Targeted Therapy and Immunotherapy in Non-small cell lung cancer

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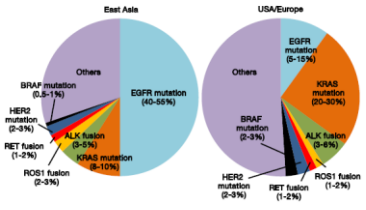
Overview

- EGFR mutation
- ALK rearrangement
- ROS-1 rearrangement
- BRAF mutation
- NTRK fusion
- Others: HER2 mutation, RET, MET
- Immunotherapy

Prevalence of Driver Mutations in NSCLC



Kohno, Takashi, et al. "Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer." Translational lung cancer research 4.2 (2015): 156.

Testing

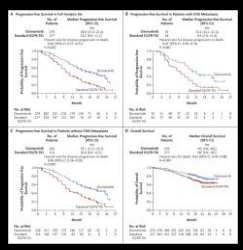
- Testing generally recommended for all adenocarcinomas and for squamous cell carcinomas with light smoking history
- PD-L1 by IHC, EGFR PCR, ALK, ROS-1 by FISH, but now NGS allows broader panel of tests with minimal specimen
- NCCN panel recommends "broad molecular profiling," which can also help identify 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**

Schwaederle, Lee Stephen, et al. "Clinical concordance study of a 57 gene liquid biopsy NGS panel for non-small cell lung cancer (NSCLC)." (2018): e23065-e23065.

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- First generation: Gefitinib (3rd line 2003, then withdrawn, 2015 for EGFR+), Erlotinib (2004 2nd line, 2010 maintenance), Afatinib (2013); PFS ~7 to 11 months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.



J Soria et al. N Engl J Med 2018;378:113-125.

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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)

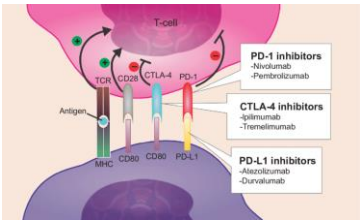
- Available options are crizotinib (1st generation, 2011), brigatinib (2017), ceritinib (2014, 2017 first-line), alectinib (2015, 2017 first line)
- Alectinib has emerged as the preferred first-line option
- Lorlatinib after progression and development of resistance mutations
- Toxicities: Nausea, vomiting, 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

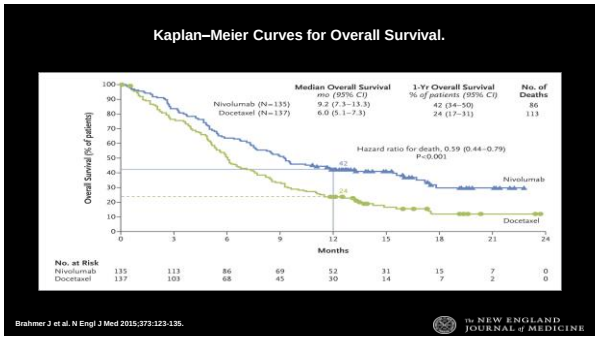
Immunotherapy

Mechanism of Action



Immunotherapy in Second Line

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



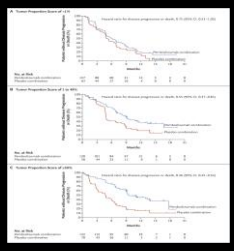
First line immunotherapy options- Adenocarcinoma

- 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

	PD-L1 TPS					
	≥50%		≥20%		≥1%	
	Pembro N = 299	Chemo N = 300	Pembro N = 413	Chemo N = 405	Pembro N = 637	Chemo N = 637
	OS					
HR (95% CI)	0.69 (0.56-0.85)		0.77 (0.64-0.92)		0.81 (0.71-0.93)	
P	.0003		.0020		.0018	
Median (95% CI), mo	20.0 (15.4-24.9)	12.2 (10.4-14.2)	17.7 (15.3-22.1)	13.0 (11.6-15.3)	16.7 (13.9-19.7)	12.1 (11.3-13.3)

Progression-free Survival, According to PD-L1 Tumor Proportion Score.



L Gandhi et al. N Engl J Med 2018;378:2078-2092.

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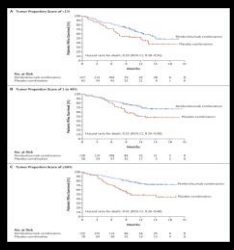
Overall Survival, According to PD-L1 Tumor Proportion Score.



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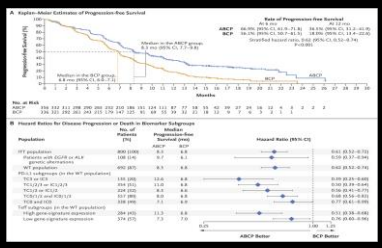
Investigator-Assessed Progression-free Survival in the ABCP Group and the BCP Group.



MA Socinski et al. N Engl J Med 2018;378:2288-2301.

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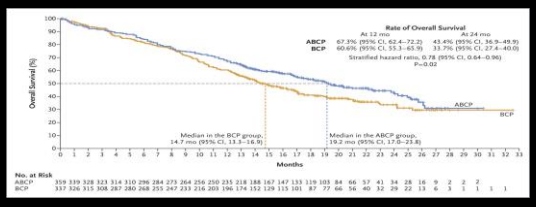
Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.



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Clinical Trial at MECC

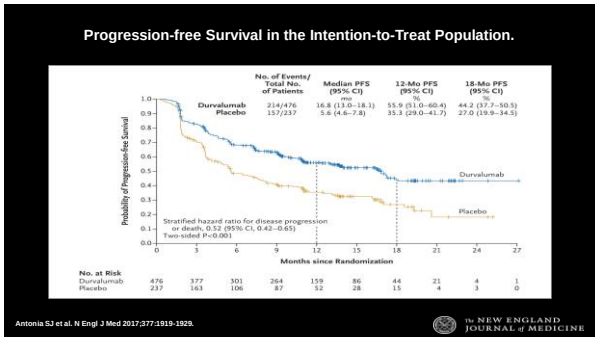
- INSIGNA trial- Arm A: 1st Line Pembrolizumab, 2nd line Pemetrexed/Carbo; Arm B: 1st line Pebrolizumab, 2nd line Pembrolizumab/Pemetrexed/Carbo; Arm C: 1st line Pembrolizumab/Pemetrexed/Carbo, Maintenance Pembrolizumab/Pemetrexed

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



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

- Kohno, Takashi, et al. "Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer." *Translational lung cancer research* 4.2 (2015): 156.
- Lopes, Gilberto, et al. "Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS)≥ 1%: Open-label, phase 3 KEYNOTE-042 study." (2018): LBA4-LBA4.
- Antonia SJ et al. N Engl J Med 2017;377:1919-1929.
- MA Socinski et al. N Engl J Med 2018;378:2288-2301.
- L Gandhi et al. N Engl J Med 2018;378:2078-2092.
- Brahmer J et al. N Engl J Med 2015;373:123-135.
- J Soria et al. N Engl J Med 2018;378:113-125.