What is Histological Transformation and Can it be Treated?

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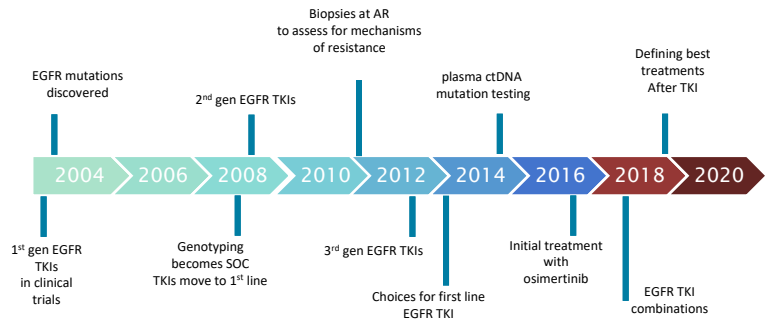
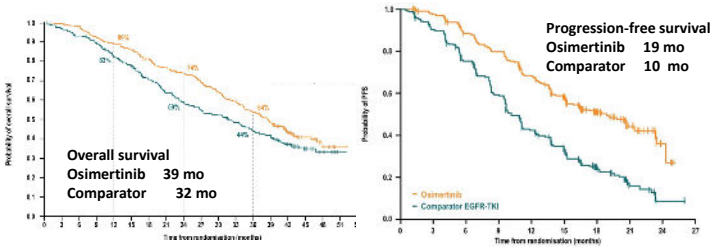
EGFR: A Timeline of Progress



Slide adapted from Lecia Sequist, MD

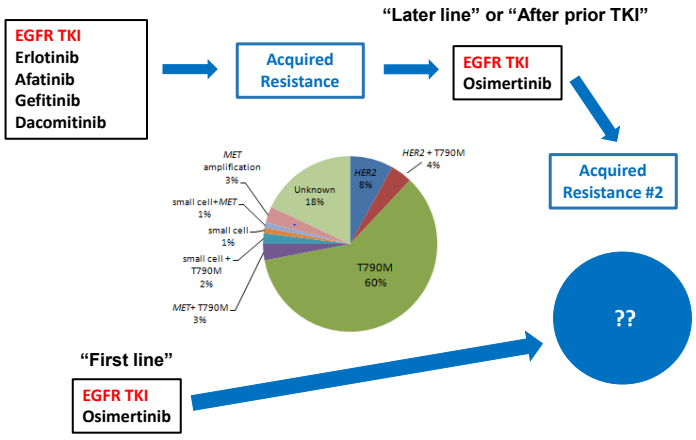
Osimertinib as Best First-line EGFR TKI



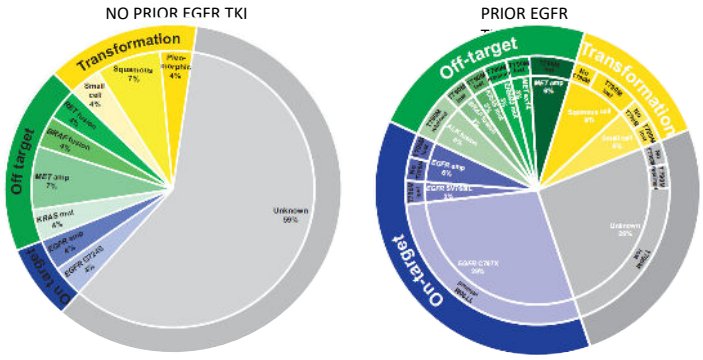
- Osimertinib is a third-generation, irreversible, mutant-specific EGFR TKI
- Other first-line treatments can also be considered, including other EGFR TKIs, TKI combinations (chemo, VEGF) or a clinical trial
- Almost all lung cancers develop resistance to osimertinib. Resistance to treatment means cancer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

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

Timing and Specific TKI May Result in Different Resistance Mechanisms



Lineage Plasticity and Gene Fusions as Mechanisms of Resistance

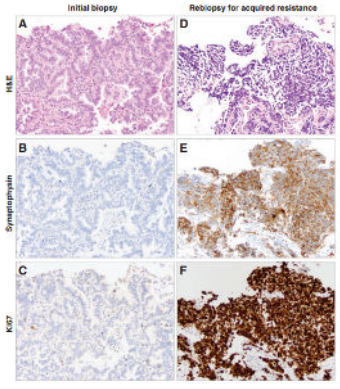


- Resistance can be divided into "on-target" and "off-target"
- Higher incidence of lineage plasticity as a resistance mechanism with first-line osimertinib
- Frequent acquired gene fusions and other alterations (*BRAF, RET, ALK*)

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

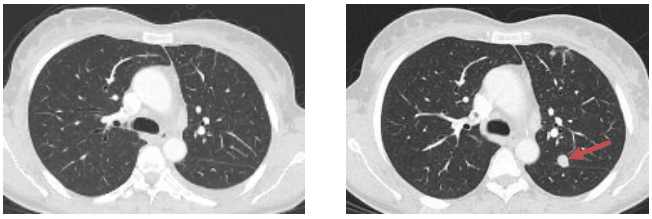
Small Cell Histologic Transformation

- Almost all *EGFR+* lung cancers are ***adenocarcinoma*** (non-small cell lung cancer; describes cell type)
- One way a lung cancer finds a way to grow on EGFR TKI is to ***change histology*** which leads to less dependence on the EGFR protein
- Once transformation occurs, **targeting EGFR is no longer effective**
- Different treatments are used to treat small cell lung cancer



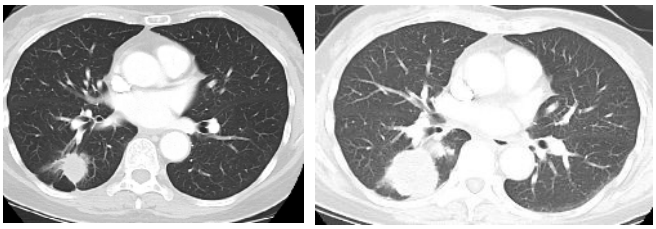
Yu HA, et al. *Clin Cancer Res*. 2013.

Patient Case #1



- 52 yo woman diagnosed with metastatic *EGFR*-mutant lung cancer who started osimertinib in Dec 2018
- She had radiographic progression in pleural nodules in July 2019. Biopsy on 7/12/19 showed small cell transformation.
- She started carboplatin and etoposide and received 2 cycles. She had a mixed response (some areas with shrinkage, others with growth) so osimertinib was added to chemotherapy. A scan after 4 cycles showed response to all sites of disease. She completed 6 cycles followed by maintenance osimertinib.

Patient Case #2



- 58 yo woman diagnosed with metastatic *EGFR*-mutant lung cancer who started erlotinib in July 2014. She then had disease progression and the *EGFR* T790M mutation was identified in her lung cancer and she started osimertinib in July 2016.
- She had radiographic progression and started carboplatin, pemetrexed and bevacizumab in May 2017.
- In April 2018, she had radiographic progression in multiple sites (lung, lymph node, liver) and the biopsy showed small cell transformation.
- She wanted a short break from treatment and in April 2018 started carboplatin and etoposide.

Testing for Small Cell

- Almost always, the lung cancers that transform have evidence of **p53** and **RB** mutations along with EGFR mutations
- These mutations are usually found **prior to treatment at initial diagnosis**. They can only be found on a **next-generation sequencing (NGS)** based large mutation panel. This should be done on everyone!
- If a lung cancer has EGFR/p53/RB mutations, it does not mean transformation will definitely occur. The risk of transformation at some point is about 25%.
- Sometimes there is significant or multi-site progression that causes symptoms, sometimes there is no way to predict a cancer has transformed. Transformation can occur early or later in the disease course.
- Transformation can only be detected through a biopsy, so for patients at risk that have progression, a **tumor tissue biopsy** is recommended over a liquid biopsy.

New Treatment Considerations: The Pivot

- Transformed small cell lung cancers should be **treated similarly, but not exactly** like *de novo* small cell lung cancers.
- EGFR targeted therapies alone do not work.
- Transformed cancers can be **mixed histology** so continuing EGFR targeted therapies WITH small cell directed treatments might make sense.
- (Transformed) small cell lung cancers can **behave more aggressively** so they need to be treated more aggressively.
- We are working to identify which small cell directed treatments might be most beneficial for transformed small cell cancers.

How Can We Prevent Small Cell?

- As of now, there are **no ways to prevent** small cell transformation.
- We do know the **molecular risk factors**, so for those patients with lung cancers at risk, it makes sense to be extra vigilant
- We are studying adding in **small cell-directed treatments** prior to transformation on a clinical trial to see if that can be effective.
- The more we learn about why transformation happens, the better we will be able to be at preventing transformation.
- There are many groups working on this!

Clinical Trials for Transformed Small Cell

- Transformed small cell is treated in many ways similarly to *de novo* small cell with small changes.
- We may continue osimertinib and not add immunotherapy to chemotherapy.
- Most patients with transformed small cell are **eligible for general small cell lung cancer trials.**
- Many EGFR-directed clinical trials exclude patients with small cell transformation - this is because transformed cancers are not driven by the EGFR protein or EGFR signaling.
- Always **ask your oncologist about studies** and **seek a second opinion** if studies are not available at your cancer treatment center.