EGFR Tyrosine Kinase Inhibitor (EGFR-TKI)

EGFR-TKIs are a class of **small-molecule drugs** that inhibit the **intracellular tyrosine kinase domain** of the **epidermal growth factor receptor (EGFR)**. They are used primarily in the treatment of cancers with dysregulated EGFR signaling, especially **non-small cell lung cancer (NSCLC)**.

Mechanism of Action

- Compete with ATP for binding to the **tyrosine kinase domain** of EGFR.
- Prevent **autophosphorylation** of EGFR and downstream activation of key pathways:
  - RAS/RAF/MEK/ERK → Cell proliferation
  - PI3K/AKT/mTOR → Cell survival
  - JAK/STAT → Immune modulation
- Result: **Inhibition of tumor growth**, **angiogenesis**, and **metastasis**

Generations of EGFR-TKIs

- **First-generation** (reversible inhibitors):
  - Erlotinib
  - Gefitinib
- **Second-generation** (irreversible, broader spectrum):
  - Afatinib
  - Dacomitinib
- **Third-generation** (T790M mutation-selective):
  - Osimertinib

Clinical Indications

- Non-small cell lung cancer (NSCLC) with activating EGFR mutations (e.g., **exon 19 deletions**, **L858R**)
- Investigational use in glioblastoma and other EGFR-driven tumors

Resistance Mechanisms

- Secondary mutations (e.g., **T790M**, **C797S**)
- Activation of bypass pathways (e.g., **MET**, **HER2**)
- Histological transformation (e.g., adenocarcinoma to small-cell)
- Tumor heterogeneity and clonal evolution

Side Effects

- Acneiform rash
- Diarrhea
- Interstitial lung disease (rare but serious)
- Paronychia and dry skin
- Liver enzyme elevation

Related Topics

- EGFR Pathway
- EGFR Inhibitors
- Targeted Therapy
- TKI Resistance Mechanisms
- Osimertinib (Tagrisso)