I Have Another Oncogene Driver! What are the Implications of This?

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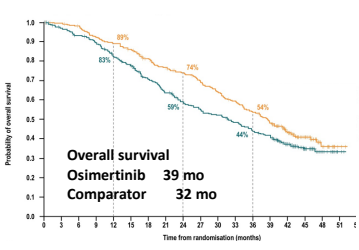
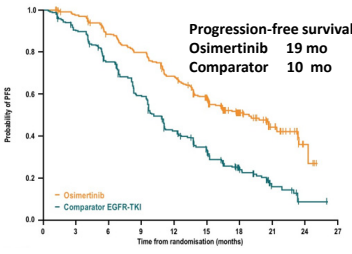
Osimertinib as Best First-line EGFR TKI





- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Other first-line treatments can also be considered, including other EGFR TKIs, TKI combinations (chemo, VEGF) or a clinical trial
- Almost all lung cancers develop resistance to osimertinib. Resistance to treatment means cancer growth and spread.

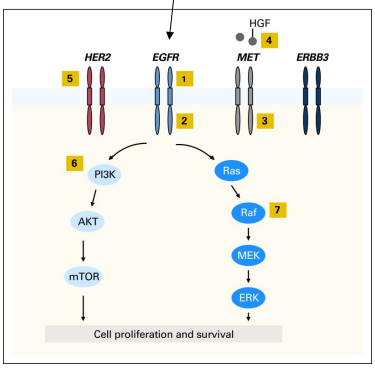
Soria JC, et al. *N Engl J Med.* 2018, Ramalingam ESMO 2019.

Progression & Resistance

How does resistance develop?

ON TARGET ALTERATIONS

EGFR C797X and other
EGFR mutations
EGFR Amplification



HISTOLOGIC CHANGES

SCLC
Transformation
Squamous Cell
Transformation

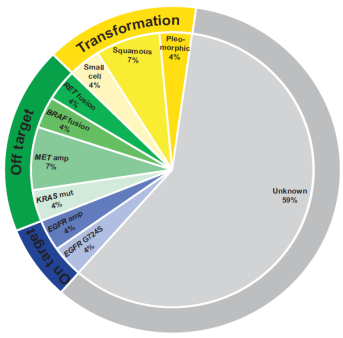
BYPASS PATHWAY ACTIVATION

MET Amplification
BRAF fusions, mutations
RET, ALK, other fusions

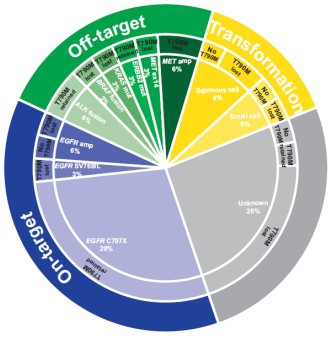
Gainor JF, et al, *J Clin Oncol.* 2013.
Additional data modified from Piotrowska, *Cancer Discovery.* 2018, Oxnard GR, *JAMA Onc.* 2018; Le X, *CCR.* 2018; Papadimitrakopoulou V, ESMO 2018

Mechanisms of Osimertinib Resistance

NO PRIOR EGFR TKI



PRIOR EGFR TKI

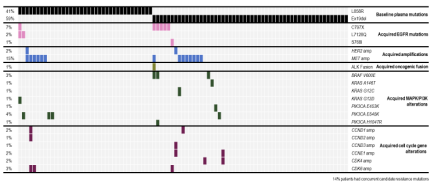


Schoenfeld AJ, et al. *Clin Cancer Res.* 2020.

Progression & Resistance

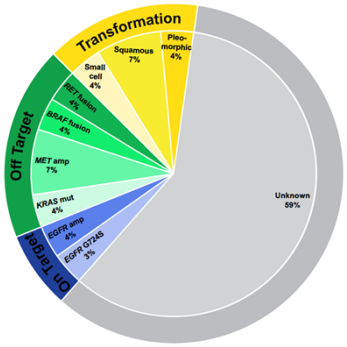
Resistance to First-Line Osimertinib - Current Data

FLAURA ctDNA analysis (n=91)



Key Findings:
- 7% C797S
- 15% MET amplification
- 3% BRAF fusions
- ctDNA analysis so no histologic changes identified.

MSKCC Experience (n=27)

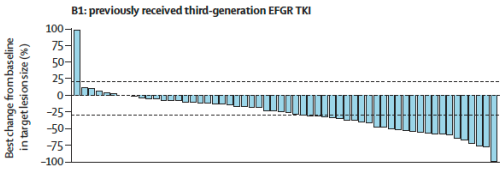


Key Findings:
- 15% histologic transformation
  - SCLC
  - Squamous
  - Pleomorphic
- 7% had MET amplification
- No EGFR C797S

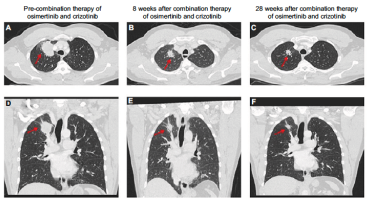
Ramalingam, ESMO 2018; Schoenfeld A, *CCR.* 2020.

Targeting MET-mediated Resistance

Osimertinib + Savolitinib[1]



Osimertinib + Crizotinib[2-4]



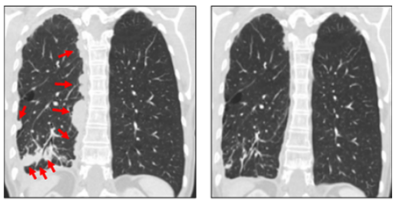
[1]Sequist LV, et al. *Lancet Oncol.* 2020; [2]Zhu V, et al. *Lung Cancer (Auckl).* 2019; [3]York E, et al. *J Thorac Oncol.* 2017; [4]Ou SH, et al. *Lung Cancer.* 2016.

Progression & Resistance

Combining EGFR + additional targeted therapies can be option in cases of bypass pathway activation

Acquired RET Fusions[1]

Response to osimertinib + Pralsetinib

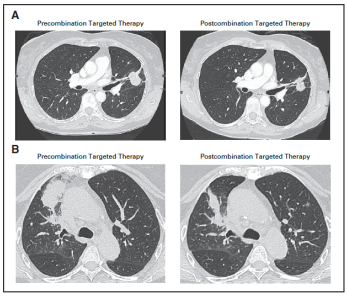


Confirmed RECIST PR (-78%)

Acquired ALK Fusions[2]

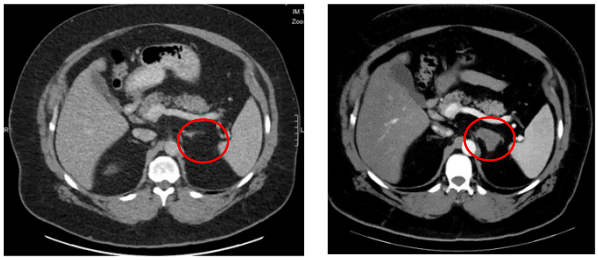
Osimertinib + Crizotinib

Osimertinib + Alectinib



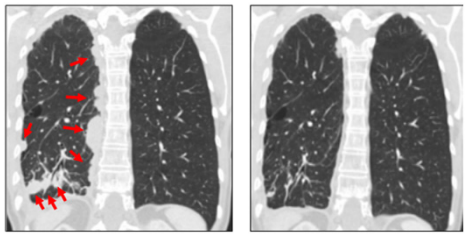
[1]Piotrowska Z, et al. *Cancer Discov.* 2018.
[2]Offin M, et al. *JCO Precis Oncol.* 2018.

Case 1: *MET* Amplification



- 58 yr old man diagnosed with EGFR-mutant metastatic lung cancer in November 2019. He started first-line osimertinib the following month.
- After about 20 months on osimertinib, scans showed a new liver metastasis.
- Liquid biopsy showed the EGFR exon 19 deletion and MET amplification. A liver biopsy confirmed high-level MET amplification.
- He started treatment with osimertinib + savolitinib (MET inhibitor) on a clinical trial with good response.

Case 2: *RET* Fusion



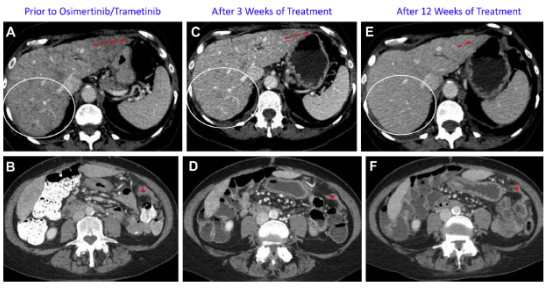
- 60 yr old woman diagnosed with EGFR-mutant lung cancer. She was initially treated with afatinib for one year, then second-line osimertinib for about 1.5 years.
- Upon cancer progression, a pleural biopsy was obtained and showed a CCDC6-RET fusion.
- She was treated with osimertinib and pralsetinib (an oral RET inhibitor) with rapid improvement in her symptoms. She stayed on the combination for over a year.

Case 3: A Cautionary Tale: Some TKI Combinations May Not be as Well Tolerated

Acquired BRAF fusion

- 59 yo woman with EGFR+ lung cancer
- She received erlotinib for one year, then osimertinib for 6 months.
- Liver biopsy upon progression showed an acquired AGK-BRAF fusion
- She was treated with the combination of osimertinib + trametinib.

Response to osimertinib + trametinib (RECIST-41%)



Treatment complicated by and ultimately discontinued due to GI toxicity.

Dagogo-Jack I, et al. *J Thorac Oncol*. 2019.