Targeted Therapy and Immunotherapy in Non-small cell lung cancer
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Overview
• EGFR mutation
• ALK rearrangement
• ROS-1 rearrangement
• BRAF mutation
• NTRK fusion
• Others: HER2 mutation, RET, MET
• Immunotherapy

Prevalence of Driver Mutations in NSCLC
Testing

• Testing generally recommended for all adenocarcinomas and for squamous cell carcinomas with light smoking history
• PD-L1 by IHC, EGFR PCR, ALK, ROS-1 by FISH, but now NGS allows broader panel of tests with minimal specimen
• NCCN panel recommends “broad molecular profiling,” which can also help identify other mutations for which a targeted therapy may become available (recently NTRK)
• Liquid biopsies - EGFR with 94%, ALK with 95.7% concordance with tissue
• Clinical Trial: Biodesix BDX-00146 INSIGHT, LUNGMAP trial for second-line

EGFR mutation

• Most common mutation deletion exon 19 (45%), point mutation exon 21, others
• First generation: Gefitinib (3rd line 2003, then withdrawn, 2015 for EGFR+), Erlotinib (2004 2nd line, 2010 maintenance), Afatinib (2013); PFS ~7 to 11 months
• Second generation: Dacomitinib (2018)
• T790M mutation positive - Osimertinib (2015, first-line 2018)
• Osimertinib is now first-line standard of care
• Clinical Trial: EGFR+ on ALCHEMIST screening, Erlotinib vs observation; EGFR insertion mutation positive-high dose Osimertinib

Progression-free Survival and Overall Survival.
Toxicities

- Rash
- Diarrhea
- Liver failure
- Corneal irritation, conjunctivitis
- All worse with first generation TKIs
- Osimertinib better tolerated, but increased risk of immune related toxicity after immunotherapy

ALK (Anaplastic Lymphoma Kinase fusion)

- Alectinib has emerged as the preferred first-line option
- Lorlatinib after progression and development of resistance mutations
- Toxicities: Nausea, vomiting, diarrhea, LFT abnormalities, constipation (alectinib), pneumonitis, QT prolongation, visual disturbance (crizotinib)
- Clinical Trials: ALK+ (ALCHEMIST) adjuvant therapy with crizotinib; second line resistance mutation trial

Other Driver Mutations

- ROS-1: crizotinib, lorlatinib, entrectinib
- BRAF: dabrafenib/trametinib, single-agent dabrafenib, vemurafenib
- NTRK fusion (across many tumor types): larotrectinib
- Off-label:
  - HER-2: ado-trastuzumab emtansine
  - MET exon 14 skipping mutation: crizotinib, cabozantinib
  - MET amplification: crizotinib
  - RET rearrangements: alectinib, cabozantinib, vandetinib
**Immunotherapy**

**Mechanism of Action**

- Available agents include Nivolumab, Pembrolizumab (PD-L1 positive), and Atezolizumab

**Immunotherapy in Second Line**

- Available agents include Nivolumab, Pembrolizumab (PD-L1 positive), and Atezolizumab
First line immunotherapy options—Adenocarcinoma

- Pembrolizumab monotherapy (PD-L1 positive)
- Pembrolizumab, Pemetrexed, and Platinum- doubled PFS at 1 year (17% versus 34%)
- Atezolizumab, Bevacizumab, Taxane, Platinum

Pembrolizumab versus Chemotherapy in First-line
Clinical Trial at MECC

- **INSIGNA trial**- Arm A: 1st Line Pembrolizumab, 2nd line Pemetrexed/Carbo; Arm B: 1st line Pembrolizumab, 2nd line Pembrolizumab/Pemetrexed/Carbo; Arm C: 1st line Pembrolizumab/Pemetrexed/Carbo, Maintenance Pembrolizumab/Pemetrexed

Squamous Cell Carcinoma First-line

- Pembrolizumab monotherapy
- Pembrolizumab, paclitaxel/nab-paclitaxel, platinum
Neoadjuvant/Adjuvant Immunotherapy

- Clinical Trial- ARM A: Neoadjuvant Atezolizumab + Platinum-Based Chemo x 4 Cycles followed by Adjuvant Atezolizumab x 16 Cycles
  ARM B: Neoadjuvant Placebo + Platinum Based Chemo x 4 Cycles followed by Observation
- Dismal survival rates after chemo-RT for Stage III disease, now durvalumab has become standard of care post chemo-RT
- Clinical Trial for Stage I-II: Duvalumab vs Placebo x 2 years post-SBRT

Progression-free Survival in the Intention-to-Treat Population.

Future Directions

- Adenocarcinoma after failure of pembrolizumab, pemetrexed, and platinum: Clinical Trial- Nivolumab + Sitravatinib versus Docetaxel
- Immunotherapy combinations: Ipilimumab/Nivolumab, Tremilimumab/Durvalumab
- Adjuvant immunotherapy
- Management of patients who would otherwise be candidates for immunotherapy but have autoimmune diseases
Summary

- Standard of care to look for targetable mutations in adenocarcinomas and well-selected squamous cell carcinomas
- Targeted therapy significantly improves outcomes, and is improving in tolerability
- First-line immunotherapy in metastatic lung cancer is now standard of care
- Moving toward immunotherapy in early stage lung cancer
- Methodist Estabrook Cancer Center is a leader, with many relevant clinical trials available for our patients

Resources