EGFR-Targeted Therapy for Lung Cancer

Osamu Tetsu, MD, PhD
Associate Professor
Department of Otolaryngology-Head and Neck Surgery
School of Medicine, University of California, San Francisco

Outline

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- **Oncogenic Addiction and Targeted Therapy**
- **Primary Drug Resistance to EGFR TKIs**
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Lung Cancer Classification

- **Pathological classification**
  - **Small cell lung cancer** (SCLC~15%)
  - **Non-small cell lung cancer** (NSCLC~85%)

    -Adenocarcinoma (40%)

    -Squamous cell carcinoma (25-30%)

    -Large cell carcinoma (10-15%)
  - **Clinically importance of the classification**

    - Treatment decisions have depended on tumor histology.

      -Localized NSCLC in an early stage is mainly treated with surgery followed by adjuvant chemotherapy.

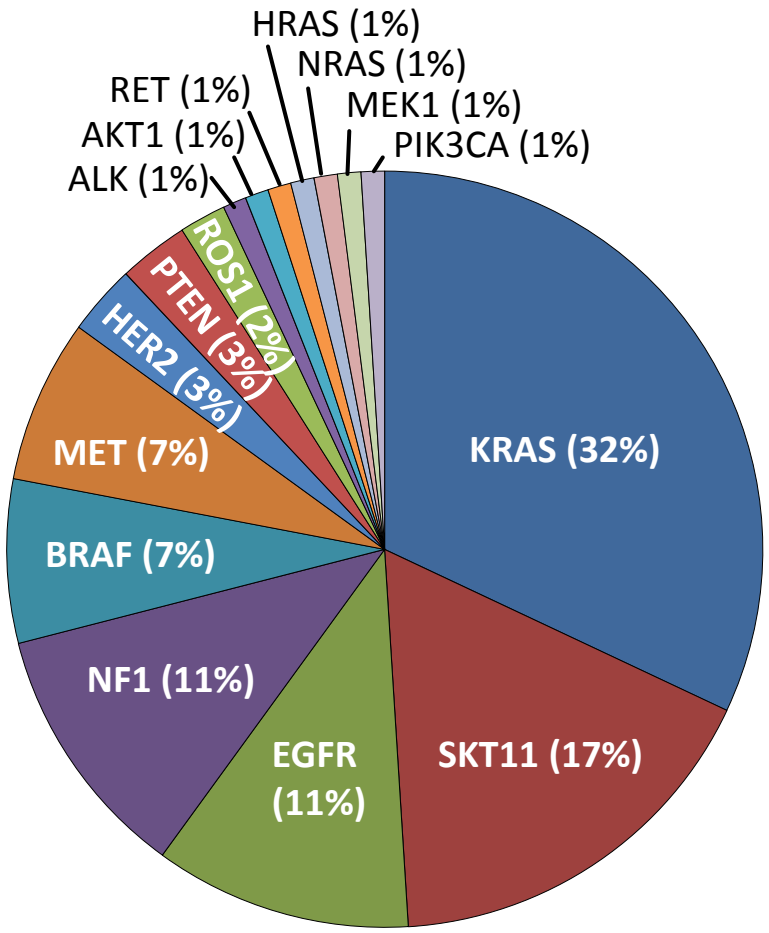
      -SCLC has rarely been treated surgically, as it tends to be more aggressive and spread more rapidly. SCLC is usually treated with chemo- and radiotherapy.

Lung Cancer Classification-cont'd

- However, histological distinctions are no longer sufficient for determining treatment plans.

- **Molecular characterization of NSCLCs**
  - Valuable information for **diagnosis**, **prognosis**, and **treatment** is provided.
  - The discovery of **mutations** in epidermal growth factor receptor (**EGFR**) and **chromosomal translocations** in anaplastic lymphoma kinase (**ALK; EML4-ALK fusion gene**) has dramatically changed the treatment of patients with lung adenocarcinoma.
  - **Targeted therapies** are currently approved for these abnormalities and show considerable promise .
  - However, **drug resistance** has become a substantial issue .

Molecular Profiling of Lung Adenocarcinoma



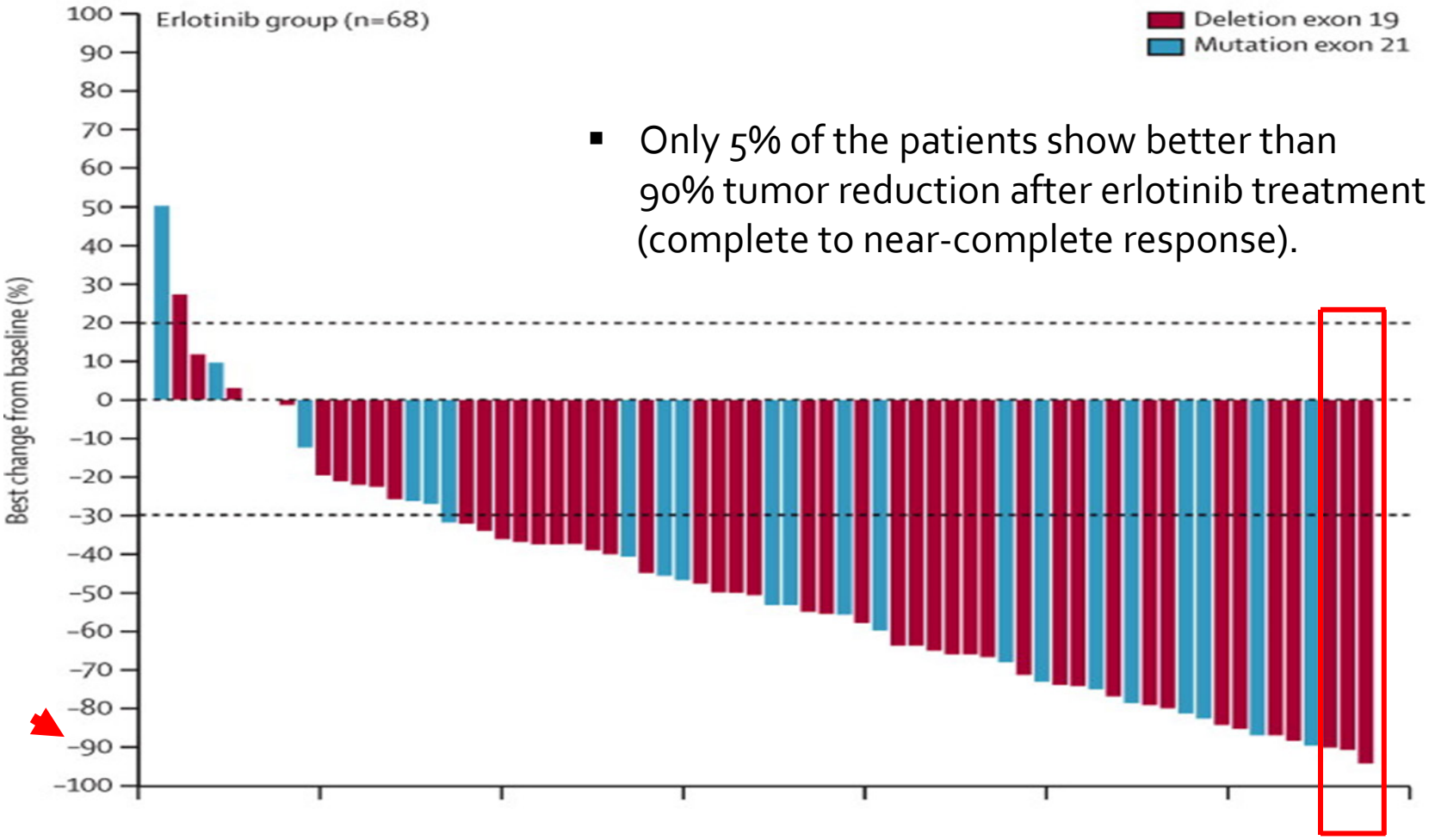
- These mutations are mutually exclusive.
- Targeted therapies are possible for most of gene mutations except for KRAS.
- 40% of KRAS mutations are G12C.
- Majority of EGFR mutations are either in-frame deletions in exon 19 (45%) and the L858R point mutation in exon 21 (41%), and they are associated with a favorable response to the EGFR TKI, including gefitinib (Iressa) and erlotinib (Tarceva).

Based on Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014;511:543-50.

Oncogenic Addiction and Targeted Therapy

- Cancer development involves multiple genetic and epigenetic changes.
- However, the inactivation of a single oncogene can often impair these altered cells' survival.
- This phenomenon—known as **oncogene addiction**—has provided a rationale for molecular targeted therapy.
- The use in lung cancer of selective tyrosine kinase inhibitors (TKIs) for EGFR or ALK represents such examples.
- Here we focus on EGFR TKIs.
  - Patients with activating EGFR mutations are identified in 10~20% of lung adenocarcinomas in Western countries9 and **40~60%** of lung adenocarcinomas in **East Asia**.

Heterogeneous Initial Responses to EGFR TKIs in NSCLCs

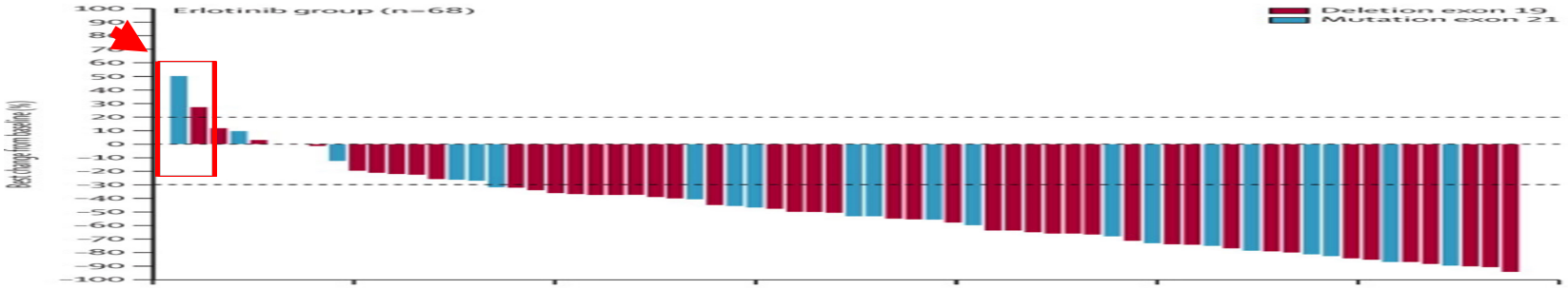


- Only 5% of the patients show better than 90% tumor reduction after erlotinib treatment (complete to near-complete response).

Adopted from Rosell et al. The Lancet Oncology 2012;13;3:239 – 46.

Primary and Acquired Drug Resistance

- Drug resistance is a major obstacle to the success of targeted therapies.
- Based on tumor response to the initial therapy, drug resistance is classified;
  - **Primary** (**innate** or **intrinsic**) drug resistance.
    - Patients with primary resistance do not respond at all to treatment.
    - 10% of patients with TKI-sensitive EGFR mutations show primary resistance to TKIs.



  - **Acquired** (**adaptive** or **secondary**) drug resistance.
    - Patients with acquired resistance may initially respond completely or partially, only to fail to do so over time.

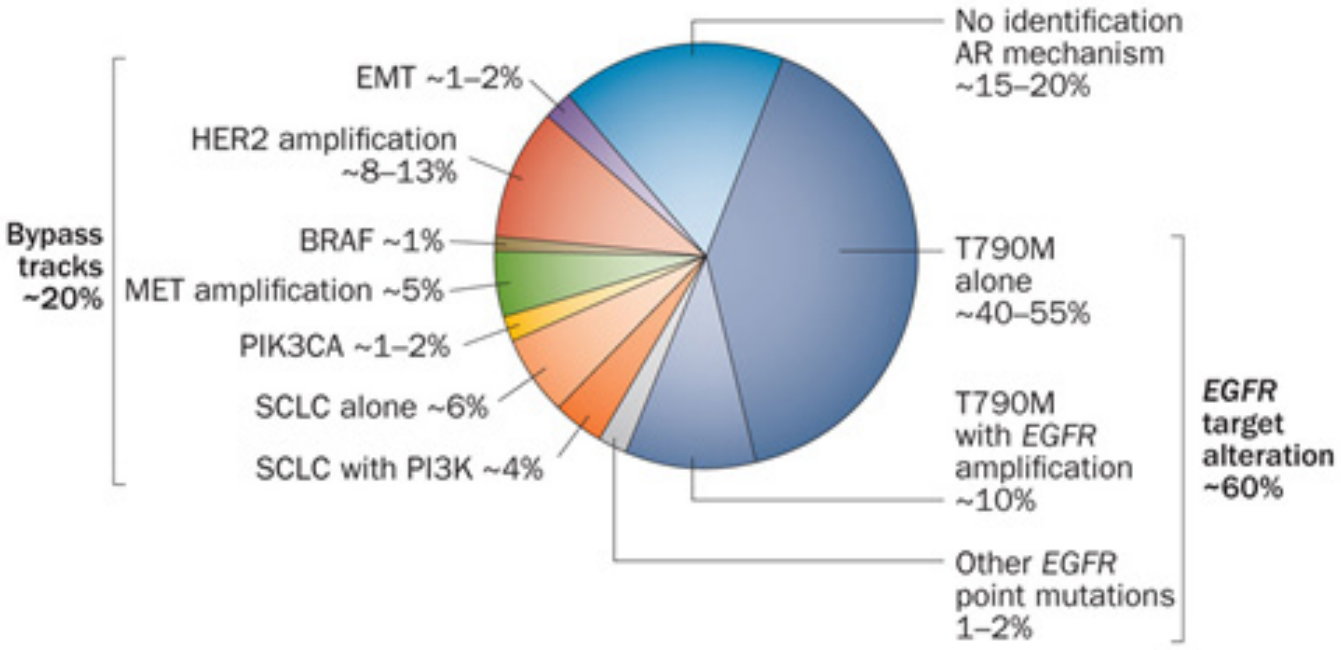
Primary Drug Resistance to EGFR TKIs

- **Wild-type EGFR**
  - Only 3% of patients harboring wild-type EGFR had a partial response to erlotinib.
- **KRAS and BRAF mutations**
  - Despite EGFR inhibition, KRAS and BRAF mutations constitutively activate downstream MAPK signaling.
- **Bim polymorphism**
  - Bim is a BH3-only protein, which is essential for apoptosis and caspase induction in EGFR-mutated NSCLC cells.
  - Genetic polymorphism generates alternative splicing variants of Bim protein lacking the BH3 domain, which is sufficient to confer primary resistance to TKIs.
- **Various EGFR mutations**
  - Less common EGFR mutations also exist. Some are sensitive to TKIs but others are not.
- **Tumor microenvironment**
  - HGF-mediated activation of the RTK MET is suspected as the most important cause of primary resistance to anticancer agents.

Acquired Drug Resistance to EGFR TKIs

- Acquired resistance to EGFR TKIs develops after an average of a year of continuous treatment.
  - **Clinical definition**
    - The tumors should harbor TKI-sensitive EGFR mutations.
    - They should have responded either partially or completely (unless stable disease has been present for more than six months).
    - The tumors have demonstrated systemic progression.
  - **4 different mechanisms**
    - **EGFR target alterations** in the drug target itself such as T790M secondary mutation (50-65%).
    - **Activation of alternative signaling** pathways to bypass the EGFR (~30%).
    - A lineage switch through histological transformation from NSCLC to SCLC or epithelial-mesenchymal transition (EMT).
    - Intratumor heterogeneity (Cancer is an evolving and systemic disease).

Mechanisms of Acquired Resistance to EGFR TKIs



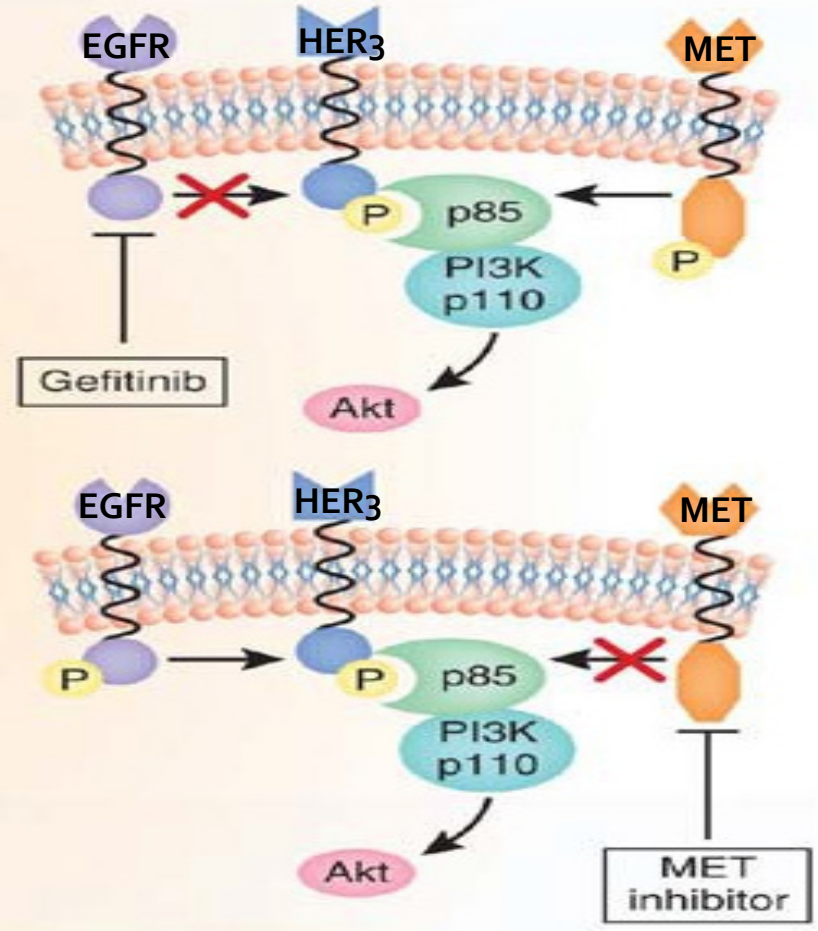
Adopted from Camidge DR et al. Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nat Rev Clin Oncol. 2014;11:473-81.

Target Alterations (~60%)

- Acquired resistance to gefitinib and erlotinib is predominantly mediated by the development of the T790M EGFR secondary mutation (50-65%).
  - Threonine 790 is the **gatekeeper residue** in EGFR, lies within the ATP-binding pocket of EGFR, and influences drug effectiveness.
  - A further chromosomal amplification of the gene locus may enhance the inhibitory effect of T790M.
- **Gatekeeper mutations** can be a common mechanism of acquired drug resistance to targeted therapies in cancer.
  - Analogous mutations are reported in malignances exposed to various TKIs:
    - Imatinib-resistant T315I BCR-ABL in chronic myelogenous leukemia (CML).
    - Imatinib-resistant T670I KIT in gastrointestinal stromal tumor (GIST).
    - Crizotinib-resistant L1196M ALK fusion gene in NSCLC .
- Other rarer TKI-induced EGFR mutations (<10%) have been reported: L747S, D761Y, and T854A.

Activation of Bypass Pathways (~20%)

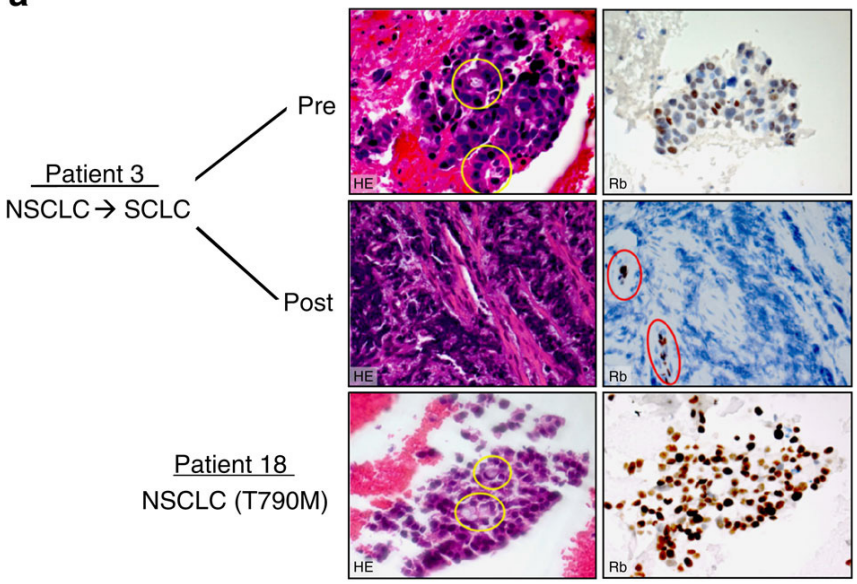
- An RTK switch.
  - Amplification of **MET** (5-20%) or HER2 (12%).
  - Activation of HER3.
  - Insulin-like growth factor 1 receptor (IGF-1R).
  - Fibroblast growth factor receptor 1 (FGFR1).
- Mutations in the signaling pathways
  - BRAF mutations.
  - Loss of PTEN or NF1 expression.



Adopted from Arteaga CL. HER3 and mutant EGFR meet MET. Nat Med. 2007;13:675-7.

Histological Transformation from NSCLC to SCLC (~10%)

a



b

Rb staining	SCLC resistant	NSCLC resistant
Negative	(10/10) – 100%	(1/9) – 11%
Positive	(0/10) – 0%	(8/9) – 89%

Fisher's exact test – $P < 0.0001$

- The lineage switch from NSCLC adenocarcinoma to SCLC was recently reported to involve the loss of RB1 (retinoblastoma 1) and EGFR proteins.
- Actually, primary SCLCs are known to have a high prevalence of inactivating mutations in RB1 and TP53. In contrast, EGFR mutations and gene amplifications are rarely found in sporadic SCLCs . Thus, the loss of RB1 expression can be the most likely scenario for lineage switching.

Adopted from Niederst et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. Nat Commun. 2015;6:6377.

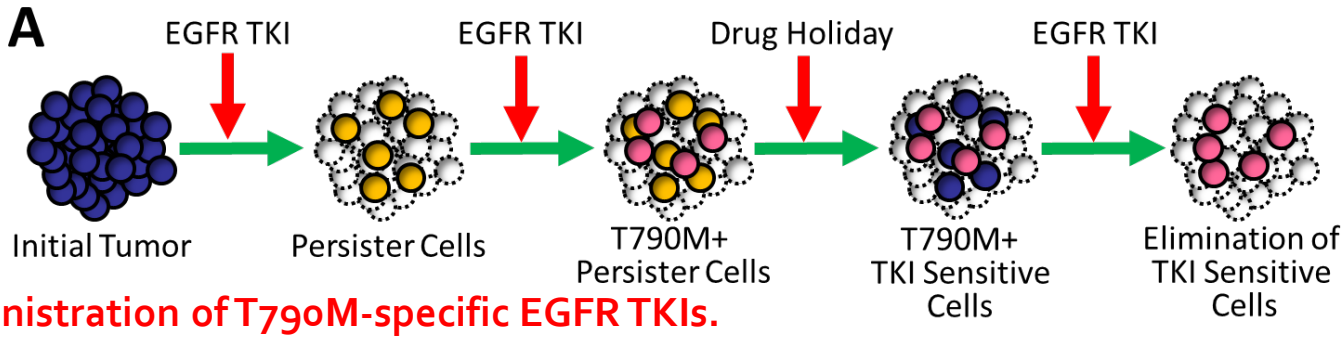
Overcome Drug Resistance by New Generation EGFR TKIs

1st-generation	2nd-generation	3rd-generation
Gefitinib [23, 24]	Afatinib [109]	AZD9291 [117]
Erlotinib [24 – 26]	Dacomitinib [110]	Rociletinib [118]
	Neratinib [111]	WZ4002 [119]

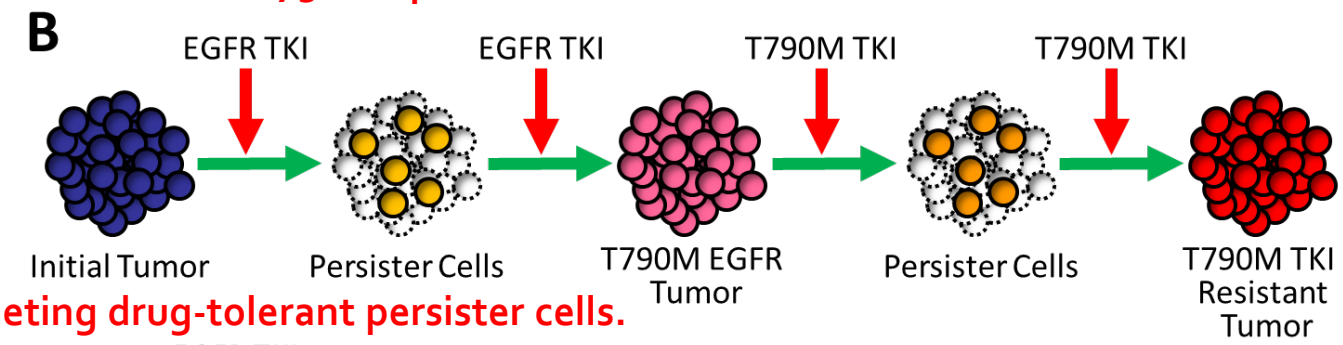
Tetsu et al. Drug Resistance to EGFR Inhibitors in Lung Cancer. Chemotherapy. 2016 ;61:223-235.

Different strategies to overcome drug resistance to EGFR inhibitors

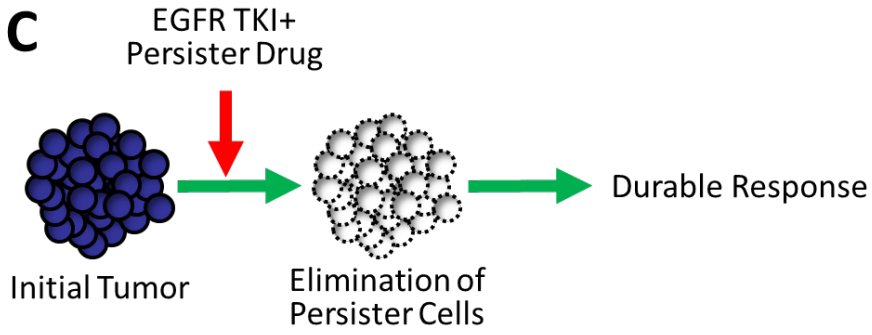
Retreatment with the same TKI after a treatment interruption.



Administration of T790M-specific EGFR TKIs.



Targeting drug-tolerant persister cells.

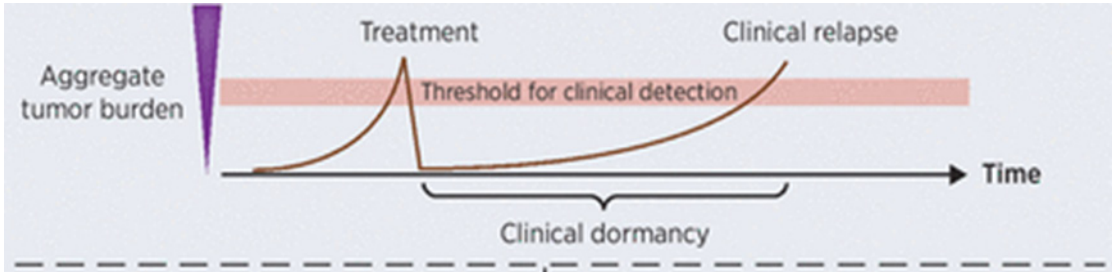


Tetsu et al. Drug Resistance to EGFR Inhibitors in Lung Cancer. Chemotherapy. 2016;61: 223-235.

Cancer Dormancy and Acquired Drug Resistance

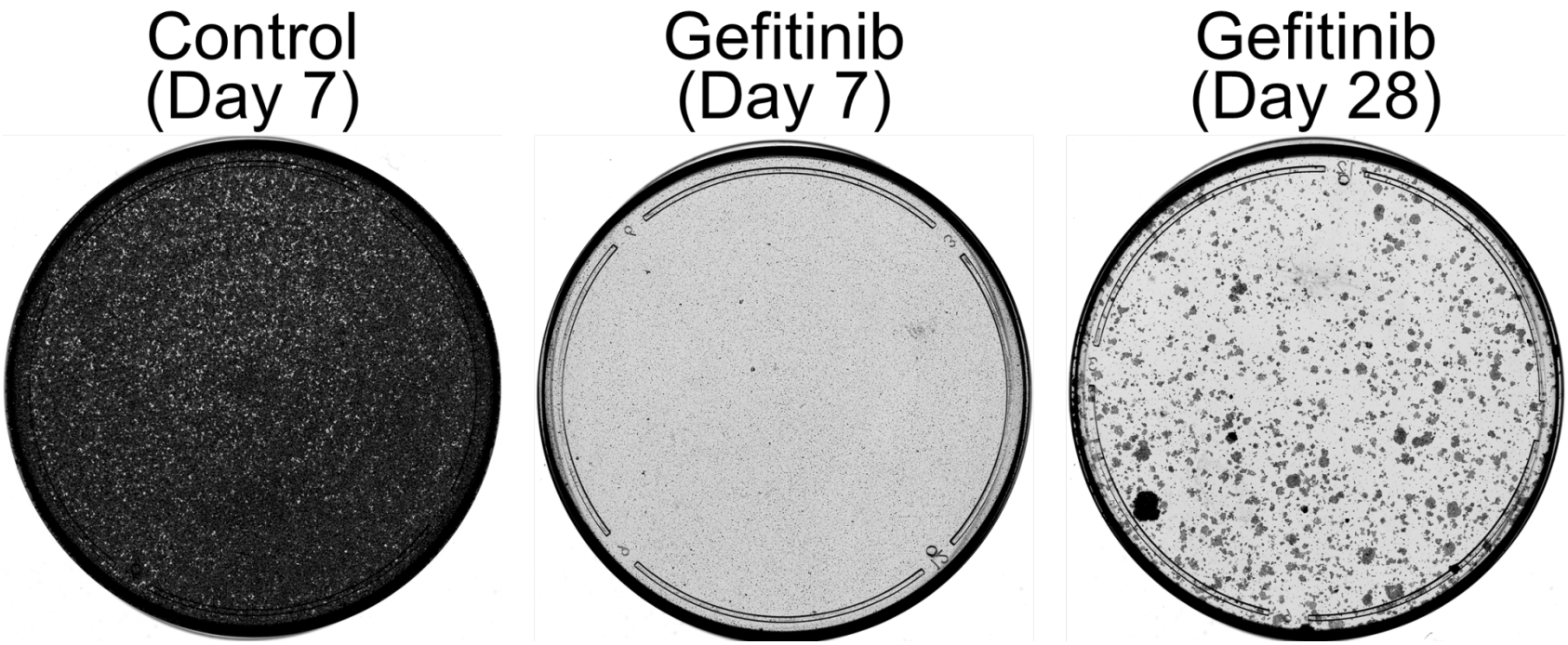
- The origin of resistant cells remains to be elucidated, but they must arise from surviving populations.
  - The surviving cells were recently referred to as drug-tolerant persisters (DTPs), which lie temporarily dormant as a means of circumventing the effects of the given therapy, but eventually regain proliferative capacity, leading to drug-tolerant expanded persisters (DTEPs).

- In the clinical setting, cancer dormancy is observed as a "grace period" after treatment: signs and symptoms of cancer have disappeared, but the patients occasionally carry surviving tumor cells in local and distant bodily regions.



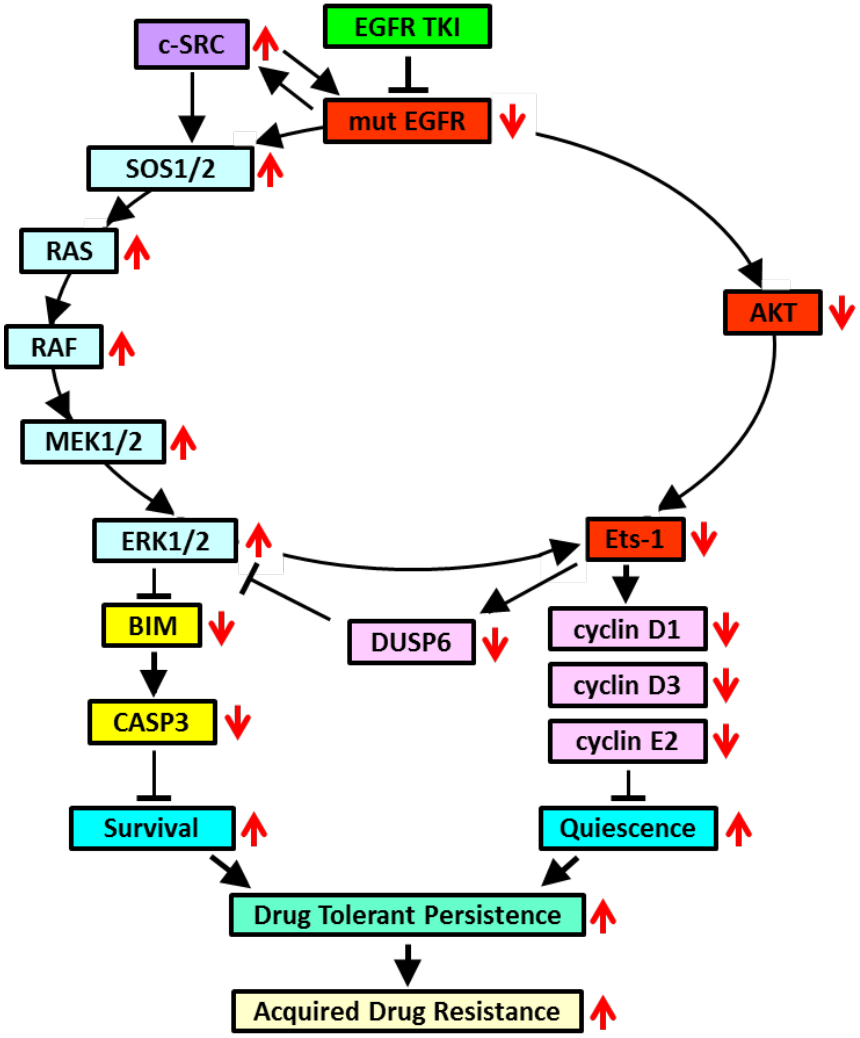
Adopted from Yeh et al. Mechanisms of Cancer Cell Dormancy—Another Hallmark of Cancer? Cancer Res. 2015 ;75: 5014-22.

EGFR TKI Exposure Develops DTPs and DTEPs



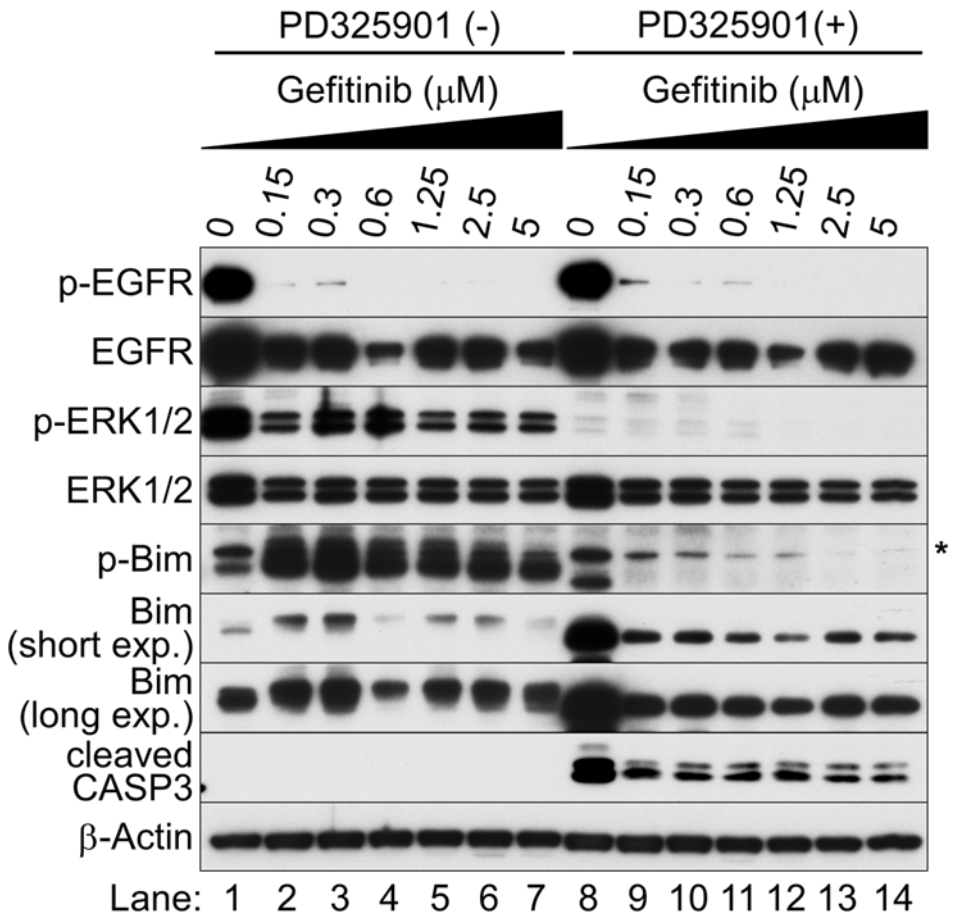
Phuchareon et al. EGFR inhibition evokes innate drug resistance in lung cancer cells by preventing Akt activity and thus inactivating Ets-1 function. Proc Natl Acad Sci U S A. 2015 ;112:E3855-63.

AKT Inactivation Causes Persistent Drug Tolerance to EGFR Inhibitors



Tetsu et al. Drug Resistance to EGFR Inhibitors in Lung Cancer. Chemotherapy. 2016;61:223-235.

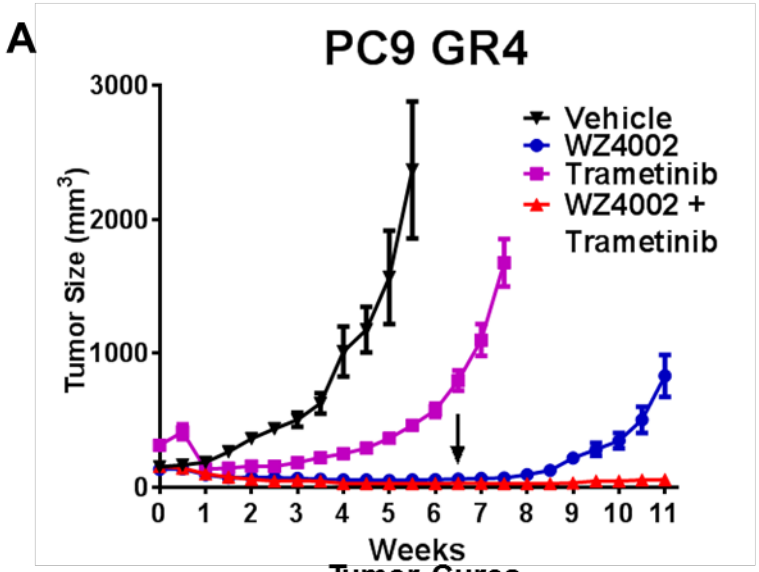
Combined EGFR and MEK Inhibition May Prevents Drug Resistance



- Sustained activation of ERK1/2 enhances DTPs' survival by accelerating Bim protein turnover.
- We may eliminate DTPs through MEK inhibition while they are quiescence.

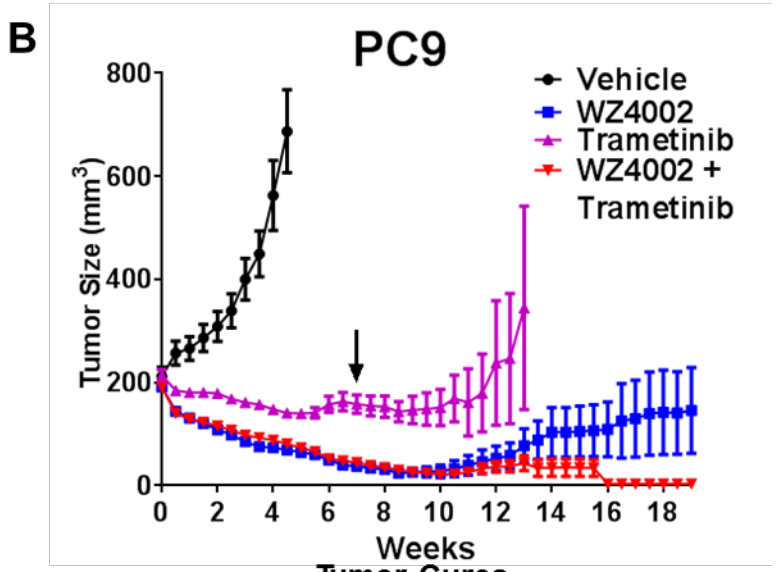
Phuchareon et al. EGFR inhibition evokes innate drug resistance in lung cancer cells by preventing Akt activity and thus inactivating Ets-1 function. Proc Natl Acad Sci U S A. 2015;112:E3855-63.

Targeting Drug-tolerant Persister Cells by a Combination Therapy



Tumor Cures

WZ4002:	0/15
Trametinib:	0/15
WZ4002 & Trametinib:	7/15



Tumor Cures

WZ4002:	4/15
Trametinib:	1/15
WZ4002 & Trametinib:	7/15

Adopted from Tricker et al. Combined EGFR/MEK Inhibition Prevents the Emergence of Resistance in EGFR mutant Lung Cancer. Cancer Discov. 2015;5:960-71 .

Conclusions

- Over the past decade, EGFR-targeted therapies have dramatically changed the treatment of patients with lung adenocarcinoma. However, drug resistance has become a substantial issue.
- Recent studies have identified the mechanisms of primary, acquired, and persistent drug resistance to TKIs, and researchers and clinicians have used these findings to develop therapeutic approaches.
- However, the stepwise use of single agents presents a formidable challenge. This suggests that researchers and clinicians should consider multi-drug combinations to overcome drug resistance.
- In this era of precision medicine, oncologists must promptly obtain an accurate diagnosis of drug resistance during the individual clinical course to design the most relevant combination to overcome the patient-specific drug resistance in this population.

References

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