What is Next for Patients with Stage III Non-Small Cell Lung Cancer?

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NRG Oncology Group Chairman
Stage III Non-Small Cell Lung Cancer

Scale of the Problem

• Over 50,000 Americans Dx’ed w Stage III NSCLC/Yr
• Major improvements in diagnosis & therapy
  • Staging (Imaging (PET) & Interventional Pulmonology)
    • Significant Stage Migration (Will Rogers Effect)
  • Radiation oncology
    • Image Guidance
    • Intensity Modulation
    • Time/Dose Considerations
  • Surgery (improved techniques & broader access)
## TNM* Staging of NSCLC: Stage III vs IV

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Image</th>
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<td>Stage IIIa</td>
<td>T1-3 T3</td>
<td>N2 N1</td>
<td>M0 M0</td>
<td>![Stage IIIa Image]</td>
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<td>Stage IIIb</td>
<td>T4 Any T</td>
<td>Any N N3</td>
<td>M0 M0</td>
<td>![Stage IIIb Image]</td>
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<td>Any N</td>
<td>M1</td>
<td>![Stage IV Image]</td>
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</table>

*T=primary tumor; N, nodal involvement; M, distant metastasis.
Mediastinoscopy vs EndoBrochial Ultrasound

Survival Trend Locally Advanced NSCLC Pts on Chemo-RT Randomized Trials since 1980-2010

Stage IV?
Stage III Non-Small Cell Lung Cancer

Scale of the Problem

• Few advances in systemic therapy for stage III patients
• Little use of tumor molecular profiling in guiding therapy
• No established predictive/prognostic biomarkers related to:
  • Treatment efficacy
  • Treatment-related toxicity
• Declining enrollment of stage III patients on clinical trials
• Is there a systemic standard of care?
Stage III NSCLC
Macro N2+ or Any N3+ or R1+ and Good PS

• Definitive concurrent chemo-RT
• Subject of most non-operative stage III trials
• Evolution of median survival times from 12 to 24+ months
Is There and Optimal Chemotherapy Regimen for Concurrent Chemo-RT?

Randomized phase II study of concurrent cisplatin/etoposide vs paclitaxel/carboplatin with RT for stage III NSCLC

Randomized phase II study of concurrent cisplatin/etoposide vs paclitaxel/carboplatin with RT for stage III NSCLC

Fig. 2. (A) The overall survival (OS) and (B) the progression-free survival (PFS) curves.

PROCLAIM: Study Design

Concurrent Phase

Pemetrexed: 500 mg/m²
Cisplatin: 75 mg/m², q3w
TRT: 66 Gy, 2 Gy/fx daily
3 CYCLES

Etoposide: 50 mg/m²
D1–5, q4w
Cisplatin: 50 mg/m²
D1, 8, q4w
TRT: 66 Gy, 2 Gy/fx daily
2 CYCLES

Recovery Period
(3–5 wks)

Consolidation Phase

Pemetrexed: 500 mg/m², q3w
4 CYCLES

Investigator’s choice:
Etoposide-Cisplatin:
(same dosing/schedule)
or
Vinorelbine-Cisplatin:
Vin: 30 mg/m² iv, D1, 8, q3w
Cis: 75 mg/m² D1, q3w
or
Paclitaxel-Carboplatin:
Pac: 200 mg/m² iv, q3w
Car: AUC=6 iv, q3w
2 CYCLES

Arm A

Previously untreated stage IIA–IIIB* nonsquamous NSCLC
PS 0/1

Arm B

PR/CR/SD per RECIST


†Stratified for: ECOG PS (0 vs 1); PET scan staging (yes vs no); gender; and disease stage (IIIA vs IIIB).

Overall Survival in PROCLAIM Trial

• Stage III NSCLC
• ECOG PS 0-1

• Weekly Chemotherapy
  • Carboplatin AUC=2
  • Paclitaxel 45 mg/m²

• Thoracic Radiotherapy
  • 60 Gy, 2Gy/day

• Veliparib:
  • -1: 40 mg BUD
  • 0: 60 mg BID
  • 1: 80 mg BID
  • 2: 120 mg BID
  • 3: 200 mg BID

• Two 21 day cycles of Carboplatin AUC=6 & Paclitaxel=200 mg/m²
• Veliparib 120 mg BID
AFT07 Trial M14-360 - Randomized Phase II

- Stage III NSCLC
- ECOG PS 0-1

Randomize:

- Carbo/Taxol
- Veliparib/RT

Randomize:

- Carbo/Taxol
- Veliparib

Randomize:

- Carbo/Taxol
- Placebo

JCO (2014)
Good PS Unresected Stage III NSCLC Pts: What Positive Level 1 Evidence is There?

• Chemo-RT:
  • Better survival than RT alone

• Concurrent chemo-RT:
  • Better survival than sequential chemo-rt

• Thrice-daily RT (CHART):
  • Better survival than standard RT

• Higher total dose RT with chemo???
Good PS Stage III NSCLC Pts: What Positive Level 1 Evidence is There?

• Chemo-RT:
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• Concurrent Chemo-RT:
  • Better Survival than Sequential Chemo-RT

• Thrice-Daily RT (CHART):
  • Better Survival than Standard RT

• Higher Total Dose RT with Chemo???
Concurrent vs Sequential Chemo-RT

RTOG 9410

concurrent vs sequential

Overall Survival: Meta-Analysis

Absolute Benefit in OS with Concomitant CT:

- At 2 years: 5.3%
- At 3 years: 5.7%
- At 5 years: 4.5%

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

START Trial
Delivery of Concurrent vs Sequential Chemo-RT

Does More Chemotherapy Help?  
Induction and Concomitant CR-RT Phase III CALGB Trial

Phase III Trial of Concurrent Chemo-RT +/- Consolidation Docetaxel & Cisplatin


Fig 2. (A) Progression-free survival. (B) Overall survival. CCRT, concurrent chemoradiotherapy; mOS, median overall survival; mPFS, median progression-free survival.
Good PS Stage III NSCLC Pts: What Positive Level 1 Evidence is There?

- Chemo-RT:
  - Better Survival than RT Alone
- Concurrent Chemo-RT:
  - Better Survival than Sequential Chemo-RT
- Thrice-Daily RT (CHART):
  - Better Survival than Standard RT
- Higher Total Dose RT with Chemo???
NRG/RTOG 0617: Trial Design

Stratify:
- RT Technique (IMRT vs 3D)
- Perf Status (0 vs 1)
- Histology (squam vs other)
- PET staging (yes vs no)

RT: 60 Gy
Paclitaxel
Carboplatin +/- Cetuximab

RT: 74 Gy
Paclitaxel
Carboplatin X 2
+/- Cetuximab

Paclitaxel
Carboplatin +/− Cetuximab

Overall and Progression-free Survival by RT dose
RTOG 0617: ASTRO 2017 Update
The effect of institutional clinical trial enrollment volume on survival of patients with stage III NSCLC treated with chemo-RT: A report of RTOG 0617

Eaton, BR, Pugh, S Bradley, J,...Curran, W. JNCI 2016

Overall Survival by Accrual Volume: RTOG 0617

Median OS 26 months HVC vs. 20 months LVC
(HR 0.70, 95% CI 0.56 – 0.88, p = 0.002)

Conclusion
RTOG 0617 Analysis by Eaton et al

Multidisciplinary Care of Stage III NSCLC Pts

• Experience matters
• Survival advantage to those treated at experienced center
• Implications for future studies?
• Did use of IMRT factor into this?

NRG/RTOG 0617 Analysis
3DCRT vs IMRT: Chun et al, JCO 2017

– **Rationale**
  - IMRT improves target conformity and reduces both high and intermediate dose volumes
  - Exchange for large low dose bath

– **Hypothesis**
  - IMRT may improve outcomes for patients with Stage III NSCLC

IMRT vs 3DCRT in NRG/RTOG 0617

- Effect of IMRT Compared to 3D-CRT
  - Similar survival despite of worse tumors in IMRT group
  - Less severe pneumonitis with IMRT
  - More chemotherapy delivered with IMRT
  - Low dose bath not associated with any severe toxicity (i.e. lung V5)

- Radiation Treatment Planning
  - Lung doses – V20 significantly associated with severe pneumonitis
  - Heart doses can be reduced with IMRT
Good PS Stage III NSCLC Pts: Selected Research Questions in 2017

• Can radiotherapy be further improved?
  • Better use of functional imaging?
  • Biomarkers for RT-responsiveness?
  • Better education of low volume centers?
  • Testing of proton therapy?

• Can new systemic therapy approaches help?
  • Targeted to a mutation defined subgroup?
  • Not targeted to a specific NSCLC subgroup?
Good PS Stage III NSCLC Pts: Selected Research Questions in 2017

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  • Biomarkers for RT-responsiveness?
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• Can new systemic therapy approaches help?
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NRG 1106: Stage III NSCLC
Adaptive RT Based on Mid-Course PET Response
138/138 Enrolled: Closed to Enrollment 3/17

REGISTRATION

PRE-TX FDG-PET/CT (FMISO-PET/CT) IMAGING

STRATIFIED RANDOMIZATION (TUMOR SIZE, NODAL DISEASE, HISTOLOGY)

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

ARM 2: CONCURRENT CHEMO-RT
RT to 48.3 Gy (2.3 Gy/Fx)
Carboplatin/Paclitaxel Weekly

DURING-TX FDG-PET/CT IMAGING (AFTER FX 18-19 BOTH ARMS)

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

ARM 2: ADAPTIVE RT
Based on during-tx FDG-PET RT 2.0 – 3.9 Gy/Fx up to 74 Gy individualized by MLD

CONSOLIDATIVE CHEMOTHERAPY
PET-Adapted Radiation Therapy
NRG/RTOG 1106

Initial PET/CT

Mid-Tx PET/CT

RTOG 1106

~3 wks
PET-Adapted Radiation Therapy

RTOG 1106
~3 wks
(47.5 Gy/19 fx @ 2.5 Gy/fx)
Good PS Stage III NSCLC Pts: Selected Research Questions in 2017

• Can radiotherapy be further improved?
  • Better use of functional imaging?
  • Biomarkers for RT-responsiveness?
  • Better education of low volume centers?
  • Testing of proton therapy?

• Can new systemic therapy approaches help?
  • Targeted to a mutation defined subgroup?
  • Not targeted to a specific NSCLC subgroup?
100 NSCLC Patients at U Michigan
Kaplan-Meier Estimates of Overall Survival According to the Serum MicroRNA Signature

P = 0.001

Low risk (N=53)
MST = 36.6 months

High risk (N=47)
MST = 13.3 months
Good PS Stage III NSCLC Pts: Selected Research Questions in 2017

- Can Radiotherapy Be Further Improved?
  - Better Use of Functional Imaging?
  - Biomarkers for RT-Responsiveness?
  - Better Education of Low Volume Centers?
  - Testing of Proton Therapy?
- Can New Systemic Therapy Approaches Help?
  - Targeted to a Mutation Defined Subgroup?
  - Not Targeted to a Specific NSCLC Subgroup?
Provmise of Proton Therapy in Lung Cancer?
3D Radiation vs Proton for NSCLC

NRG 1308: Protons vs IMRT

Phase III Randomized Trial Comparing Overall Survival after Photon vs Proton Radiochemotherapy for Stage II-IIIB NSCLC

Sample size = 560 Pts
Enrolled by 9/17: 105 Pts

Xing Liao, MD: PI

- Stratify Stage
  1. I
  2. II
  3. III

- Zubrod
  1. 0
  2. 1

- GTV
  1. $\leq 130$ cc
  2. $>130$ cc

- Histology
  1. Squamous
  2. Non-Squamous

- Induction chemotherapy
  1. Yes
  2. No

Arm 1
- Photon: 60 Gy at 2 Gy once a day plus weekly platinum based doublet chemotherapy

Arm 2
- Protons: 74 Gy(RBE) at 2 Gy (RBE) once a day plus weekly platinum based doublet chemotherapy

Arms 1 and 2: Consolidation Chemotherapy x 2 is allowed
Good PS Stage III NSCLC Pts: Selected Research Questions in 2016

• Can Radiotherapy Be Further Improved?
  • Better Use of Functional Imaging?
  • Biomarkers for RT-Responsiveness?
  • Better Education of Low Volume Centers?
  • Testing of Proton Therapy?

• Can New Systemic Therapy Approaches Help?
  • Targeted to a Mutation Defined Subgroup?
  • Not Targeted to a Specific NSCLC Subgroup?
Lung Cancer Mutation Consortium: Incidence of Single Driver Mutations 2015

Kris, M, Johnson BE, P Bunn et al, LCMC: Mutation found in 63% of the 733 tumors completely tested (CI 50-59%)
NRG/Alliance 1306 Current Design

Eligibility:
- Stage III
- Good PS

EGFR\textsubscript{m} or ALK\textsubscript{m} at CLIA Lab

EGFR\textsubscript{m} or ALK\textsubscript{m}

Stratify:
- Wt. Loss
- IIIA vs. IIIB
- Chemo (EP vs. CboTax)

Stand Concurrent ChemoRT

Erlotinib x 12 wks

ALK\textsubscript{m}

Crizotinib x 12 wks

Stand Concurrent ChemoRT

Stand Concurrent ChemoRT
NRG/Alliance 1306: Proposed Re-Design

**Pt. with Known EGFR/ALK Status**
- **R:** Stand Concurrent Chemo-RT

**Pt. with Unknown Molecular Status**
- **R:** Stand Concurrent Chemo-RT
  - **EGFRm:** Erlotinib x 12 weeks → Stand Chemo-RT
  - **ALKm:** Crizotinib x 12 weeks → Stand Chemo-RT
  - **PDL1 +:** Stand Concurrent Chemo-RT + anti-PD1

**Testing at Central Facility (similar to MATCH)**
- Stand Concurrent Chemo-RT + anti-PD1
A Multicenter, Randomized, Open-label, Phase II Trial Erlotinib vs EP with Concurrent RT for Unresectable Stage III NSCLC Pts with Activating Mutation of EGFR

(RECEL ML 28545; PI: Jinming Yu & Spring Kong)

- Chemo-naïve, inoperative stage IIIA/IIIB NSCLC
- EGFR mutation (+)
- Age 18 - 75

Primary Endpoint:
- PFS

Secondary Endpoint:
- ORR / LCR / OS / QOL / Toxicity / Molecular Marker
### RECEL Interim Results: May 2015

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<th>% (n)</th>
<th>Erlotinib+RT</th>
<th>EP+RT</th>
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<td>CR</td>
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<tr>
<td>PR</td>
<td>15.4</td>
<td>16.7</td>
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<tr>
<td>SD</td>
<td>46.2</td>
<td>33.3</td>
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<tr>
<td>PD</td>
<td>0</td>
<td>8.33</td>
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<tr>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.69</td>
<td>25</td>
</tr>
<tr>
<td>ORR</td>
<td>46.2</td>
<td>33.3</td>
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<tr>
<td>DCR</td>
<td>92.3</td>
<td>66.7</td>
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</table>

**Progression-free survival (%):**

- **TKI**: PFS: 21.3 vs 6.2 mos
- **EP**: PFS: 6.2 mos

<sup>a</sup> Cases with missing data.
Candidate Tyrosine Kinase Inhibitors? Current State

- EGRF TKI’s
  - First Generation: Erlotinib, Gefitinib
  - Subsequent Generation: Afatinib, Osimertinib
- ALK TKI’s
- Others:
  - Carbozanib
  - Crizotinib, Ceritinib, Alectinib
  - Vandetanib
  - Lenvatinib
  - Camatinib
Winship Team Approach to Targeting LKB1 Vulnerabilities in Lung Cancer

LKB1 is mutated in ~20% of lung adenocarcinomas

R01CA201340
DEFINING EARLY ESCAPE STRATEGIES IN LKB1 MUTANT LUNG CANCER

R01CA194027
DEVELOPING A PHARMACOLOGIC APPROACH TO TREAT LKB1 MUTANT NSCLC PATIENTS

Project 1
“Cell metabolism dependent restriction of LKB1 in lung cancer”

Project 2
“Interrogating the LKB1-CDK4 interaction in lung cancer”

Project 3
“Defining a combinatorial anti-metastatic strategy in LKB1 mutant lung cancer”

Cell Adhesion
Cell Cycle
Metastasis
Proliferation
Planned Phase II Clinical Trial with FAK Inhibitor

Stage IV NSCLC
4-6 cycles of platinum-based therapy
PR/SD
N=35

Tumor biopsy
exclud CR patients

PF-4554878*
Oral daily administration at 425 mg BID
Maintenance therapy

LKB1 sequencing

• PIs: Ramalingam, Sica, Rossi
• Primary endpoint: median PFS
• Secondary endpoint: new metastatic foci, overall survival, safety
• Treatment will be continued until disease progression or unacceptable toxicity
• Imaging studies will be performed every 6 weeks (2 cycles)
Good PS Stage III NSCLC Pts: Selected Research Questions in 2016

• Can Radiotherapy Be Further Improved?
  • Better Use of Functional Imaging?
  • Biomarkers for RT-Responsiveness?
  • Better Education of Low Volume Centers?
  • Testing of Proton Therapy?

• Can New Systemic Therapy Approaches Help?
  • Targeted to a Mutation Defined Subgroup?
  • Not Targeted to a Specific NSCLC Subgroup?
RT-Induced IFN $\rightarrow$ Increases MHC-I $\rightarrow$ Overcomes anti-PD1 Resistance

Mechanism of Radio-Immunotherapy
Radiation Enhances Cross-Presentation of Tumor Antigens

A. without RT

B. with RT

PACIFIC (NCT02125461/D4191C00001): Study Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)

Primary endpoints: PFS, OS
Secondary endpoints: ORR, DoR, DSR, Safety/tolerability, PK, immunogenicity, QoL

DoR, duration of response; DSR, deep sustained response; FPD, first patient dosed; i.v., intravenous; LPD, last patient dosed; NSCLC, non-small cell lung cancer; ORR objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; q2w, every 2 weeks; QoL, quality of life.
Pacific Trial Update 2017:
Chemo-RT +/- Adjuvant Durvalumab

- Enrollment Completed: 2/1 Balance
- Interim DMC Report: PFS Endpoint Reached
- No Comment on Survival Endpoint
- Survival Outcome Expected in late 2017 to 2018?

- New Standard of Care???
- Influence on Ongoing Trials? Durva only?
- No RT QA or Other Typical Parameters
- Majority Ex-US Enrollment
Pacific: Progression-free Survival: 2017

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<tr>
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<th>Total No. of Patients</th>
<th>Median PFS (95% CI)</th>
<th>12-Mo PFS (95% CI)</th>
<th>18-Mo PFS (95% CI)</th>
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<tr>
<td>Durvalumab</td>
<td>214/476</td>
<td>16.8 (13.0–18.1)</td>
<td>55.9 (51.0–60.4)</td>
<td>44.2 (37.7–50.5)</td>
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<tr>
<td>Placebo</td>
<td>157/237</td>
<td>5.6 (4.6–7.8)</td>
<td>35.3 (29.0–41.7)</td>
<td>27.0 (19.9–34.5)</td>
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No. at Risk

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<tr>
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<th>Durvalumab</th>
<th>Placebo</th>
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<td>476</td>
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Overall and Progression-free Survival by RT dose
RTOG 0617: ASTRO 2017 Update

**Overall Survival**
- **60 Gy**: 218, 171, 123, 89, 70, 54
- **74 Gy**: 207, 143, 82, 64, 52, 37

**Progression-Free Survival**
- **60 Gy**: 218, 105, 63, 44, 36, 30
- **74 Gy**: 207, 84, 44, 35, 30, 22

---

- **60 Gy**
  - # of Patients: 218
  - Dead: 150
  - Censored: 68
  - Median Survival (95% CI): 2.4 (2.0, 3.2)
  - Hazard Ratio (95% CI): RL

- **74 Gy**
  - # of Patients: 207
  - Dead: 163
  - Censored: 44
  - Median Survival (95% CI): 1.7 (1.5, 2.0)
  - Hazard Ratio (95% CI): 1.35 (1.08, 1.69)

---

- **80 Gy**
  - # of Patients: 218
  - Dead: 178
  - Censored: 40
  - Median Survival (95% CI): 1.0 (0.9, 1.2)
  - Hazard Ratio (95% CI): RL

- **74 Gy**
  - # of Patients: 207
  - Dead: 181
  - Censored: 26
  - Median Survival (95% CI): 0.8 (0.7, 1.0)
  - Hazard Ratio (95% CI): 1.22 (1.00, 1.51)
### Pacific Subgroup Analysis: Prognostic Factors

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Durvalumab</th>
<th>Placebo</th>
<th>Unstratified Hazard Ratio for Disease Progression or Death (95% CI)</th>
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<tr>
<td>All patients</td>
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<td>237</td>
<td>0.55 (0.45–0.68)</td>
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<td>Male</td>
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<td>166</td>
<td>0.56 (0.44–0.71)</td>
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<tr>
<td>Female</td>
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<td>71</td>
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<tr>
<td>&lt;65 yr</td>
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<td>130</td>
<td>0.43 (0.32–0.57)</td>
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<td>≥65 yr</td>
<td>215</td>
<td>107</td>
<td>0.74 (0.54–1.01)</td>
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<td>Smoking status</td>
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<td>Smoker</td>
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<td>216</td>
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<td>Non-smoker</td>
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<td>NSCLC disease stage</td>
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<tr>
<td>IIIA</td>
<td>252</td>
<td>125</td>
<td>0.53 (0.40–0.71)</td>
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<tr>
<td>IIIB</td>
<td>212</td>
<td>107</td>
<td>0.59 (0.44–0.80)</td>
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<td>Tumor histologic type</td>
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<tr>
<td>Squamous</td>
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<td>102</td>
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<td>Non-squamous</td>
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<td>135</td>
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<td>Best response</td>
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<td>Complete response</td>
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<td>Partial response</td>
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<td>111</td>
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<td>Stable disease</td>
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<td>114</td>
<td>0.55 (0.41–0.74)</td>
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<td>PD-L1 status</td>
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<td>≥25%</td>
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<td>44</td>
<td>0.42 (0.26–0.65)</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>187</td>
<td>105</td>
<td>0.59 (0.43–0.82)</td>
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<td>Unknown</td>
<td>174</td>
<td>88</td>
<td>0.59 (0.42–0.83)</td>
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<tr>
<td>EGFR mutation</td>
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<tr>
<td>Positive</td>
<td>29</td>
<td>14</td>
<td>0.76 (0.35–1.64)</td>
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<tr>
<td>Negative</td>
<td>315</td>
<td>165</td>
<td>0.47 (0.36–0.60)</td>
</tr>
<tr>
<td>Unknown</td>
<td>152</td>
<td>58</td>
<td>0.79 (0.52–1.20)</td>
</tr>
</tbody>
</table>
Pacific Trial Update 2017: Toxicity Chemo-RT +/- Adjuvant Durvalumab

• Grade 3-4 Toxicities:
  • 30% Durva Arm
  • 26% Placebo Arm

• Adverse Events Requiring Discontinuation:
  • 15% Durva Arm
  • 10% Placebo Arm
Pacific Trial Update 2017: Chemo-RT +/- Adjuvant Durvalumab

• New Standard of Care???
• Influence on Ongoing Trials?
• Durva only anti-PD1 in this space?
• No RT QA or Other Typical Parameters
• Majority Ex-US Enrollment
RTOG Foundation 3505
Phase III Trial of Chemo-RT +/- Adj Nivolumab: Activated in 2017

Stage III NSCLC
• No prior Tx
• ECOG 0-1
• Any histology
• No known sensitizing EGFR mutation or ALK rearrangement
• Availability of 10-15 slides archival tissue

REGISTER

Thoracic RT to 60 Gy
CDDP 50 mg/m² Days 1, 8, 29, 36
VP16 50 mg/m² Days 1-5, 29-33

RANDOMIZE

Nivolumab every 2 weeks until disease progression or unacceptable toxicity or a total of 1 year

Placebo every 2 weeks until disease progression or unacceptable toxicity or a total of 1 year

3-8 wks
Eligibility Criteria

- "Good Prognosis" locally advanced NSCLC
- PS 0-1
- < 5% Baseline weight loss
- Adequate end-organ indices
- Estimated V20 < 35%
- FEV1 > 1.2 liters; DLCO ≥ 50% predicted
- No autoimmune disease or interstitial lung disease
- If EGFR, ALK + cases enroll in RTOG 1306

↑ proportion of squamous histology (appears to have greatest benefit from immunotherapy therapy in NSCLC)


<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies of pembrolizumab or nivolumab in combination with radiotherapy in non-small cell lung cancer (NSCLC)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study name/NCT number</th>
<th>Study intervention</th>
<th>Phase</th>
<th>Host institution</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>PEMBRO-RT [34]</td>
<td>Pembrolizumab after SABR versus pembrolizumab alone in advanced NSCLC</td>
<td>Randomised phase II</td>
<td>Netherlands Cancer Institute, Amsterdam</td>
<td>Open, recruiting</td>
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<tr>
<td>NCT02444741[35]</td>
<td>Dose escalation study of pembrolizumab and SABR in stage IV NSCLC</td>
<td>Phase I/phase II</td>
<td>M.D. Anderson Cancer Center, Houston, Texas</td>
<td>Open, recruiting</td>
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<tr>
<td>PEAR Study [36]</td>
<td>Pembrolizumab and palliative radiotherapy in lung</td>
<td>Phase I</td>
<td>Royal Marsden Hospital, London</td>
<td>In set-up.</td>
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<tr>
<td>NCT02343952 [37]</td>
<td>Previous Study</td>
<td>Phase I</td>
<td>Hoosier Cancer Research Network, USA</td>
<td>Open, recruiting</td>
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<tr>
<td>NCT02621398 [38]</td>
<td>Pembrolizumab, paclitaxel, carboplatin, and radiation therapy in treating patients with stage II-IIIB non-small cell lung cancer</td>
<td>Phase I</td>
<td>Rutgers Cancer Institute of New Jersey and the National Cancer Institute (NCI)</td>
<td>Open, recruiting</td>
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<tr>
<td>NCT02508385 [39]</td>
<td>Study of PD1 blockade by pembrolizumab with stereotactic body radiotherapy in advanced solid tumours</td>
<td>Phase I</td>
<td>University of Chicago</td>
<td>Open, recruiting</td>
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<tr>
<td>NCT02407171 [40]</td>
<td>Evaluating the combination of MK-3475 and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC</td>
<td>Phase I/II</td>
<td>Yale University</td>
<td>Open, recruiting</td>
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<tr>
<td>NICOLAS [41]</td>
<td>Nivolumab Consolidation After Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B NSCLC (NICOLAS)</td>
<td>Phase II</td>
<td>European Thoracic Oncology Platform</td>
<td>Open, recruiting</td>
</tr>
</tbody>
</table>
Eligibility Criteria

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• Estimated V20 < 35%
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• No autoimmune disease or interstitial lung disease
• If EGFR, ALK + cases enroll in RTOG 1306 → ↑ proportion of squamous histology (appears to have greatest benefit from immunotherapy therapy in NSCLC)

Accrual completed.
Results pending
Phase I Trial: Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients with Stage II-IIIB NSCLC

PI: Salma Jabbour, MD
Rutgers University
Jabbour Phase I Schema

- Backbone
- Weekly paclitaxel and carboplatin
- 60 Gy RT in 30 fractions

- Pembro – every 21 days for 1 year
- 2-6 weeks after CRT completion
- Final 2 weeks of CRT
- At start of CRT

<table>
<thead>
<tr>
<th>Part</th>
<th>Start of Pembrolizumab</th>
<th>Dose of Pembrolizumab</th>
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<tbody>
<tr>
<td>1</td>
<td>2-6 weeks after completing chemotherapy and radiation</td>
<td>200 mg</td>
</tr>
<tr>
<td>2</td>
<td>Week 5 of chemotherapy and radiation</td>
<td>100 mg</td>
</tr>
<tr>
<td>3</td>
<td>Week 5 of chemotherapy and radiation</td>
<td>200 mg</td>
</tr>
<tr>
<td>4</td>
<td>Week 1 of chemotherapy and radiation</td>
<td>100 mg</td>
</tr>
<tr>
<td>5</td>
<td>Week 1 of chemotherapy and radiation</td>
<td>200 mg</td>
</tr>
</tbody>
</table>
Advancing the Care of Stage III Pts

• Extraordinary progress: Are we at a plateau?
• Lots of improvement necessary in rad onc
• Drug discovery and alignment with science
• Immunomodulation: Exciting progress
• Committed networks of investigators needed!