EGFR-Targeted Therapy for Lung Cancer

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Outline

- **Lung Cancer Classification**
  - Pathological Classification
  - Molecular Classification
- **Oncogene Addiction and Targeted Therapy**
- **Primary Drug Resistance to EGFR Inhibitors**
- **Acquired Drug Resistance to EGFR Inhibitors**
  - T790M and Other Secondary EGFR Mutations
  - Activation of Alternative Pathways
  - Histologic Transformation
- **Overcoming Drug Resistance to EGFR Inhibitors**
  - T790M-specific EGFR TKIs
  - Targeting Dormant Cancer Cells
- **Conclusions**

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.

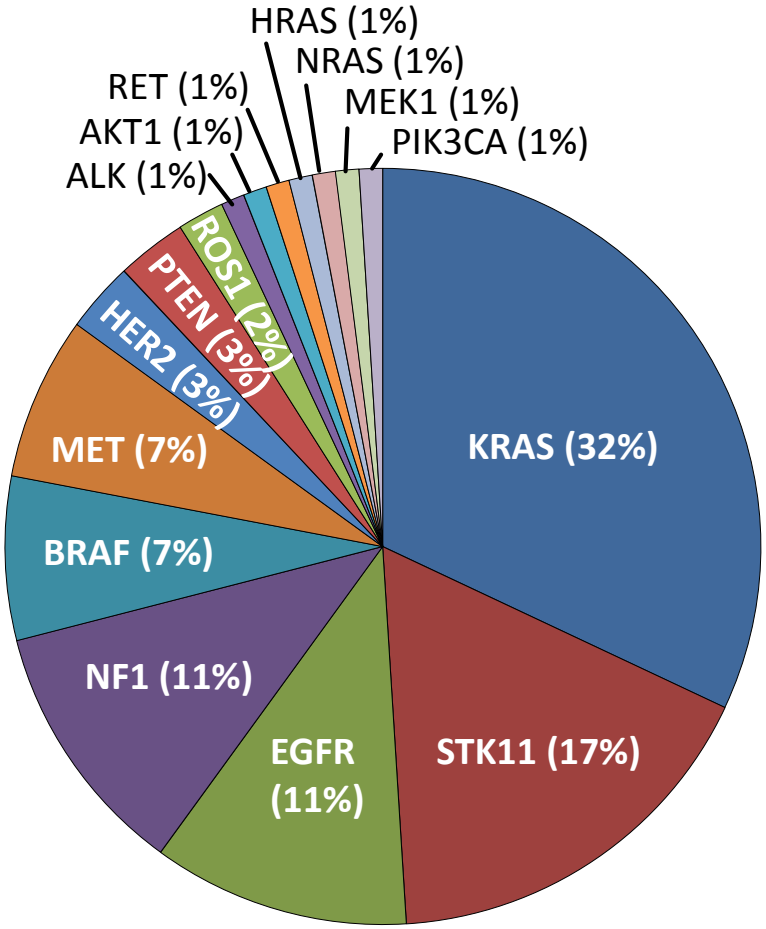
      -SCLC has rarely been treated surgically, as it tends to be more aggressive and spread more rapidly. SCLC is usually treated with chemo- and radiotherapy.

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



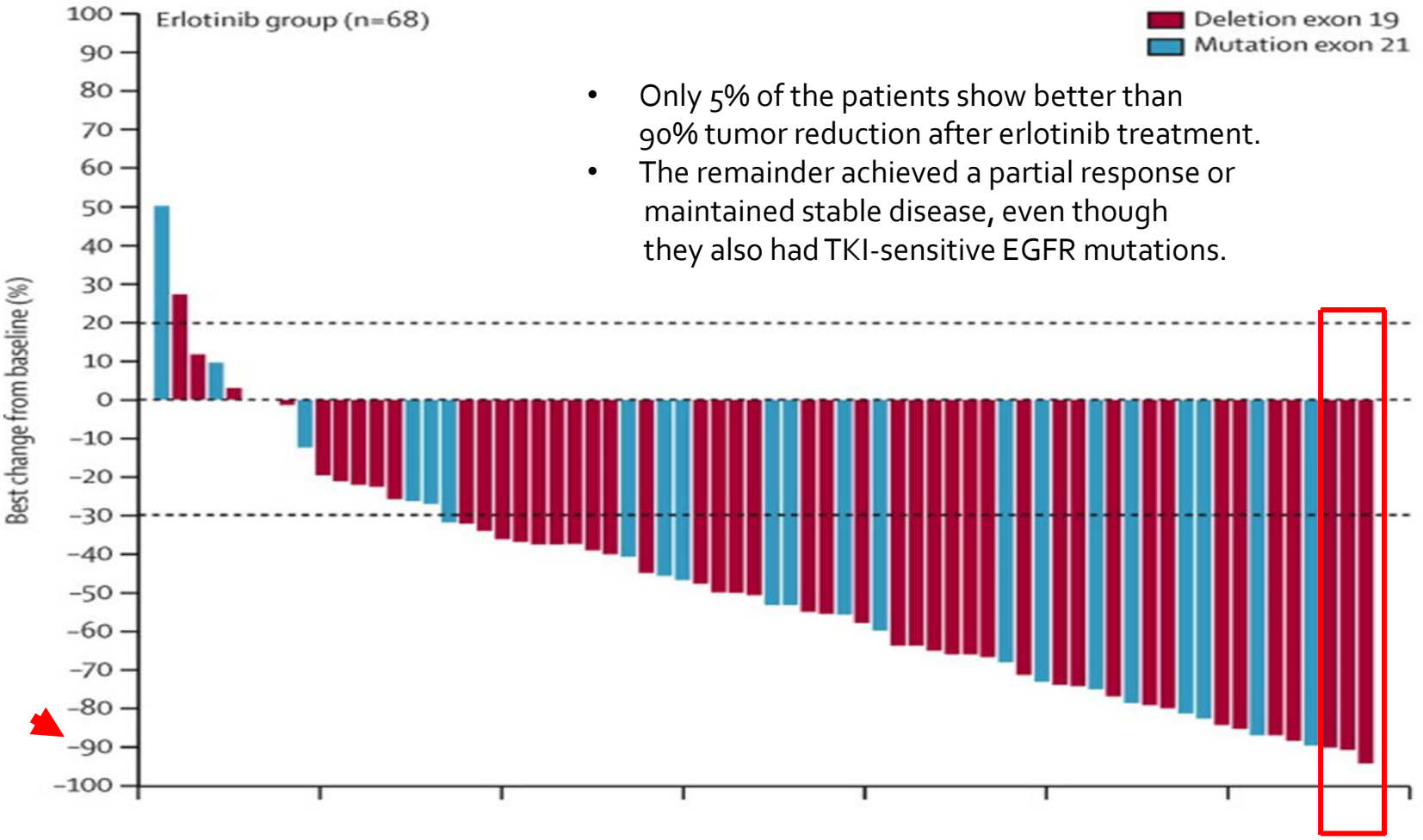
- Lung adenocarcinomas have recurrent mutations in multiple oncogenes.
- These mutations are mutually exclusive.

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

Oncogene 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 Caucasians and **40~60%** of lung adenocarcinomas in **East Asians**.
  - 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 TKIs, including gefitinib (Iressa) and erlotinib (Tarceva).

Heterogeneous Initial Responses to EGFR TKIs in NSCLCs

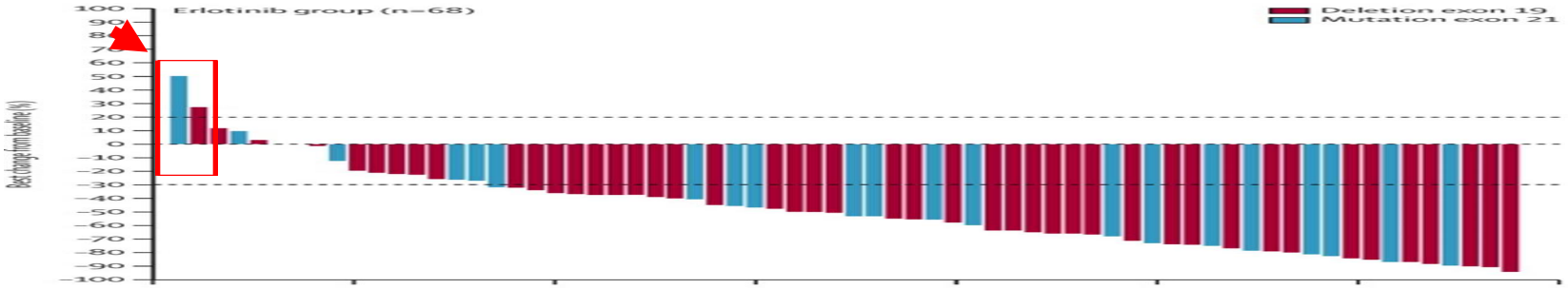


- Only 5% of the patients show better than 90% tumor reduction after erlotinib treatment.
- The remainder achieved a partial response or maintained stable disease, even though they also had TKI-sensitive EGFR mutations.

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 BH_3-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 BH_3 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

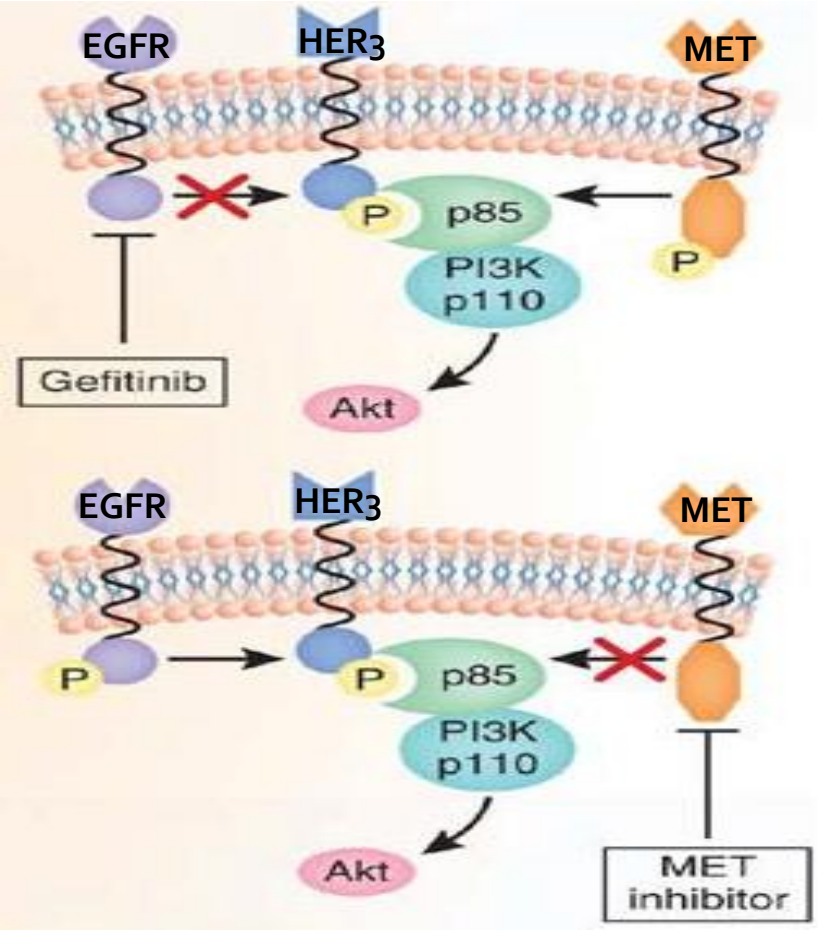
- Acquired resistance to EGFR TKIs develops after an average of a year of continuous treatment.
  - **Clinical definition**
    - The tumors should harbor TKI-sensitive EGFR mutations.
    - They should have responded either partially or completely (unless stable disease has been present for more than six months).
    - The tumors have demonstrated systemic progression.
  - **4 different mechanisms**
    - **EGFR target alterations** in the drug target itself such as T790M secondary mutation (~60%).
    - **Activation of alternative signaling pathways** to bypass the EGFR inhibition (~20%).
    - **A lineage switch through histological transformation** from NSCLC to SCLC (~10%) or epithelial-mesenchymal transition (EMT;~5%).
    - **Intratumor heterogeneity** (Cancer is an evolving and systemic disease).

EGFR Target Alterations (~60%)

- Acquired resistance to TKIs is predominantly mediated by the development of the **T790M EGFR secondary mutation** (50-60%).
  - 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%): L747S, D761Y, and T854A.

Activation of Bypass Pathways (~20%)

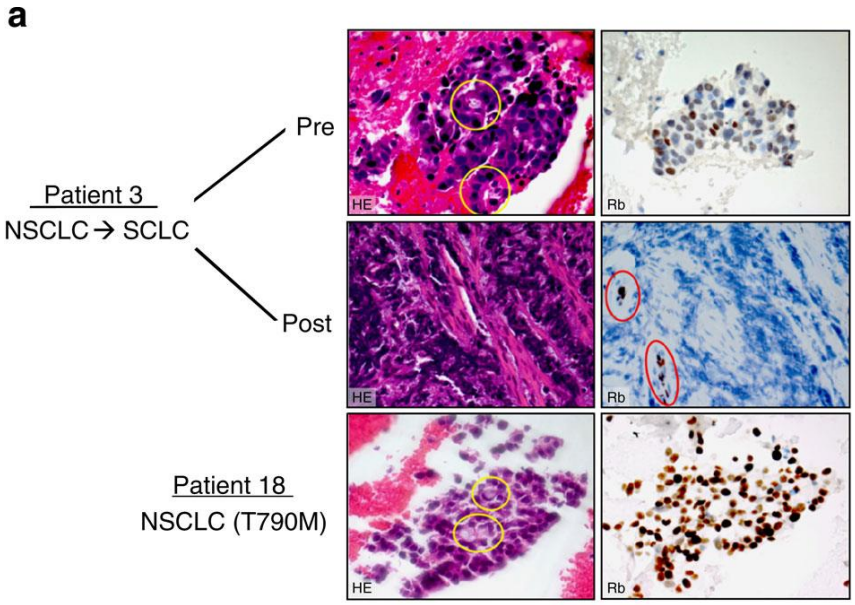
- An RTK switch is a common mechanism of acquired resistance to EGFR TKIs.
  - Amplification of **MET** (5-20%) or **HER2** (12%).
  - Activation of **HER3,** insulin-like growth factor 1 receptor (**IGF-1R**), or fibroblast growth factor receptor 1 (**FGFR1**).
- Mutations occurring in other driver oncogenes and tumor suppressors may also affect acquired drug resistance to EGFR TKIs.
  - **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%

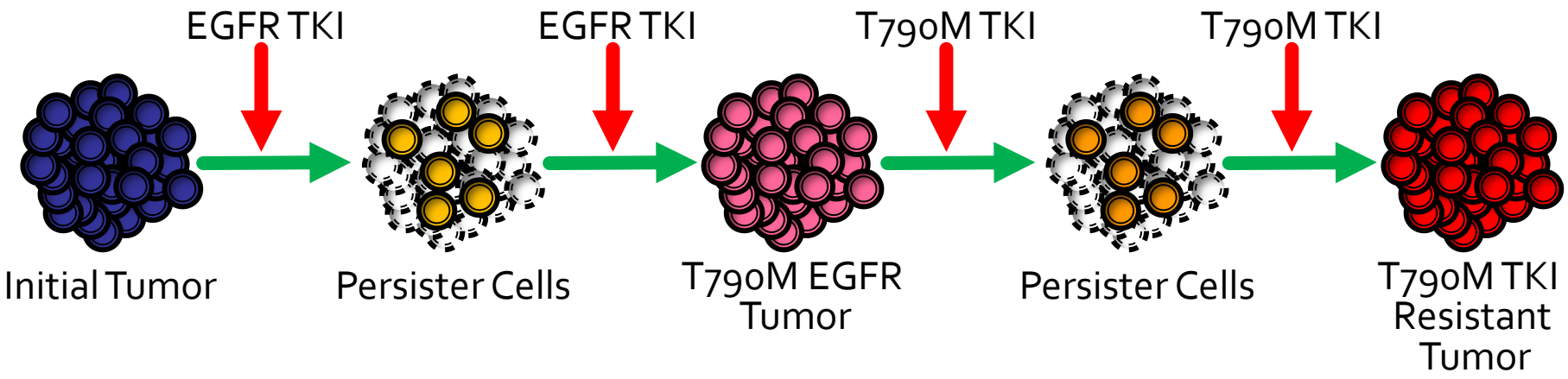
Fisher's exact test – $P < 0.0001$

- The lineage switch from NSCLC adenocarcinoma to SCLC has been reported to involve the loss of retinoblastoma 1 (RB1) and EGFR proteins.
- Primary SCLCs 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

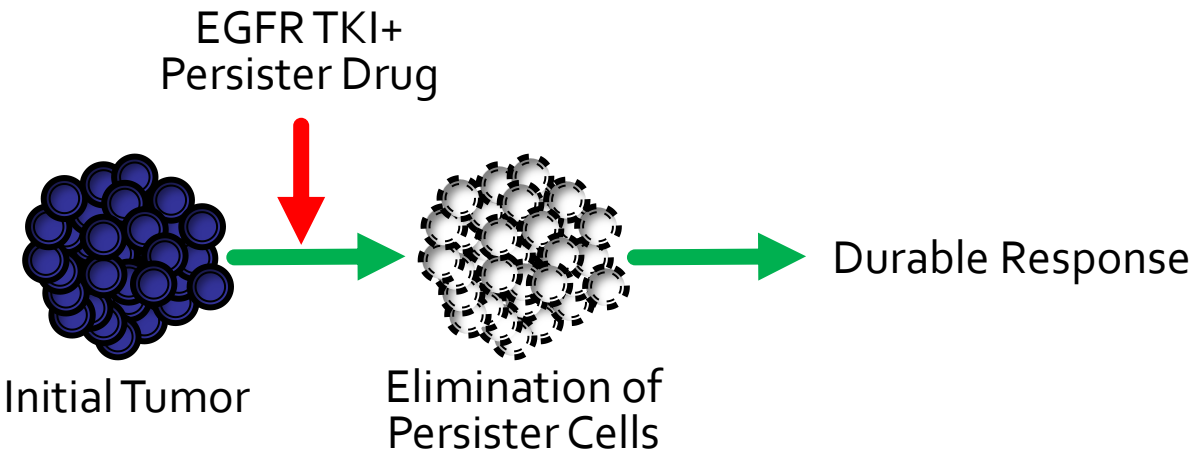
Administration of T790M-specific EGFR TKIs.



- Among the numerous therapeutic investigations to improve patient outcomes, a focus has narrowed on T790M EGFR.
- T790M-specific EGFR TKIs inhibit both mutations of EGFR activation and drug-resistance. In early-phase studies, they demonstrated promising response rates (~60%) in tumors with T790 M EGFR mutation. Unfortunately, acquired resistance was developed in EGFR.

Targeting Origin of Acquired-Resistance Cells

Targeting origin of acquired-resistance cells.

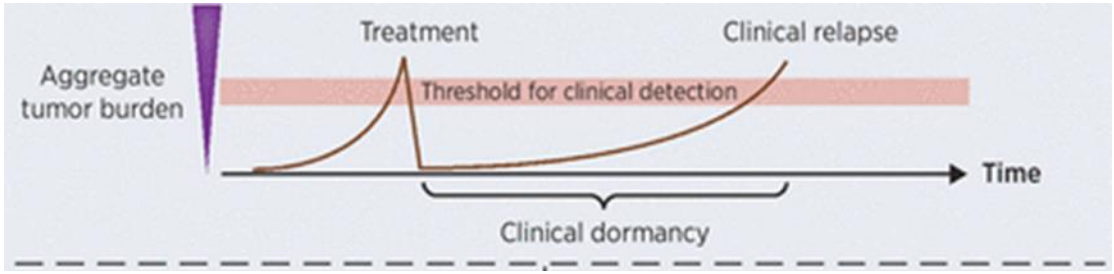


- The origin of acquired-resistance cells (drug-tolerant persister [DTP] cells) could be a therapeutic target, as reduction of this subset may prevent emergent resistance to EGFR inhibitors.
- We recently proposed combined EGFR and MEK inhibition therapy to target the origin of acquired-resistance cells.

Cancer Dormancy and Acquired Drug Resistance

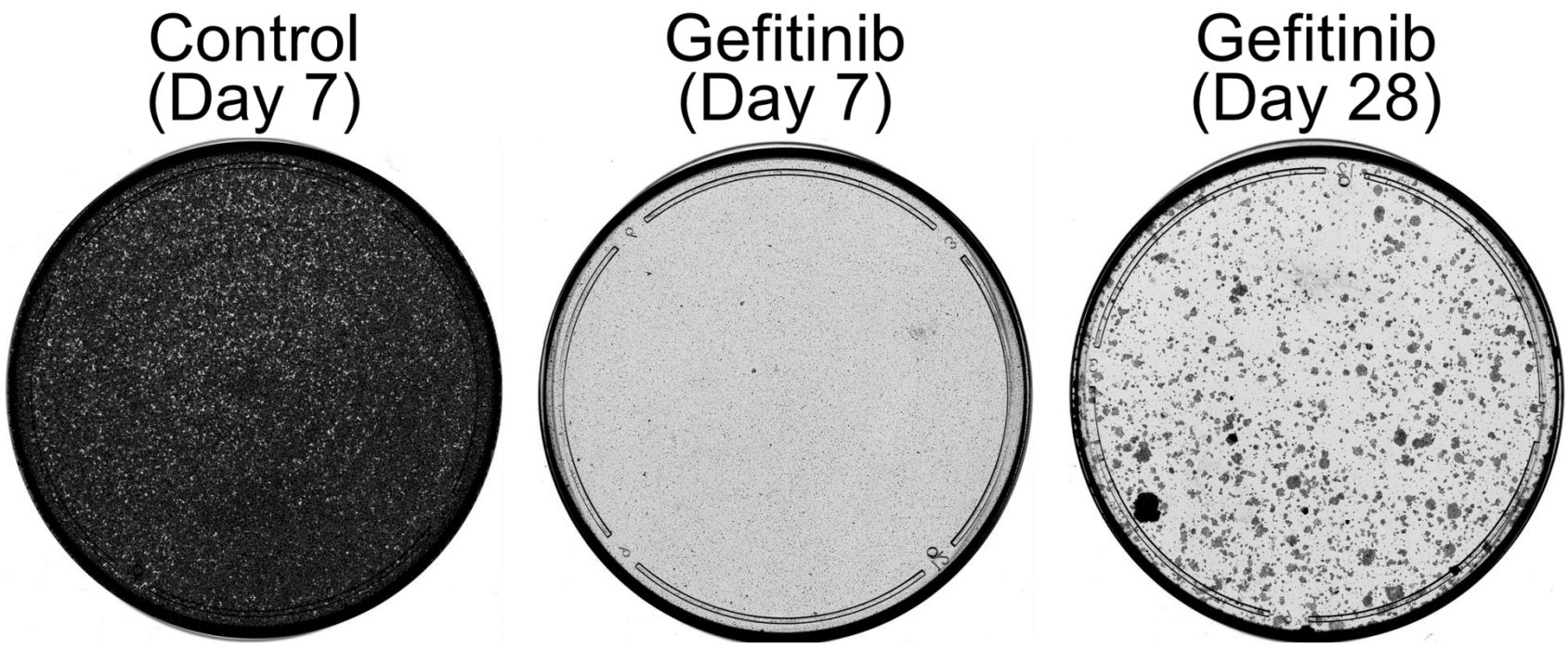
- The origin of resistant cells remains to be elucidated, but they must arise from surviving populations.
  - The surviving cells were recently referred to as drug-tolerant persisters (DTPs), which lie temporarily dormant as a means of circumventing the effects of the given therapy, but eventually regain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

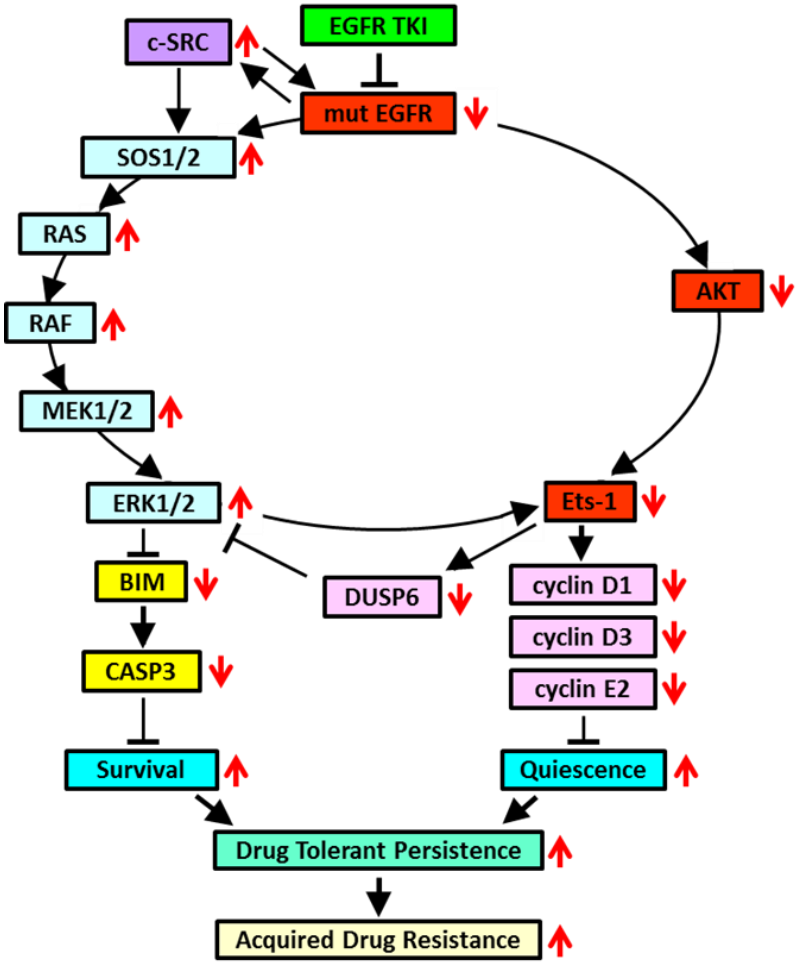


Drug-tolerant persisters (DTPs)

Drug-tolerant expanded persisters (DTEPs)

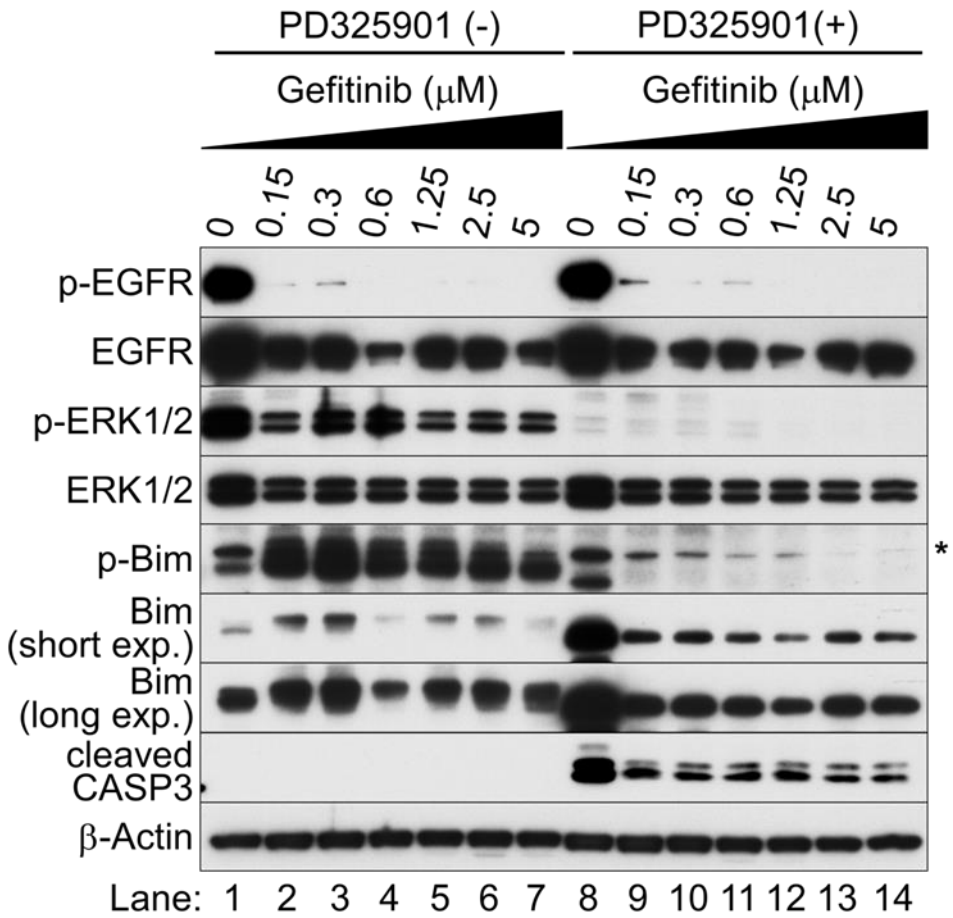
Phuchareon et al. EGFR inhibition evokes innate drug resistance in lung cancer cells by preventing Akt activity and thus inactivating Ets-1 function. Proc Natl Acad Sci U S A. 2015 ;112:E3855-63.

AKT Inactivation Causes Persistent Drug Tolerance to EGFR Inhibitors



- EGFR inhibition in lung cancer cells generates a drug-tolerant subpopulation by blocking AKT activity and thus inactivating Ets-1 function.
- The remaining cells enter a dormant state because of the inhibited transactivation of Ets-1 target genes cyclins D1, D3, and E2.
- Ets-1 inactivation inhibits transcription of dual specificity phosphatase 6 (DUSP6), a negative regulator specific for ERK1/2.
- As a result, ERK1/2 is activated, which combines with c-Src to renew activation of the Ras/MAPK pathway, causing increased cell survival by accelerating Bim protein turnover.

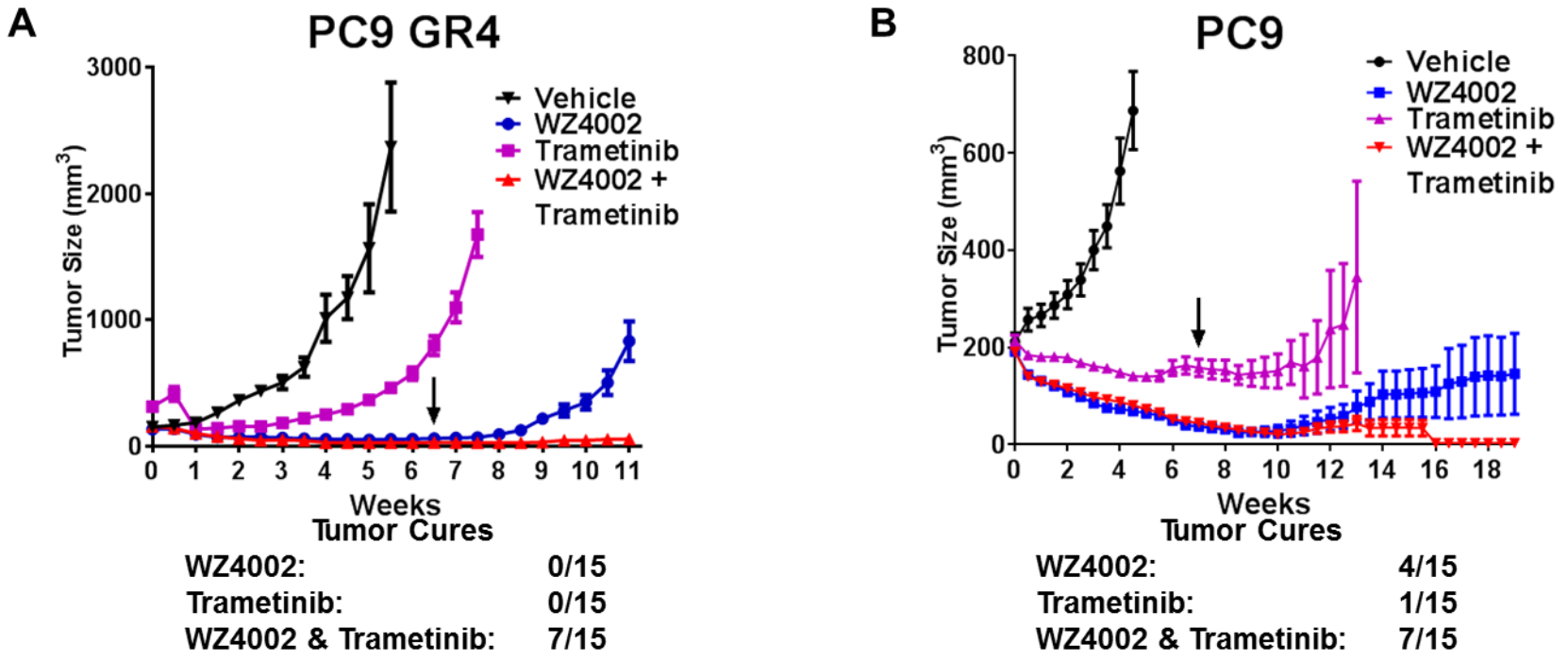
Combined EGFR and MEK Inhibition May Prevents Drug Resistance



- Sustained activation of ERK1/2 enhances DTPs' survival by accelerating Bim protein turnover.
- We may eliminate DTPs through MEK inhibition while they are quiescence.
- This novel therapy has also been proposed by another laboratory, as it is thought to be effective not only in TKI-sensitive EGFR mutations , but also in acquired resistance with the T790M gatekeeper mutation in EGFR.

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



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.
- Likewise, 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.

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