

Targeted Therapy in NSCLC

Master Lecture Series: Evolving Treatments in Immunotherapy and Targeted Therapies

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Disclosures

- Consulting
 - AstraZeneca, Beyond Spring, Boehringer Ingelheim, Bristol-Myers Squibb, Inivata, Takeda
- Research Funding (to institution)
 - Celgene, Merck, Novartis, OncoMed, Roche
- I will discussing non-FDA approved treatment/ indications during my presentation today (research findings)



















- 2nd and 3rd generation approaches in EGFR and ALK
- 1st generation approaches in "emerging" alterations



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EGFR

 2009 IPASS study– gefitininb (Mok et al in NEJM)



- ...but resistance inevitably develops
- ~50-60% T790M "gatekeeper"

ALK

 2014 PROFILE 1014– crizotinib (Solomon et al in NEJM)



- ...but resistance inevitably develops
- Middling ALK inhibitor
- Poor CNS penetration



EGFR-Osimertinib first line: FLAURA trial

Osimertinb vs gefitinib or erlotinib



- And overall survival advantage: 38.6 vs 31.8mo
- And superior safety profile

Soria, NEJM 2017, Ramalingam, NEJM 2020



After osimertinib first-line?

- Cancers evolve...
- ...resistance inevitably develops
- Role for repeat biopsy?
 - MET amp → add MET inhibitor?
 - SCLC transformation → SCLC chemo?
 - Clinical trials
 - Specific to mechanism of resistance
 - Eg C797S inhibitor
 - Broader mechanisms
 - Eg osimertinib + alisertib (aurora kinase inhibitor)

Mechanism of Acquired Resistance in Osimertinib-Resistant Patients (N = 23)



Pietrowska, ASCO 2017



ALK-Moving 2nd generation to 1st line?

- ALEX (ASCO 2017, NEJM 2017), alectinib vs crizotinib
 - RR 83 vs 76%

A Progression-free Survival



Peters, NEJM 2017



FDA approved 11/17



ALK-Moving 2nd generation to 1st line?

- ALTA-1L (NEJM 2018), alectinib vs crizotinib
 - RR 71 vs 60%





D Survival without Intracranial Disease Progression among Patients with Brain Metastases at Baseline



Not yet FDA approved for 1L

Camidge, NEJM 2018



ALK- 3rd generation

- Lorlatinib
 - ORR in pts after previous TKI failure, n=215: 48%
 - Median DoR 12.5 mos
 - Intracranial ORR, n=89, 60%
- FDA approved 11/18 for 2nd line (after 2nd gen) or 3rd line (after 1st and 2nd gen)



After alectinib first line?

- Cancers evolve...
- ...resistance inevitably develops
- Consider biopsy at progression to determine next drug?
 - Or empiric lorlatinib:
 - ORR 44% after 1 prior TKIs
 - ORR 25% after 2 prior TKIs
 - ORR 31% after 3 prior TKIs

Cellular ALK phosphorylation mean IC ₅₀ (nmol/L)						
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib	
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8	
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3	
<i>EML4–ALK</i> C1156Y	61.9	5.3	11.6	4.5	4.6	
<i>EML4–ALK</i> I1171N	130.1	8.2	397.7	26.1	49.0	
<i>EML4–ALK</i> I1171S	94.1	3.8	177.0	17.8	30.4	
<i>EML4–ALK</i> I1171T	51.4	1.7	33.6 ^a	6.1	11.5	
<i>EML4–ALK</i> F1174C	115.0	38.0 ^a	27.0	18.0	8.0	
<i>EML4–ALK</i> L1196M	339.0	9.3	117.6	26.5	34.0	
<i>EML4–ALK</i> L1198F	0.4	196.2	42.3	13.9	14.8	
<i>EML4–ALK</i> G1202R	381.6	124.4	706.6	129.5	49.9	
<i>EML4–ALK</i> G1202del	58.4	50.1	58.8	95.8	5.2	
<i>EML4–ALK</i> D1203N	116.3	35.3	27.9	34.6	11.1	
<i>EML4–ALK</i> E1210K	42.8	5.8	31.6	24.0	1.7	
<i>EML4–ALK</i> G1269A	117.0	0.4	25.0	ND	10.0	
<i>EML4–ALK</i> D1203N+F1174C	338.8	237.8	75.1	123.4	69.8	
<i>EML4–ALK</i> D1203N+E1210K	153.0	97.8	82.8	136.0	26.6	

IC₅₀ ≤ 50 nmol/L C₅₀ > 50 < 200 nmol/L

IC₅₀ ≥ 200 nmol/L

Gainor, Cancer Discovery, 2016; ASCO Proc 2017 #9006



Immunotherapy in metastatic EGFR-Mutated NSCLC?

- Phase 2 study– advanced EGFR TKI-naïve– planned 25 EGFR+ patients
 - Pembrolizumab single agent
 - Primary endpoint ORR
- Results: Stopped after stage 1, 11 patients
 - 1/11 had an objective response
 - ...and that responder was later found to be EGFR negative
 - This despite 73% with PD-L1 expression >=50%
 - 2 deaths within 6 months of enrollment, including 1 attributed to pneumonitis
- Take-home messages: first line IO not appropriate for EGFR and likely other driver mutations where targeted therapy available
 – poor effectiveness even with high PD-L1... and potential toxic interaction with TKI

Lisberg, ASCO 2017



- 2nd and 3rd generation approaches in EGFR and ALK
- 1st generation approaches in "emerging" alterations



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FDA-approved oncogene-targeted agents in NSCLC

- EGFR
 - Erlotinib (2009)
 - Gefitinib (2015)
 - Afatinib (2013)
 - Dacomitinib (2018)
 - Osimertinib (2015)
- ALK
 - Crizotinib (2011)
 - Ceritinib (2014)
 - Alectinib (2015)
 - Brigatinib (2017)
 - Lorlatinib (2018)

- ROS1
 - Crizotinib (2016)
 - n=53
 - ORR 70%, mPFS 19.3mo
 - Entrectinib (2019)
 - N=51
 - ORR 78%, DoR 24.6mo
- BRAF
 - Dabrafenib/trametinib approved 2017
 - 1st line n=36
 - ORR 64%. 14.6mo

Bare minimum for non-squamous NSCLC: EGFR, ALK, ROS1, and BRAF

Shaw A, Ann Onc 2016. Planchard D Lancet Onc 2017.











Squamous Cell Cancer



Li, JCO 2013.



Emerging targets

- TRK fusions
 - Larotrectinib
 - N=55
 - 4 lung
 - RR 76%
 - Including 22% CR
 - mDOR NR
- FDA approved, tumor site agnostic, 11/18
- Entrectinib also now approved, 2019 (n=54, RR 57%)

Hyman DM, ASCO Proc 2017.



Estimated 1,500-5,000 patients harbor TRK fusion-positive cancers in the United States annually

Sarcoma (multiple)



Emerging targets

- MET exon 14 skipping mutation
 - Often older patients, current/former smokers, sarcomatoid pathology
 - 3-4% of NSCLC
 - Crizotinib ORR 44%, PFS not yet reached (ASCO 2016)
 - FDA breakthrough designation
- RET rearrangement
 - Vandetanib ORR 53% (ASCO 2016)
 - Cabozantinib ORR 38% (ASCO 2016)
 - Selpercatinib (LOXO-292) ORR 85%, CNS ORR 91%, mPFS 18.4mo
- HER2 mutation
 - T-DM1 ORR 33% (ASCO 2017)





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NCCN Guidelines Index Table of Contents Discussion

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer		
High-level MET amplification or MET exon 14 skipping mutation	Crizotinib ¹⁻⁵		
RET rearrangements	Cabozantinib ^{6,7} Vandetanib ⁸		
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine ⁹		
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab ¹⁰ Nivolumab ¹¹		

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

¹Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.

²Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32(Suppl 5): Abstract 8001.

³Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov 2015;5:850-859.

⁴Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. Cancer Discov 2015;5:842-849.

⁵Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpression. J Clin Oncol 2016;34:721-730.

⁶Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.

⁷Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol 2016;17:1653-1660.

^BLee SH, Lee JK, Ahn MJ, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. Ann Oncol 2017;28:292-297.

⁹Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncol 2018;36:2532-2537.
 ¹⁰Hellmann MD, Ciuleanu TE, Pluzanski A et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018; 378:2093-2104.
 ¹¹Carbone DP, Reck M, Paz-Ares L et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376:2415–2426.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NSCL-H

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Phase 1 Study of AMG 510, a Novel KRAS^{G120} Inhibitor, in Advanced Solid Tumors With KRAS p. G12C Mutation: ESMO 2019

Emerging targets

- KRAS ~30% of NSCLC
 - Difficult to "drug"
 - KRAS G12C ~1/3 of KRAS NSCLC
 - Direct inhibitors include AMG510, MRTX849, JNJ-74699157
 - Registrational and combo studies available

BEST TUMOR RESPONSE WITH ALL DOSE LEVELS, ALL TUMOR TYPES

Efficacy outcomes	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3	
Best overall response				
PR - n (%)	11 (48)	1 (3)	1 (33)°	
SD - n (%)	11 (48)	22 (76)	1 (33)4	
PD - n (%)	1 (4)	6 (21)	1 (33)°	
Objective response rate*	48%	3%	N/A	
Disease control rateb	96%	79%	N/A	

Phase 1 Study of AMG 510, a Novel KRAS^{G120} Inhibitor, in Advanced Solid Tumors With KRAS p. G12C Mutation: ESMO 2019



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NCCN Guidelines Index Table of Contents Discussion



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NSCL-17



You can't treat a mutation you don't know!





Li, JCO 2013.



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NCCN Guidelines Index **Table of Contents** Discussion

TESTINGhh TESTING RESULTShh CLINICAL PRESENTATION HISTOLOGIC **SUBTYPE**^a Sensitizing EGFR mutation positive • (see NSCL-18) Molecular testing • EGFR mutation testing ALK positive (see NSCL-21) (category 1) Adenocarcinoma + ALK testing (category 1) ROS1 positive (see NSCL-24) Large cell ► ROS1 testing NSCLC not BRAF V600E positive (see NSCL-25) Establish histologic BRAF testing otherwise Testing should be subtype^a with ٠ specified (NOS) PD-L1 ≥50% and EGFR. ALK negative adequate tissue for conducted as part of broad or unknown (see NSCL-27) molecular profiling^{ii,jj} molecular testing EGFR, ALK, ROS1, BRAF negative or Advanced (consider rebiopsy^{gg} PD-L1 testing (category 1) unknown, PD-L1 <50% or unknown or if appropriate) (see NSCL-28) metastatic Smoking cessation Molecular testing Disease counseling Sensitizing EGFR mutation positive (see NSCL-18) Consider EGFR mutation Integrate palliative and ALK testingkk in never care^c (See NCCN smokers or small biopsy ALK positive (see NSCL-21) **Guidelines for** specimens, or mixed Palliative Care) ROS1 positive (see NSCL-24) histology Squamous cell Consider ROS1 and BRAF BRAF V600E positive (see NSCL-25) carcinoma testing in small biopsy specimens or mixed PD-L1 ≥50% and EGFR, ALK negative histology or unknown (see NSCL-27) Testing should be conducted as part of broad EGFR, ALK, ROS1, BRAF, negative molecular profiling^{II,JJ} or unknown, PD-L1 <50% or unknown PD-L1 testing (category 1) (see NSCL-29) ^aSee Principles of Pathologic Review (NSCL-A). ^cTemel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742. ^ITesting should include the neurotrophic receptor tyrosine kinase (NTRK) gene fusion; if positive, see NSCL-26. kkIn patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% ⁹⁹If repeat biopsy is not feasible, plasma testing should be considered. with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G,

Genet 2008;chapter 10:unit 10.11.

Cancer Ther 2012:11:2535-2540.

hhSee Principles of Molecular and Biomarker Analysis (NSCL-G).

ⁱⁱThe NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-H)

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progression on

Protocol

chemo +/immunotherapy

Squamous cell lung ca

No standard of care

actionable mutations

Mutation testing

Start treatment after

either at dx or

progression

Lung-MAP Master

Match to a sub-study based on alteration (eq PI3K, FGFR) or non-match (immunotherapy)

Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIC). Curr Protoc Hum

Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant

advanced non-small cell lung cancers with a squamous or squamous-like component. Mol



NSCL-17

- EGFR:
 - Osimertinib with clear survival benefit
 - Consider biopsy to determine mechanism of resistance
- ALK:
 - Alectinib clear standard of care in first line
 - Lorlatinib appropriate empirically in subsequent line
 - But again, may consider biopsy to determine mechanism of resistance
- And a cautionary tale
 - Single agent immunotherapy does NOT work well



- 1st generation approaches in "emerging" alterations
 - FDA approvals for ROS1, BRAF, NTRK
 - Other targets like MET, RET, HER2 "on deck," some with off-label opportunities (NCCN can help)
 - KRAS is (finally) coming!
- You can't treat what you haven't identified

• YOU CAN'T TREAT WHAT YOU HAVEN'T IDENTIFIED!

- Think about testing squamous cell patients, esp non-smokers, scant samples and mixed histology, and/or Lung-MAP
- Clinical trials!



Thank you!



