td>
<td>213</td>
<td>100.0%</td>
<td>204</td>
</tr>
<tr>
<td>6</td>
<td>91.0%</td>
<td>190</td>
<td>87.3%</td>
<td>178</td>
</tr>
<tr>
<td>12</td>
<td>81.3%</td>
<td>161</td>
<td>69.4%</td>
<td>135</td>
</tr>
<tr>
<td>15</td>
<td>77.0%</td>
<td>141</td>
<td>61.0%</td>
<td>112</td>
</tr>
<tr>
<td>18</td>
<td>66.9%</td>
<td>108</td>
<td>53.9%</td>
<td>87</td>
</tr>
</tbody>
</table>

Dead/Total: 90/213 vs. 117/206

Median Sv: 28.7 mo (95% CI: 22.0, NR) vs. 19.5 mos (16.5, 23.2)

**Overall Survival**

Progression free survival:
- 18 mos
  - Standard Dose: 60 Gy: 36.6%
  - High Dose: 74 Gy: 26.3%
  - P value: 0.0116

Local failure:
- Standard Dose: 60 Gy: 25.1%
- High Dose: 74 Gy: 34.3%
- P value: 0.0319

(RTOG 9410 CON-QD one-year survival = 62.1%, MST = 17.0 months)
CRT-CT ± Gefitinib - SWOGS0023

CRT-CDDP+Etopside, 61 Gy, n=571
Consolidation Docetaxel x 3 if no DP, n=429
Gefitinib maintenance if no PD, n=243

**Fig 2.** Overall survival for patients receiving gefitinib or placebo.

**Fig 3.** Progression-free survival for patients receiving gefitinib or placebo.

Trials for stage III NSCLC – on going

• **Molecularly-based**
  – RTOG 1306 (EGFR mutation or ALK translocation)
    ▪ Erlotinib + CRT
    ▪ Crizotinib + CRT
  – 2012-1053 (Kras mutation): Trametinib (MEK1/2i) + CRT

• **Immunotherapy combined**
  – PACIFIC (MEDI4736, PD-L1) (induction chemo allowed) (sequential)
  – DETERRED (MPDL3280A, PD-L1) (concurrent and sequential)

• **Non-Molecular-based**
  – RTOG 1327/NRG-LU001 (Metformin)
Proton therapy
A Bayesian Randomization Trial of Intensity Modulated Radiation Therapy (IMRT) vs. 3-Dimensional Passively Scattered Proton Therapy (3DPT) for Locally Advanced Non-Small Cell Lung Carcinoma

(clinicaltrials.gov identifier NCT00915005)


Supported in part by NCI grants P01 CA021230 and U19 CA021239.
Why Protons?

- Exquisite dose distributions
- Potential for reduction in normal tissue doses
- Potential for escalation of tumor doses
- Reduction in toxicity, improvements in QOL
- Improvement in local control and survival
- Possible biological advantages
Advantage of Proton Over IMRT in Planning Studies
Hypothesis

Proton therapy will

- Reduce irradiated lung volume, hence reduce radiation pneumonitis (RP)
- Achieve same local control (LC) with same biological effective radiation dose (RBE=1.1)
Rationale for Trial Design

• Bayesian adaptive randomization
  – more patients allocate to the more effective treatment if difference exits
  – Otherwise, patients will be assigned with equal probability to either treatment

• Randomize only when both IMRT and proton pretreatment plans met dose constraints at same prescription dose
  – Address the believe that “...for virtually all clinical situations that the dose to the tumour target can be increased, meaning higher tumour control probabilities and/or the dose to normal, non-tumour containing volumes can be decreased, reducing the risks of normal tissue complications” – Glimelius B, Montelius A. Proton beam therapy – do we need the randomised trials and can we do them? Radiother Oncol 2007;83:105–9.
Primary Objective

Protocol Failure (Dual endpoints):

- RP grade $\geq 3$ (CTCAE 3.0)
  - IMRT = 15%
  - 3DPT = 5%

- Local failure (PET, CT, biopsy):
  - IMRT = 3DPT
  - 15% 6mo, 25% 12mo.
Randomization Schema

- Eligible Stage II-IIIb, IV NSCLC patients; Informed consent
- 4D simulation; Delineation of targets and normal tissues
- 74 CGE proton & photon plans achievable
- 66 CGE proton & photon plans achievable
- Randomize at achieved dose level
- Photons (Group 1)
- Protons (Group 2)
- Insurancne
- OK
- Denied
- Photons @ highest dose achievable (Group 4)
- Modality that allows higher dose (Group 3)

During treatment
- Weekly CT images
- Re-planning if indicated
- MDASI - Lung (optional)
- Blood samples (optional)

Follow-up (see table)
- Monthly tox. Assessment
- Tests on each follow-up visit

Peer reviewed contours and plans

Endpoint evaluation:
- Internal Outcomes Review Committee
- External Expert Review Committee – reviewed all RPs
Total 26 patients were denied insurance coverage for protocol treatment
8 patients wanted protons

Excluded from analysis N=49:
1. Chemotherapy only: 1
2. Consented twice
3. Closed to patient accrual: 3
4. Disease progression: 8
5. GTV movement > 2 cm: 1
6. Ineligible body weight: 1
7. Insurance denied: 8

Signed informed consent N = 274

N = 105
- Treated with IMRT N=92
- Preferred protons N = 6
- Off protocol N = 7
  (3 insurance denial protocol)

N = 76
- Treated with 3DPT N = 57
- Insurance denied protons so treated with IMRT N =15
- Off protocol N = 4

8 patients wanted protons
Baseline Characteristics

- Demographics (age, gender, ECOG, smoking status, histology, stage) no difference.

- Target Volumes:

<table>
<thead>
<tr>
<th>Target Volumes (cc)</th>
<th>IMRT</th>
<th>3DPT</th>
<th>Total</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>Median</td>
<td>66.10</td>
<td>77.7</td>
<td>70.3</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(5.75-686.59)</td>
<td>(1.9-673.7)</td>
<td>(1.9-686.59)</td>
</tr>
<tr>
<td>ITV</td>
<td>Median</td>
<td>257.655</td>
<td>320.7</td>
<td>292.7</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(42.01-1316.24)</td>
<td>(30-1384)</td>
<td>(30-1384)</td>
</tr>
<tr>
<td>PTV</td>
<td>Median</td>
<td>429.35</td>
<td>524.9</td>
<td>480.31</td>
</tr>
<tr>
<td></td>
<td>Min-Max</td>
<td>(103.92-1776.06)</td>
<td>(76-1906)</td>
<td>(76-1906)</td>
</tr>
</tbody>
</table>

- RT dose 74 Gy: IMRT vs. 3DPT = 63% vs. 75.4% (p<0.001)
Lung, Esophagus and Heart Mean Dose

Mean Lung Dose      Mean Esophagus Dose      Mean Heart Dose

- P=0.16
- P<0.01
- P=0.59
Lung and Heart V5-V80

Lung V5 – V80

Heart V5 – V80

Note: Analysis carried out using the Wilcoxon rank-sum test (also known as Mann-Whitney Two Sample Statistic)
Protocol Failure - Randomized and Treated According to Protocol

Protocol Failure Free Survival

Grade ≥3 TRP

Local Failure

P=0.55

Number at risk

IMRT 92 (16) 62 (10) 36 (1) 20 (0) 13 (0) 6 (1) 0
Proton 57 (12) 38 (7) 21 (1) 12 (0) 9 (0) 3 (1) 1

Number at risk

IMRT 92 (1) 86 (3) 78 (2) 74 (0) 72
Proton 57 (0) 56 (5) 48 (1) 44 (0) 41

Number at risk

IMRT 92 (10) 66 (11) 38 (1) 21 (0) 14 (1) 6 (1) 0
Proton 57 (6) 40 (8) 21 (1) 12 (0) 9 (0) 3 (1) 1
# Radiation Pneumonitis

<table>
<thead>
<tr>
<th>RP Grade</th>
<th>IMRT N=92</th>
<th>3DPT N=57</th>
<th>Total N=149</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>36</td>
<td>101</td>
<td>0.36</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>11</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Gr 0-2 86 51 137 0.54

Gr 3-5 6 (6.5%) 6 (10.5%) 12 (8.1%)

Median Time to RP:

- All = 4.3 month,
- IMRT= 4.5 month,
- 3DPT= 4.0 month (p=0.15)
• Cancer death similar
• More treatment related death at 74 Gy
• Higher Heart V5 and V35
• Non compliance to Chemotherapy
• Prolonged overall Treatment Time - OTT

Heart Exposure and Cardiac Biomarker

Xu, et al., ASTRO 2014
An Example of 3D Isodose Comparison for 3DPT vs. IMRT Plans

PSPT 90% IRV\textsubscript{NT} = 1041 cc

IMRT 90% IRV\textsubscript{NT} = 74 cc
Continuous Improvement in Both IMRT and Proton (steeper learning curve)

### IMRT

<table>
<thead>
<tr>
<th>Analysis Time (Months)</th>
<th>Proportion</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 12 24 36 48 60 72</td>
<td>0.00 0.25 0.50 0.75 1.00</td>
<td>&lt;= 9/27/2011 49 (9) 32 (9) 18 (1) 15 (0) 13 (0) 6 (1) 0 &gt; 9/27/2011 43 (7) 30 (1) 18 (0) 5 (0) 0 (0) 0 (0) 0</td>
</tr>
</tbody>
</table>

**P=0.05**

### 3DPT

<table>
<thead>
<tr>
<th>Analysis Time (Months)</th>
<th>Proportion</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 12 24 36 48 60 72</td>
<td>0.00 0.25 0.50 0.75 1.00</td>
<td>&lt;= 9/27/2011 30 (9) 19 (6) 11 (0) 8 (0) 8 (0) 3 (1) 1 &gt; 9/27/2011 27 (3) 19 (1) 10 (1) 4 (0) 1 (0) 0 (0) 0</td>
</tr>
</tbody>
</table>

**P=0.027**

### Multivariate Analysis

<table>
<thead>
<tr>
<th>Time of Enrollment</th>
<th>HR</th>
<th>P-Value</th>
<th>95% C.I.</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;9/27/2011</td>
<td>0.35</td>
<td>0.002</td>
<td>0.18</td>
<td>0.68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Mean Dose</th>
<th>HR</th>
<th>P-Value</th>
<th>95% C.I.</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>1.03</td>
<td>0.011</td>
<td>1.01</td>
<td>1.05</td>
</tr>
</tbody>
</table>
All RP in PT Arm Occurred in the Early Group
Conclusions

• Considerably fewer RP events occurred in IMRT group
• PSPT
  – Significant heart sparing – impact on OS to be determined (RTOG 1308)
  – Irradiated larger lung volume at the high dose end of the DVH – proton specific dose constraints needed
  – Insurance denial impacted on patient allocation (n=26)
Conclusions

- No difference in RP or Local Failure when pretreatment comparative IMRT and PSPT plans met the standard dose constraints for the same prescription dose
  - Future designs should allow the use of the best achievable plans for each modality in terms of prescription dose and/or normal tissue sparing
- Patient enrolled after 9/27/2011 did better – learning and improving on both modalities
RTOG 1308: Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Chemoradiation Therapy for Inoperable Stage II-IIIB NSCLC

PI: Zhongxing Liao
<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>Stage</th>
<th>R A N D O M I Z E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.II</td>
<td>Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</td>
</tr>
<tr>
<td></td>
<td>2.IIIA</td>
<td>Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy**</td>
</tr>
<tr>
<td></td>
<td>3.IIIB</td>
<td>Both Arms: Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>Histology</th>
<th>R A N D O M I Z E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.Squamous</td>
<td>Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy**</td>
</tr>
<tr>
<td></td>
<td>2.Non-Squamous</td>
<td>Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy**</td>
</tr>
</tbody>
</table>

**The total prescribed dose will be 70 Gy (Relative Biological Effectiveness (RBE)) without exceeding tolerance dose-volume limits of all critical normal structures. (See Section 6.1.3 when 70 Gy (RBE) is not achieved)**

**Chemotherapy delivered concurrently, cisplatin/ etoposide or carboplatin/paclitaxel doublets, is required. The site/investigator must declare the chemotherapy regimen that the patient will receive prior to the patient’s randomization. See Section 7.0 for details.**

***If carboplatin and paclitaxel is administered concurrently with radiotherapy, 2 cycles of carboplatin and paclitaxel consolidation chemotherapy are required. If cisplatin and etoposide is administered concurrently with radiotherapy, consolidation chemotherapy is not allowed.**
Simultaneous Integrated Boost IMRT vs. IMPT with Concurrent Chemo-Radiotherapy Randomized NSCLC Trial Schema

**Stage:**
1. II
2. IIIA
3. IIIB

**Histology:**
1. Squamous
2. Non-squamous

**Induction Chemotherapy**
1. Yes
2. No

Arm 1: IMRT SIB plus platinum-based doublet chemotherapy
- PTV dose: 60 Gy (RBE)/2Gy (RBE)
- SIBV* dose: 78** Gy(RBE)/ 2.6 Gy(RBE)

Arm 2: Arm 1: IMPT SIB plus platinum-based doublet chemotherapy
- PTV dose: 60 Gy (RBE)/2Gy (RBE)
- SIBV dose: 78** Gy(RBE)/ 2.6 Gy(RBE)

*The total prescribed dose to SIBV will be 78 Gy (Relative Biological Effectiveness (RBE)) without exceeding tolerance dose-volume limits of all critical normal structures. The SIBV dose can be lowered to 66Gy in 30 Fractions to meet normal tissue dose constraints.
Therapy of Lung Cancer

I-IIIa: Surgery ± adjuvant chemotherapy + PORT

IIIA, IIIB, Combined Chemoradiation

Distant

IV: Systemic therapy + Palliative/consolidative RT

Local

Regional
RT for stage IV Disease

Stage T1N2M1, stage IV oligomet
Local Consolidative Therapy (LCT) Improves Progression-Free Survival (PFS) in Patients with Oligometastatic Non-Small Cell Lung Cancer (NSCLC) who do not Progress after Front Line Systemic Therapy (FLST): Results of a Multi-Institutional Phase II Randomized Study

Daniel Gomez, George Blumenschein, Jack Lee, Mike Hernandez, Ross Camidge, Robert Doebele, Laurie Gaspar, Don Gibbons, Jose Karam, Brian Kavanagh, Ritsuko Komaki, Alexander Louie, David Palma, Anne Tsao, William William, Jianjun Zhang, Stephen Swisher*, John Heymach*, on behalf of the MD Anderson Cancer Center Lung Cancer Moon Shot Initiative

Gomez et al., Lancet Oncol 2016; 17: 1672–82
Trial Design

Major eligibility criteria:

– 1) Histologic confirmation of NSCLC
– 2) AJCC 7th Edition Stage IV Disease
– 3) No RECIST progression after front line systemic therapy (FLST)
– 4) ≤3 metastasis after FLST (N1-N3 included as 1 site in setting of stage IV disease)
– 5) No malignant pleural effusion

Definition of FLST:

– ≥4 cycles of platinum-doublet chemotherapy
– ≥3 months of erlotinib, afatinib, or gefitinib therapy if EGFR mutation
– ≥3 months of crizotinib therapy if EML4-ALK fusion

Gomez et al., Lancet Oncol 2016; 17: 1672–82
Trial Design

Step 1: Enrollment

Front Line Systemic Therapy

Step 2: Enrollment Non-PD, Enroll, Randomize

Physician choice for standard maintenance or surveillance*

Consider LCT (surgery ± radiation to primary and metastases)

PD/Toxicity

LCT (surgery ± radiation to primary and metastases)

Physician choice for standard maintenance or surveillance*

Crossover Allowed at Progression

Surgery and RT Allowed

Gomez et al., Lancet Oncol 2016; 17: 1672–82
74 Patients Enrolled into Step 1 (Induction Phase)

49 Patients Enrolled into Step 2 and Randomization

25 Patients Not Enrolled into Step 2 and Randomization

25 Patients Receiving LCT

24 Patients Receiving No LCT

<table>
<thead>
<tr>
<th>Treatment regimens of LCT arm</th>
<th>N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypofractionated RT/SBRT</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Combination chemoRT &amp; hypofractionated RT</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Combination surgery &amp; RT</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>ChemoRT alone</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Progressed prior to local treatment</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

N=12 progression
N=5 refused randomization
N=4 lost to follow-up
N=3 further studies deemed ineligible
N=1 study closed prior to randomization
Outcomes

One patient inevaluable (24 in each group)

Median PFS times:

No-LCT arm: 3.9 months (95% CI 2.2-6.6 months)

LCT arm: 11.9 months (95% CI 5.4 months-NA)

Gomez et al., Lancet Oncol 2016; 17: 1672–82
Prognostic Factors for PFS

- Two other factors associated with PFS:
  - Number of Mets after FLST
  - EGFR/ALK Status

![Graphs showing progression-free survival probability for different numbers of mets and EGFR/ALK status.]

P-value = 0.043

Presented at ASCO 2016 by: Daniel Gomez, M.D.
Conclusions

• In patients with oligometastatic NSCLC who do not progress after FLST, LCT associated with improved PFS

• Exploratory Analysis - LCT also increased time to development of new lesions – suggests reduction in metastatic spread

• LCT with acceptable toxicity and without substantial differences in toxicity compared to no-LCT arm

• OS data not yet mature, patients continue to be followed
General Approaches for Cancer Immunotherapy

- **Active immunotherapy**
  - Peptide vaccine
  - DC vaccine
  - Genetic vaccine
  - IL-2
  - IFN
  - IL-15
  - IL-21

- **Adoptive cell transfer immunotherapy**
  - T cell cloning
  - TCR or CAR genetic engineering

- **Checkpoints**
  - PD-1
  - CTLa-4
  - CD137
  - OX40
  - CD40
Nivolumab vs Docetaxel for Stage 4 NSCLC with progression after 1\textsuperscript{st} line chemotherapy

**Checkmate 017: SCCA**

Brahmer J et al., NEJM 2015

**Checkmate 057: non-SCCA**

Borghaei H et al., NEJM 2015

FDA Approval 2015 (for both SCCA and non-SCCA NSCLC)
KEYNOTE-010: Pembrolizumab vs. Docetaxel in PD-L1 + NSCLC Failed First Line

- Previously treated NSCLC with PD-L1 expression on at least 1% of tumour cells
- 8/28/2013-2/27/2015,
- 1034/2699 pts 1:1:1 randomization
- 345 at 2 mg/kg, MST 10.4 month
- 346 10 mg/kg, MST 12.7 month
- 343 docetaxel, MST 8.5 month.

Herbst et al., Lancet 2016; 387: 1540–50
KEYNOTE -010: Pembrolizumab vs. Docetaxel

Herbst et al., Lancet 2016; 387: 1540–50

<table>
<thead>
<tr>
<th>Sex</th>
<th>Events/patients (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>332/634</td>
<td>0.65 (0.52–0.81)</td>
</tr>
<tr>
<td>Female</td>
<td>189/399</td>
<td>0.69 (0.51–0.94)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>317/604</td>
<td>0.63 (0.50–0.79)</td>
</tr>
<tr>
<td>≥65</td>
<td>204/429</td>
<td>0.76 (0.57–1.02)</td>
</tr>
<tr>
<td>ECOG status</td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>149/348</td>
<td>0.73 (0.52–1.02)</td>
</tr>
<tr>
<td>1</td>
<td>367/678</td>
<td>0.63 (0.51–0.78)</td>
</tr>
<tr>
<td>PD-L1 tumour proportion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>204/442</td>
<td>0.53 (0.40–0.70)</td>
</tr>
<tr>
<td>1–49%</td>
<td>317/581</td>
<td>0.76 (0.60–0.96)</td>
</tr>
<tr>
<td>Tumour sample</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archival</td>
<td>266/455</td>
<td>0.70 (0.54–0.98)</td>
</tr>
<tr>
<td>New</td>
<td>255/578</td>
<td>0.64 (0.50–0.83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>128/232</td>
<td>0.74 (0.50–1.09)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>332/708</td>
<td>0.63 (0.50–0.79)</td>
</tr>
<tr>
<td>EGFR status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>46/86</td>
<td>0.88 (0.65–1.20)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>447/875</td>
<td>0.66 (0.55–0.80)</td>
</tr>
<tr>
<td>Overall</td>
<td>521/1033</td>
<td>0.67 (0.56–0.80)</td>
</tr>
</tbody>
</table>

(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.
POPLAR: Atezolizumab versus docetaxel Previously Treated NSCLC

- Phase II randomized trial 5/13-3/14
- 144 atezolizumab, OS 12.6 mo
- 143 docetaxel, OS 9.7 mo, p=0.04
- PD-L1 expression associated with OS
- Atezolizumab significantly improved survival compared

Fehrenbacher et al., Lancet 2016; 387: 1837–46
POPLAR: Atezolizumab versus docetaxel Previously Treated NSCLC

Fehrenbacher et al., Lancet 2016; 387: 1837–46
POPLAR: Atezolizumab versus docetaxel Previously Treated NSCLC

Figure 3: Overall survival
(A) Kaplan-Meier estimates in intention-to-treat population. (B) HRs for overall survival in programmed death ligand 1 (PD-L1) subgroups. (C) Kaplan-Meier estimates in the TC3 or IC3 population. (D) Kaplan-Meier estimates in the TC2/3 or IC2/3 population. (E) Kaplan-Meier estimates in the TC1/2/3 or IC1/2/3 population. (F) Kaplan-Meier estimates in the TC0 and IC0 population. Grey dashed line represents minimum follow-up of 13 months. NE=non-estimable. HR=hazard ratio. TC=tumour cell. IC=immune cell. *Unstratified hazard ratios were used for subgroup analyses. †p value for exploratory purposes only.
POPLAR: Atezolizumab versus docetaxel Previously Treated NSCLC

Fehrenbacher et al., Lancet 2016; 387: 1837–46
RT Combined with Immunotherapy

Potential to use as curative treatment for stage IV disease?
Rationale to Combine Immunotherapy with Radiotherapy to Enhance Anti-tumor Effect

Figure 2: Immunological interpretation of the abscopal effect
Ag=antigen. TCR=T-cell receptor. iT=immature T-cell. Th=T-helper cell. Tc=cytotoxic T cell. IL2=interleukin 2. IFNα=interferon α. TNFβ=tumour necrosis factor β.

Abscopal after Progression on Nivolumab

Welsh et al. The Cancer Journal Vol 22 Num 2, April 2016
Ongoing Clinical I/O + XRT trials

- Phase I trial of ipilimumab plus XRT (Sponsor: BMS; PI: Welsh)
- Phase I/II trial of the anti-PD1 agent MK-3475 plus XRT in NSCLC (Sponsor: Merck; PI: Welsh)
- Phase I/II trial of MK-3475 plus XRT in SCLC (Sponsor: Merck; PI: Welsh)
- Phase I/II trial of XRT for patients progressing on immunotherapy (Sponsor: Varian; PI: Welsh, Hahn, Tang)
- Phase I/II trial of nivolumab/ ipilimumab plus XRT in NSCLC brain mets (Sponsor: BMS; PI: Jing Li)
- Phase I/II trial of anti-PD1 plus XRT in lymphoma (Sponsor: Merck; PI: Chelsea Pinnix)
- Phase I/II trial of anti-PD1 plus XRT in mesothelioma (Sponsor: Merck; PI: Daniel Gomez)
- I-SABR, Oligo Mets, PI: Chang
<table>
<thead>
<tr>
<th>Institution and study details</th>
<th>SABR dose (Gy)/fraction</th>
<th>SABR Target</th>
<th>Immunotherapy agent</th>
<th>Sequence of treatments</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins University, NCT01950195 (REF. 45)</td>
<td>NS</td>
<td>Brain, spine</td>
<td>Ipilimumab</td>
<td>Immunotherapy, then SABR, then immunotherapy</td>
<td>I</td>
</tr>
<tr>
<td>University of Pennsylvania, NCT01497808 (RADVAX)(^6)</td>
<td>NS</td>
<td>NS</td>
<td>Ipilimumab</td>
<td>SABR then immunotherapy</td>
<td>I/II</td>
</tr>
<tr>
<td>MD Anderson Cancer Center, NCT02239900 (REF. 47)</td>
<td>• 50/4 • 60/10</td>
<td>Liver, lung, adrenal</td>
<td>Ipilimumab</td>
<td>Concurrent; or immunotherapy then SABR</td>
<td>I/II</td>
</tr>
<tr>
<td>Chiles Research Institute, NCT01862900 (REF. 68)</td>
<td>• 15/1 • 20/1</td>
<td>Lung, liver</td>
<td>Anti-OX40</td>
<td>Concurrent</td>
<td>I/II</td>
</tr>
<tr>
<td>Stanford University, NCT01769222 (REF. 69)</td>
<td>20/2</td>
<td>Any</td>
<td>Ipilimumab</td>
<td>Concurrent</td>
<td>I/II</td>
</tr>
<tr>
<td>New York University, NCT01401062 (REF. 70)</td>
<td>22.5/3</td>
<td>Any</td>
<td>Fresolimumab</td>
<td>Concurrent</td>
<td>I/II</td>
</tr>
<tr>
<td>NIH/NCI, NCT02298946 (REF. 71)</td>
<td>• 8/1 • 24/3</td>
<td>Liver</td>
<td>PD-1 inhibitor</td>
<td>SABR then immunotherapy</td>
<td>I</td>
</tr>
<tr>
<td>Thomas Jefferson University, NCT01703507 (REF. 72)</td>
<td>• 24/1 • 21/1 • 18/1 • 15/1</td>
<td>Brain</td>
<td>Ipilimumab</td>
<td>Concurrent</td>
<td>I</td>
</tr>
<tr>
<td>MD Anderson Cancer Center, NCT02444741 (REF. 73)</td>
<td>50/4</td>
<td>Lung, liver</td>
<td>PD-1 inhibitor</td>
<td>Concurrent</td>
<td>I/II</td>
</tr>
</tbody>
</table>

ISABR; Immunotherapy and stereotactic ablative radiotherapy; NCI, National Cancer Institute; NS, not specified; PD-1, programmed cell death protein 1; SABR, stereotactic ablative radiotherapy.
Radiotherapy for NSCLC-Summary

- Early stage NSCLC: SBRT
- LA-NSCLC
  - Preop ChemoRT plus lobectomy (INT 0139)
  - PORT: Indicated for N2 disease (OS benefit)
  - Concurrent CRT
    - Concurrent ChemoRT (60Gy standard RTOG 617)
    - High Dose RT was associated with poorer OS in RTOG 0617:
    - Rationale for proton therapy - RTOG 1308
    - Targeted agents combined with chemoradiation – patient selection by mutation status
    - Immunotherapy combined with chemoradiation – clinical trial ongoing
- Stage IV
  - LCT for oligometastasis - improve PFS
  - ISABR – under clinical investigation
Overall Conclusions

- Definitive concurrent chemoradiation (RTOG9410, Auperin Meta-Analysis) to 60-66 Gy
  - Dose escalation to 74 Gy – worse survival (RTOG 0617)
  - Addition of Cetuximab not beneficial (RTOG 0617)
  - No clinical trials comparing cisplatin+etoposide (MS ~17 months?) vs carboplatin+paclitaxel (MS ~26 months?)
- Consider triple therapy (INT0139) if clear surgical candidate
  - Contraindicated if risk of not conducting surgery or if pneumonectomy likely
- Consider clinical trials
  - RTOG 1106 – mid-treatment PET adapted hypofractionated boost
  - RTOG 1308 – phase III protons vs photons to escalate dose to 70 Gy
  - Combination of RT + immune-checkpoint inhibitors/targeted agents
Acknowledgement

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My colleagues
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My Research staff
MD Anderson Cancer Center
Our host