Surviving Lung Cancer

- Living with, through and beyond lung cancer
- Lung cancer survivorship has become a reality
Lung Cancer Treatment has Evolved

Newer surgical techniques

More precise radiation treatment

Progress in systemic treatment:
• Targeted therapy
• Immunotherapy
• Antiangiogenic therapy
### Stage and survival at the time of diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>% of patients</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10%</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>II</td>
<td>20%</td>
<td>30-50%</td>
</tr>
<tr>
<td>IIIA/IIIB</td>
<td>30%</td>
<td>5-30%</td>
</tr>
<tr>
<td>IV</td>
<td>40%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>
Stage I NSCLC cancer
Stage I NSCLC cancer

Stage 1A
Cancer up to 3cm in size

Stage 1B
Cancer up to 5cm in size
T1 Tumor
Size $\leq 3$ cm
Stage I NSCLC

**Tumor size: 0-4 cm**

- Tx, T0, Tis, T1a (<1 cm), T1b (1-2 cm), T1c (2-3 cm), T2a (3-4 cm)
- Lymph nodes are not involved
- No distant metastasis

**Treatment for Stage I NSCLC is local therapy**

- Surgery
- Radiation
- No systemic therapy (no chemotherapy) after local therapy
Minimally Invasive Surgery

- Robotic and video assisted thoracoscopic surgery vs open thoracotomy
  - Incisions are smaller, less tissue damage, less blood loss
    - Less pain
    - Less time in the operating room
    - Less recovery time, less hospital time, less cost
    - Smaller scar
    - Reduced chance for post operative wound complication
  - More accurate staging: 30% upstaged (worse than expected), 12% downstaged (better than expected)*

*JTO 8(9), 9/16 Velez-Cubian et al
Stereotactic Body Radiation Therapy

- Medically inoperable early stage NSCLC
- RTOG –0236 Survival rate 55% at 3 years, 97% rate of tumor control
- Metastatic disease: Patients with < 3 metastatic lesions
- Less toxicity
- Less fractions (doses, example 5 treatments instead of 34)

Complications:
- Inflammation at the treatment site that looks like pneumonia
- Bronchial injuries if too central
- Chest wall toxicity: pain, fracture
Stereotactic radiosurgery

Courtesy of: Washington University School of Medicine Department of Radiation oncology
Courtesy of: Dr Hak Choy
Stage II Lung cancer
Stage II NSCLC

Tumor size: 3-5 cm in size or lymph node involvement (N1)

- IIA T2b (4-5 cm) N0
- IIB T1a-T2b (1-5 cm) N1 or T3 (5-7 cm) N0
- Simpler said, a tumor up to 5 cm, and positive N1 lymph node or a large tumor 5-7 cm without N1
- No distant metastasis

Treatment is local (surgery/radiation) and systemic (chemotherapy)
T2 Tumor
3-5 cm or invasive to other structures
N1 Lymph Nodes
Chemotherapy after surgery

- Adjuvant (after surgery) chemotherapy for stage I-III lung cancer
- Not recommended for stage IA
- 5-10% improvement in 5 year survival

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Chemo</th>
<th># pts</th>
<th>5 yr OS Chemo</th>
<th>Observe</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IALT</td>
<td>PE,PN, PV</td>
<td>1867</td>
<td>44%</td>
<td>40%</td>
<td>0.03</td>
</tr>
<tr>
<td>JBR.10</td>
<td>PN</td>
<td>482</td>
<td>69%</td>
<td>54%</td>
<td>0.002</td>
</tr>
<tr>
<td>ANITA</td>
<td>PNP</td>
<td>840</td>
<td>+8.6%</td>
<td></td>
<td>0.017</td>
</tr>
</tbody>
</table>

Choice of Chemotherapy

- Chemotherapy selection depends upon histology
  - Adenocarcinoma: cisplatin/pemetrexed
  - Squamous cell carcinoma: Cisplatin/navelbine, cisplatin/docetaxel or cisplatin/gemcitabine
- Chemotherapy given after surgery
- 4 cycles of treatment
Stage III Lung Cancer
Stage IIIA

T1a – T2b N2 (1-5 cm tumor)

T3 N1 (5-7 cm)

T4 N0-N1 (>7 cm or invading structures)
T3 Tumor

- 5-7 cm
- Separate tumor nodules in the same lobe
- Tumor invading chest wall, pericardium or phrenic nerve
N2 Lymph Nodes
Stage IIIA Treatment

- Concurrent chemoradiotherapy is the standard of care
  - Chemotherapy 4 cycles
  - Radiation 7 week course
- Undetected N2 disease prior to surgery is followed by adjuvant chemotherapy
- Neoadjuvant chemotherapy followed by surgery, select circumstances
  - Single station N2, T< 3m, responded to therapy, lobectomy resection feasible
<table>
<thead>
<tr>
<th>Stage IIB</th>
<th>Stage IIIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>• T2a – T2b N3</td>
<td></td>
</tr>
<tr>
<td>• T3N2</td>
<td></td>
</tr>
<tr>
<td>• T4N2</td>
<td></td>
</tr>
<tr>
<td>• T3N3</td>
<td></td>
</tr>
<tr>
<td>• T4N3</td>
<td></td>
</tr>
</tbody>
</table>
T4 Tumor

- >7 cm or invasive to major structures
- Separate nodule in a different ipsilateral lobe
- Invades diaphragm, mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, or esophagus
N3 Lymph Nodes
New Approach in Stage III lung cancer

- Unresectable stage III NSCCA treated with concurrent chemoradiotherapy followed by 12 months of durvalumab
- Historical 5 year OS (overall survival) for stage III lung cancer is 5-30%
- PACIFIC study NEJM 2017, 2018
  - 700 patients randomized to observation vs durvalumab
  - Progression free survival 5.6 months vs 16.8 months
  - 12 month survival rates 75% vs 83%
  - 24 month survival rates 55% vs 66%
  - 3 year survival: 44% w placebo vs 57% with durvalumab

Stage IV Lung Cancer
Survival Benefit for Treatment

- Standard chemotherapy compared to supportive care
  - 2714 patients evaluated in a meta-analysis
  - Standard chemotherapy (4-6 cycles)
  - 29% vs 20% one-year survival
Stage IV NSCCA

Factors influencing therapy

- Immunohistochemistry
  - Nonsquamous Squamous cell carcinoma
- Molecular characterization of the tumor
  - Somatic driver mutations predict sensitivity to specific inhibitors
- PDL-1 testing
Testing prior to treatment

- Determine histology and site of origin
  - Squamous cell carcinoma
    - PDL-1 testing
  - Non-squamous carcinoma
    - PDL-1 testing
    - Molecular testing
      - EGFR/ALK/ROS1/BRAF
Molecular testing in lung cancer

- Molecular testing is standard of care for metastatic lung cancer
  - Targeting a specific driver mutation
  - Targeted therapy
    - More convenient dosing
    - Milder toxicity
    - Improved survival
    - Improved quality of life
Molecular testing in lung cancer

- Molecular tests
  - Targets with approved targeted therapies
    - EGFR/ALK/ROS1/BRAF/NTKF
  - Targets with off label targeted therapies
    - HER2/MET/RET
- Testing individual genotypes vs NGS Next Generation Sequencing
**GENOMIC VARIANTS**

<table>
<thead>
<tr>
<th>Somatic - Potentially Actionable</th>
<th>Variant Allele Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 p.V217fs Frameshift - LOF</td>
<td>64.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Somatic - Biologically Relevant</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMARCA4 p.A903fs Frameshift - LOF</td>
</tr>
<tr>
<td>MEF2B Copy number loss</td>
</tr>
</tbody>
</table>

**Germline - Pathogenic / Likely Pathogenic**

No pathogenic variants were found in the limited set of genes on which we report.

**Pertinent Negatives**

No pathogenic single nucleotide variants, indels, or copy number changes found in:

- EGFR
- KRAS
- BRAF
- ALK
- ROS1
- RET
- MET
- ERBB2 (HER2)

**IMMUNOTHERAPY MARKERS**

<table>
<thead>
<tr>
<th>Tumor Mutational Burden</th>
<th>Microsatellite Instability Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8 m/Mb 79th percentile</td>
<td>Stable</td>
</tr>
<tr>
<td></td>
<td>Equivocal</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

**INVESTIGATIONAL THERAPIES**

- **WEE1 Inhibitor**
- **Adavosertib**

TP53 p.V217fs Loss-of-function
Clinical research, Solid Tumors: [PMID 27601554](https://www.ncbi.nlm.nih.gov/pubmed/27601554)

**CLINICAL TRIALS**

- **A Study to Evaluate the Safety, Tolerability, and Activity of TAK-931 in Participants With Metastatic Pancreatic Cancer, Metastatic Colorectal Cancer, and Other Advanced Solid Tumors** ([NCT03241347](https://clinicaltrials.gov/ct2/show/NCT03241347))
  - Phase II
  - Seattle, WA - 31 mi
  - TP53 mutation

- **Nintedanib in Molecularly Selected Patients With Advanced Non-Small Cell Lung Cancer** ([NCT02299141](https://clinicaltrials.gov/ct2/show/NCT02299141))
  - Phase I
  - Madison, WI - 1615 mi
  - TP53 mutation

---

**Laboratory Information**

- **LAB ID** 042116007
- **Date Signed** 07/03/2019
- **Laboratory Medical Director** Nike Beaubier, MD, FACP, MG
- **Tempus ID** TL-19-36117E
- **Pipeline Version** 2.3.1

Tempus Avenue, Ste 500 • Chicago, IL • 60654 • tempus.com • Support@tempus.com
EGFR mutation

- EGFR tyrosine kinase inhibitor
- 15% of NSCLC, more frequent in nonsmokers and women
- 13 phase III trials EGFR TKI to chemotherapy prolonged PFS
- Osimertinib is recommended first line for EGFR mutated NSCLC
  - PFS 18.0 vs 10.2 months (compared to erlotinib or gefitinib)
  - Duration of response 17.2 months vs 8.5 months
  - Overall response rate 80%
**ALK mutation**

- Anaplastic lymphoma kinase fusion oncogene (ALK)
- Highly sensitive to ALK TKI treatment
  - alectinib, brigatinib, ceritinib, crizotinib
- 5% of NSCLC, more frequent in nonsmokers, younger patients, adenocarcinoma
- Alectinib vs crizotinib PFS: 35 months vs 10.9 months
- Alectinib is recommended first line
ROS1 mutation

- C-ROS-oncogene 1 is a receptor tyrosine kinase
- 1-2% of NSCLC, more frequent in nonsmokers, younger patients, adenocarcinoma
- Sensitive to crizotinib
- Crizotinib therapy after 1 or more prior chemotherapy regimens
  - ORR 72%
  - Median duration of response 17.6 months
  - Median PFS 15.9 months
- Cabozantinib, entrectinib, repotrectinib are in development
BRAF mutation

- 1-3% of NSCLC, more frequent in smokers
- Second line treatment BRAF + MEK inhibitor
- Dabrafenib + trametinib: ORR 63%, PFS 9.7 months
Immunotherapy in Lung Cancer
Immune checkpoint blockade

- Immune cells can recognize cancer cells as foreign and attack them.
- Cancer cells can evade the immune system.
- Checkpoints PD1 and CTLA4 normally serve to protect the normal cells by dampening the immune response to prevent collateral damage to healthy tissue.
- Removal of these blockades make the immune system stronger and fight the cancer.
PDL-1 Testing and 1st line Treatment

PD-1 absent or low
- Chemotherapy combined with pembrolizumab is superior to chemotherapy

PDL1 high > 50%
- Pembrolizumab monotherapy
- Pembrolizumab and chemotherapy (if rapidly progressive)
Immunotherapy Drugs Approved

- PD-1 inhibitors
  - Nivolumab approved for metastatic disease, after first line therapy
  - Pembrolizumab
    - 1st line in metastatic disease in combination with chemotherapy
    - 1st line in metastatic disease monotherapy in high PDL1 +

- PDL1 inhibitor
  - Atezolizumab
    - 1st line metastatic disease nonsquamous with chemotherapy
    - Previously treated metastatic disease
  - Durvalumab approved for adjuvant therapy after concurrent chemoradiotherapy for unresectable stage III NSCCA
Overall survival by stage

<table>
<thead>
<tr>
<th>8th edition</th>
<th>Events / N</th>
<th>MST</th>
<th>24 month</th>
<th>60 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>* IA1</td>
<td>68 / 781</td>
<td>NR</td>
<td>97%</td>
<td>92%</td>
</tr>
<tr>
<td>IA2</td>
<td>505 / 3105</td>
<td>NR</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>Δ IA3</td>
<td>546 / 2417</td>
<td>NR</td>
<td>90%</td>
<td>77%</td>
</tr>
<tr>
<td>♦ IB</td>
<td>560 / 1928</td>
<td>NR</td>
<td>87%</td>
<td>68%</td>
</tr>
<tr>
<td>§ IIA</td>
<td>215 / 585</td>
<td>NR</td>
<td>79%</td>
<td>60%</td>
</tr>
<tr>
<td>* IIIA</td>
<td>605 / 1453</td>
<td>66.6</td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>† IIIB</td>
<td>2052 / 3200</td>
<td>29.3</td>
<td>55%</td>
<td>36%</td>
</tr>
<tr>
<td>†† IIIIA</td>
<td>1551 / 2140</td>
<td>19.0</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>** IIIIC</td>
<td>831 / 986</td>
<td>12.6</td>
<td>24%</td>
<td>13%</td>
</tr>
<tr>
<td>‡‡ IVA</td>
<td>336 / 484</td>
<td>11.5</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td>ΔΔ IVB</td>
<td>328 / 398</td>
<td>6.0</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>
National Lung Cancer Screening Trial

- 53,454 patient, high risk for lung cancer
- Low dose CT scan vs chest x ray
- High risk population
  - Age 55-74
  - 30+ pack years of tobacco use
  - Current smokers or quit within 15 years
- Results: REDUCED MORTALITY 20%
- LUNG CANCER SCREENING SAVES LIVES
Criteria for Screening

- Who is eligible
  - Age 55-74
  - At least 30 pack years of tobacco use
  - Current smoker or quit within 15 years
  - Annual screening until 15 years elapsed since smoking cessation
Tobacco use: Why quit now

- Smoking increases lung cancer risk 30 fold
- 14% of patients continue to smoke 5 months after diagnosis
- Smoking intensity at diagnosis is an independent prognostic risk factor
- Chemotherapy less effective
- Higher recurrence risk
- Higher secondary cancer risk (2.3X)
- Mortality 2.9 times higher
Survivor plan after treatment

- Surveillance for recurrence
  - CT scan every 6 months for 2-4 years
  - CT scan annually year 3-5
- Surveillance for second primary lung cancers
- Diet: increased fruits and vegetables reduce risk
- Weight gain is associated with improved survival
- Physical activity improves QOL
- Treatment of sequelae of surgery, radiation, chemotherapy
Summary of Progress

- Minimally invasive surgery
- Stereotactic body radiotherapy
- Adjuvant chemotherapy after surgery, stage II
- Adjuvant immunotherapy after concurrent chemoradiotherapy for stage III
- Immunotherapy and chemotherapy in Stage IV
- Immunotherapy alone in Stage IV for high PDL-1
- Targeted therapy
- Next generation sequencing testing
- Screening has demonstrated benefit
Thank you!