

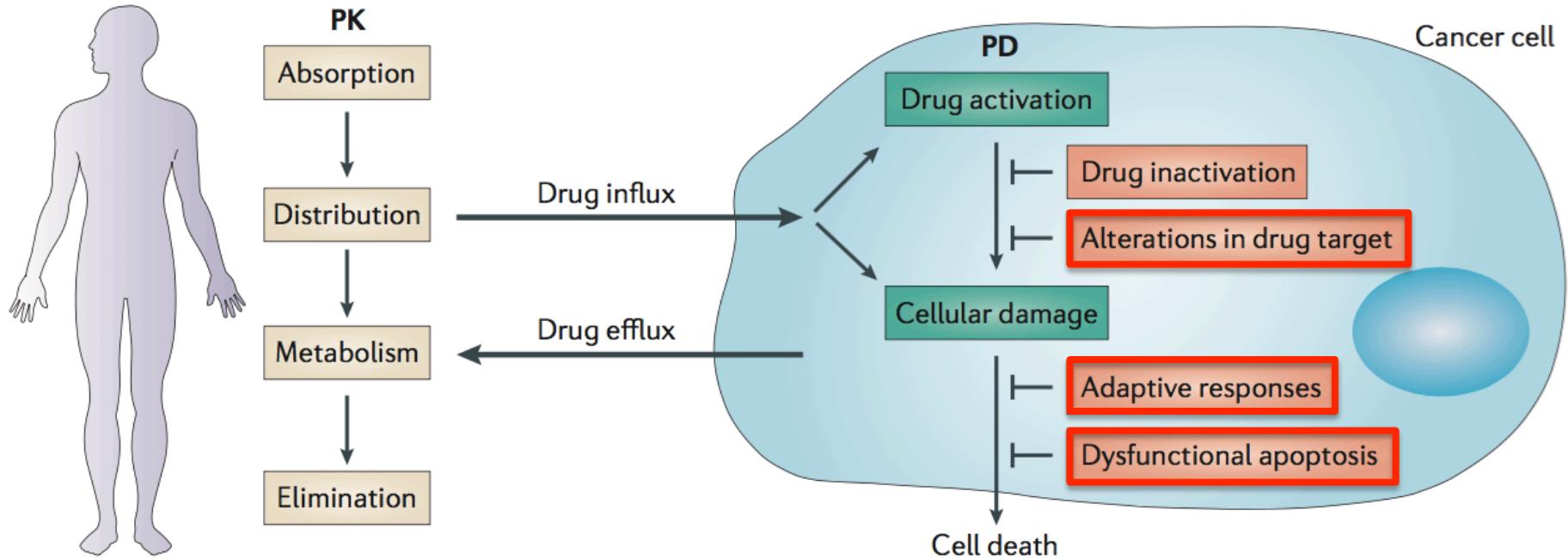
Wed. 10 - Fri. 12 February 2016
Antwerp, Belgium

Resistance mechanisms in new drugs and how to overcome it: the point of view of the **pharmacologist**

37th EORTC-PAMM Winter Meeting

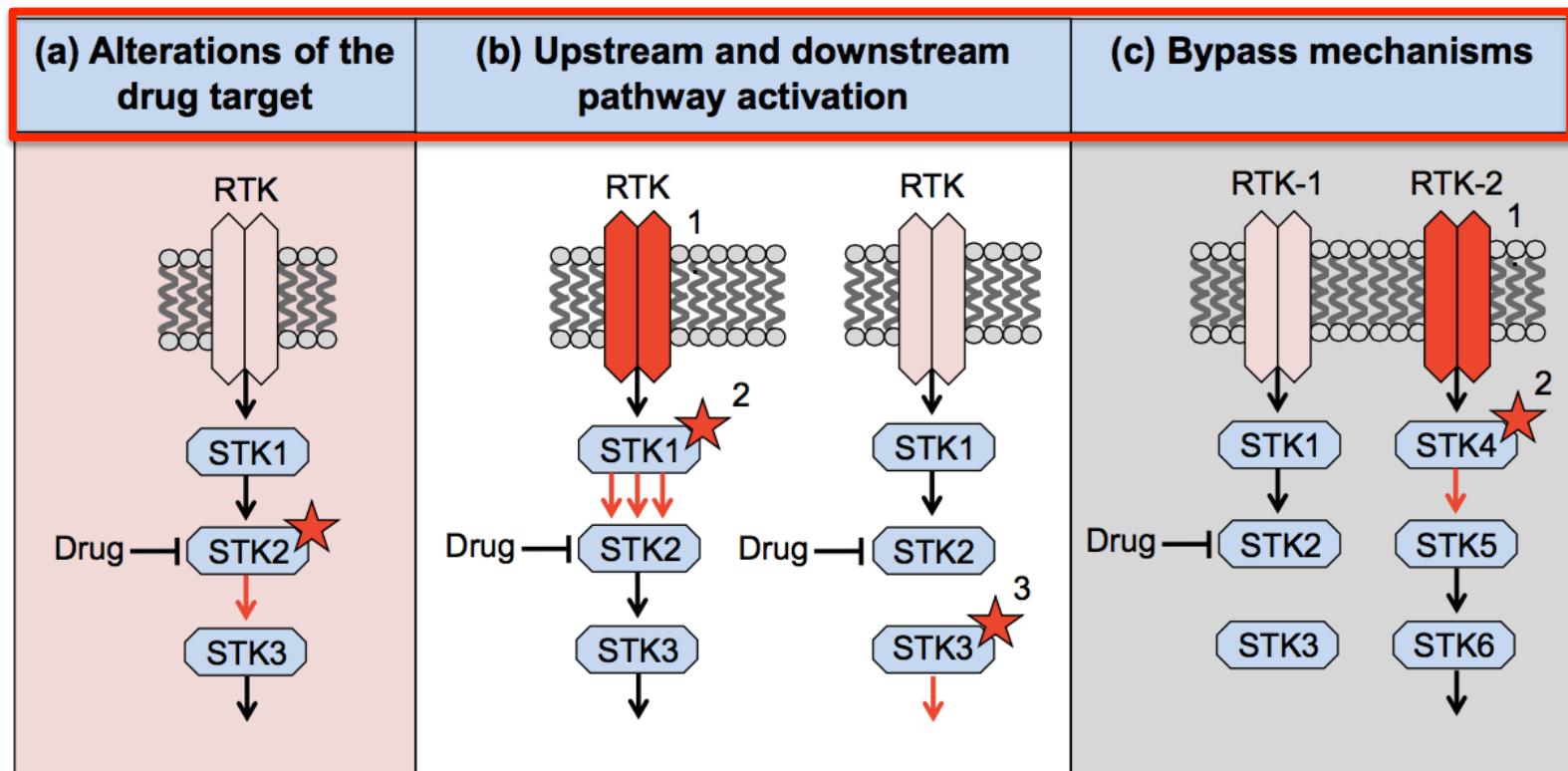
Elisa Giovannetti
Cancer Pharmacology Lab, Pisa University, Italy
Lab Medical Oncology, Vumc, Amsterdam, The Netherlands

General principles of anticancer drug resistance

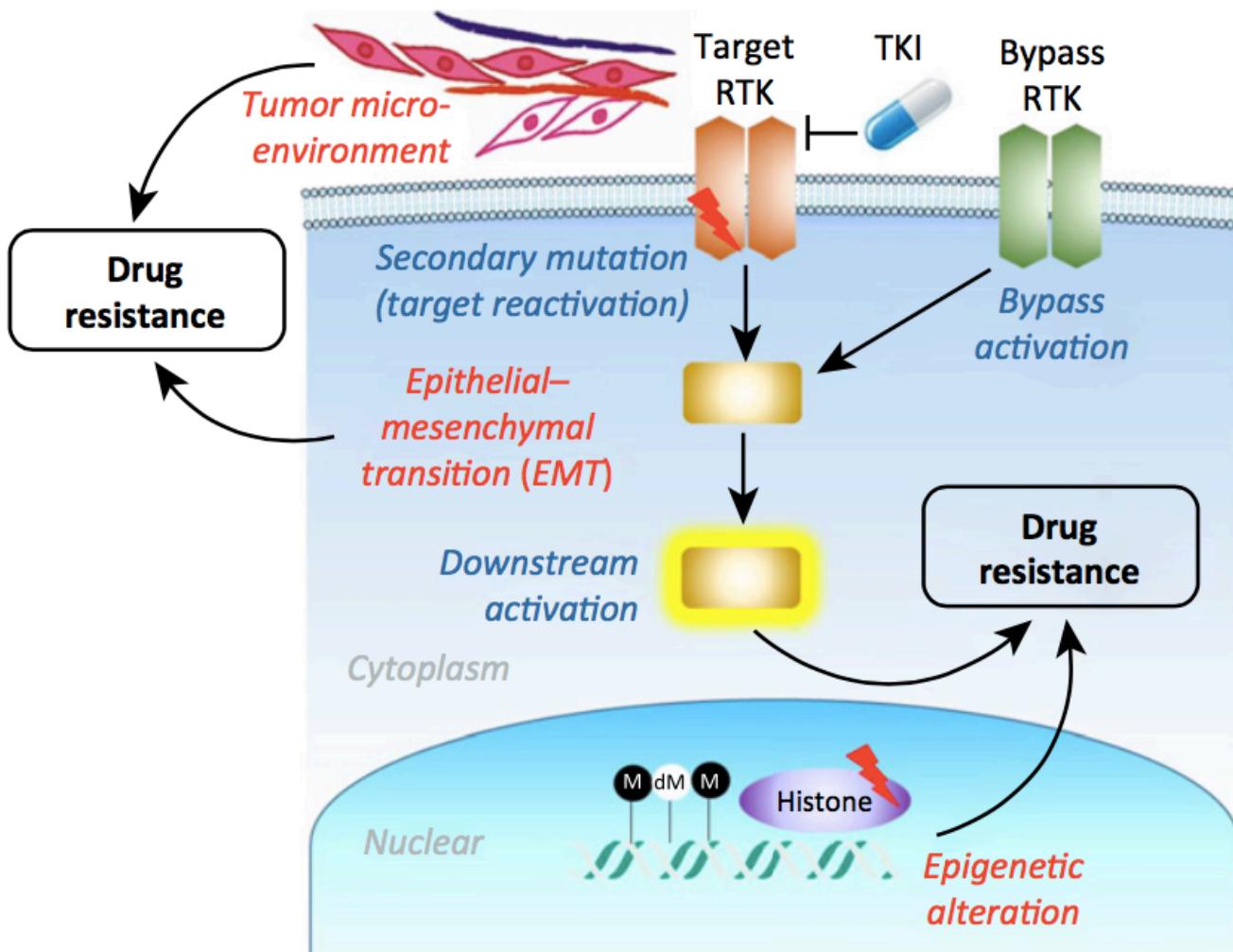


Resistance to targeted therapies

the presence of molecular changes that enable a cancer cell to escape the intended effect of targeted agents



Examples of resistance to antitargeted anticancer drugs

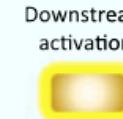


Resistance to gefitinib in NSCLC

1. kinase domain mutations (T790M, exon 20 insertion)

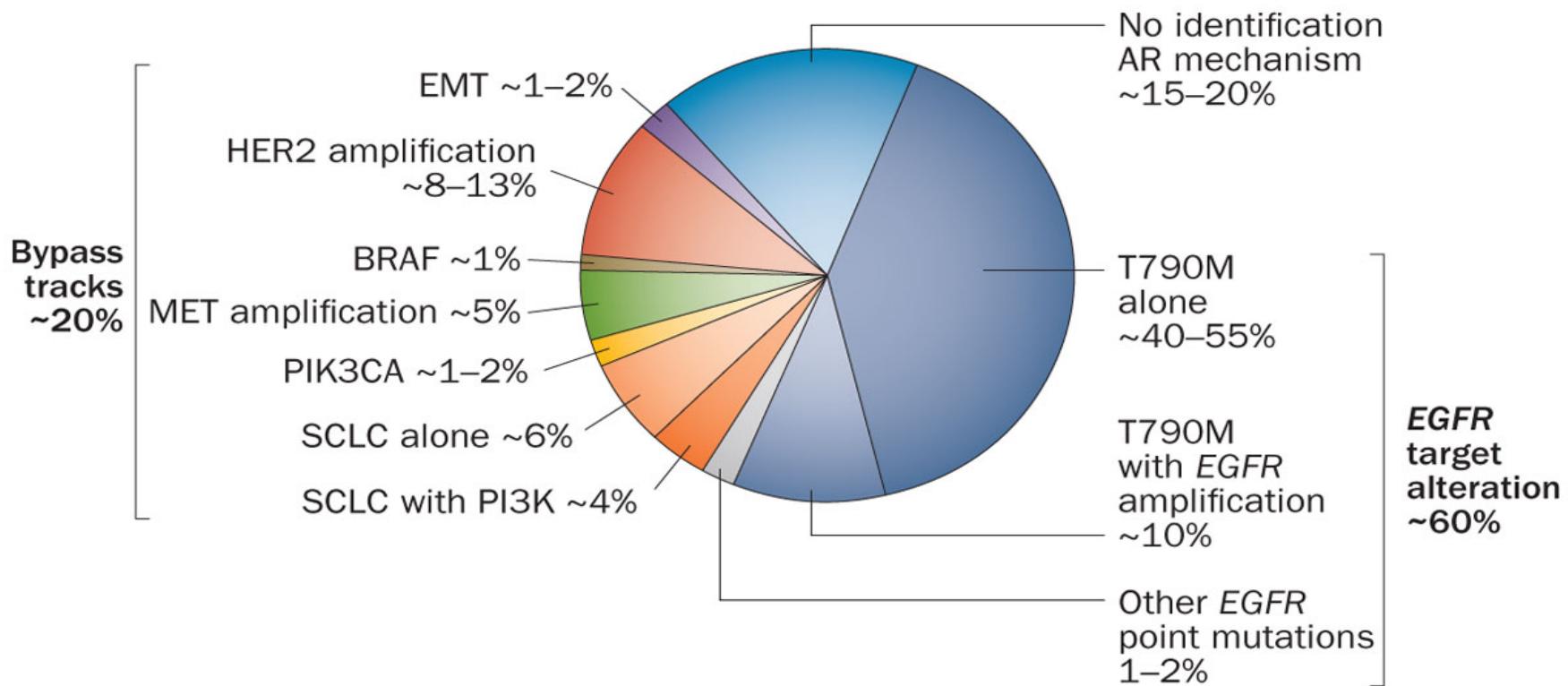


1. PIK3CA mutation
2. BRAF mutation
3. PTEN loss



1. HER2 or HER3 amplification
3. MED12 suppression
4. NF- κ B signaling activation
5. FGFR family activation
6. Neuregulin-1 and P2Y receptors high expression
7. MET amplification

Role of T790M



EGFR-TKIs evolution

How the EGFR Story Has Unfolded in NSCLC

Identification of EGFR overexpression in lung cancer tissue sparks development of EGFR-targeted therapies

Gefitinib withdrawn from US market after failure to provide survival benefit in confirmatory trials

First reports of the T790M gatekeeper mutation in patients who become resistant to EGFR TKI therapy

OPTIMAL and EURTAC trials confirm importance of molecular selection of Asian and European patients for erlotinib treatment

FDA approval of gefitinib as 1st-line therapy for EGFR-mutant patients

Breakthrough therapy status given to EGFR resistance-targeting TKIs rociletinib (CO-1686) and osimertinib (AZD9291)

1993 2003 2004 2005 2009 2010 2011-2012 2013 2014 2015

Gefitinib becomes first FDA-approved EGFR TKI for the treatment of NSCLC

Several studies find EGFR mutations in NSCLC patients

FDA approval of erlotinib in 2nd-line setting

IPASS trial demonstrates efficacy of gefitinib in patients with EGFR mutations

Gefitinib approved in Europe as 1st-line therapy for EGFR-mutant patients

Molecular mechanisms of acquired resistance to EGFR TKIs begin to be unraveled

Afatinib FDA-approved for 1st-line treatment of EGFR-mutant patients

FDA approval of erlotinib for 1st-line treatment of EGFR-mutant patients

FDA approval of osimertinib in 2nd-line setting for EGFR T790M-positive patients

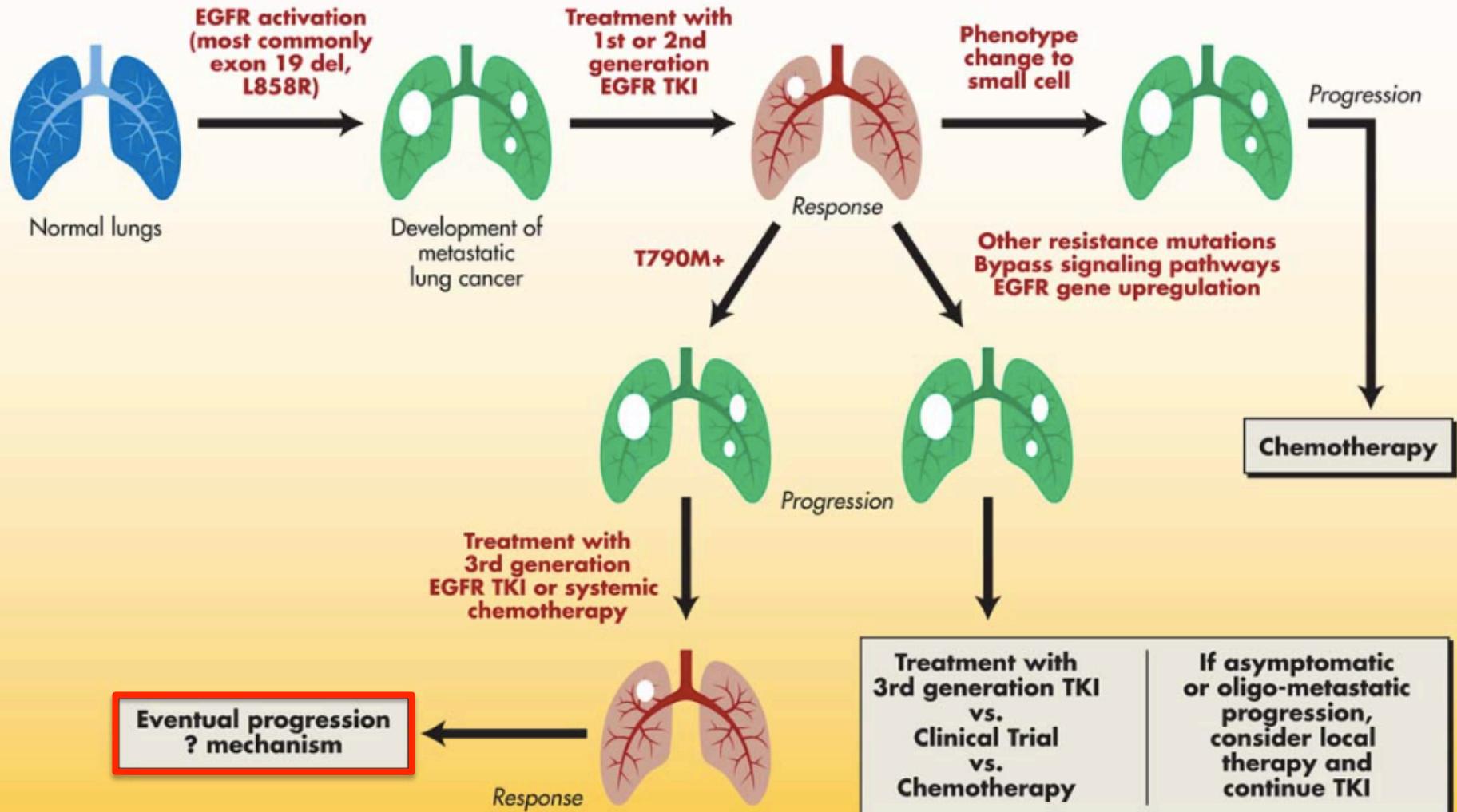
■ FDA approved

First generation

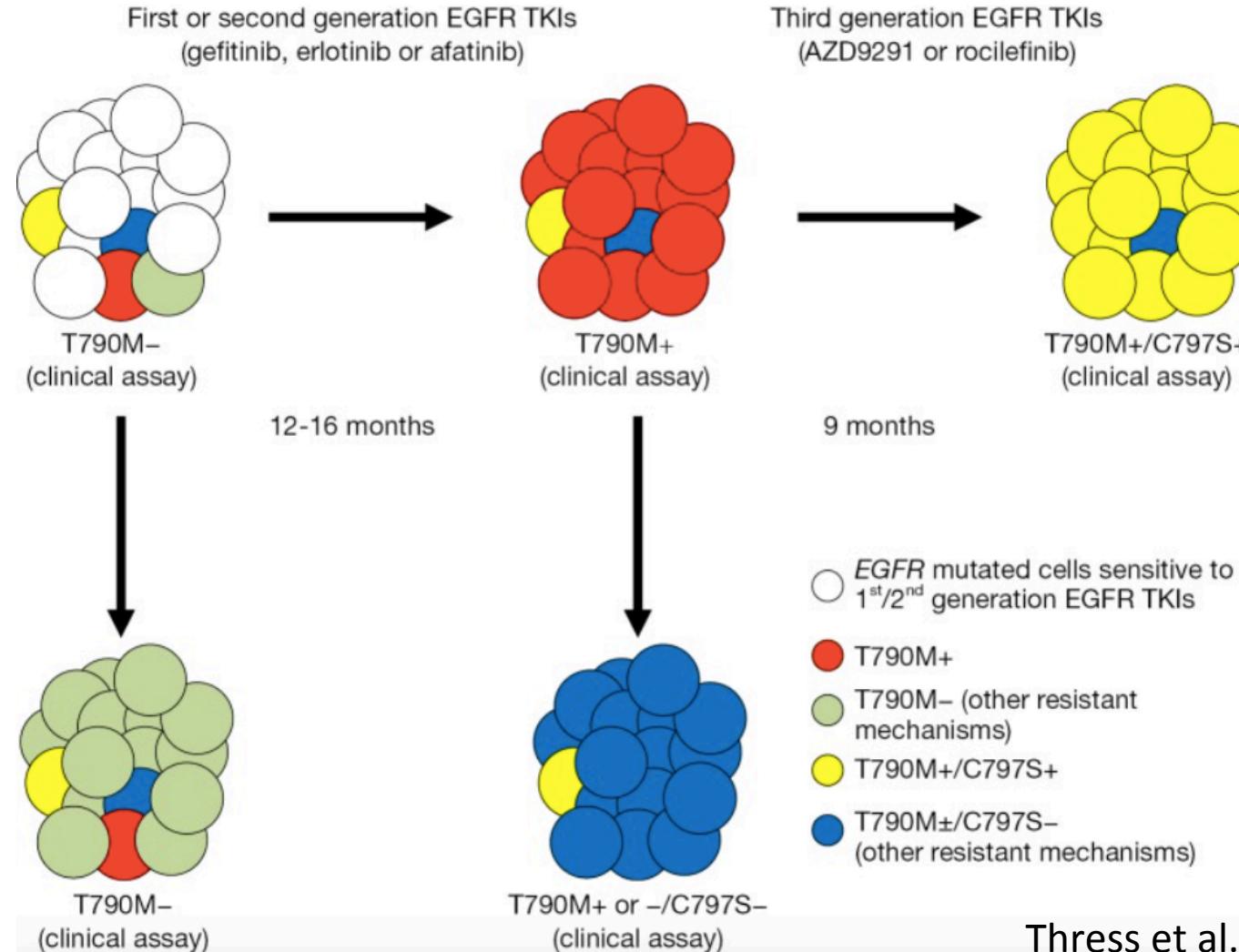
Second generation

Third generation

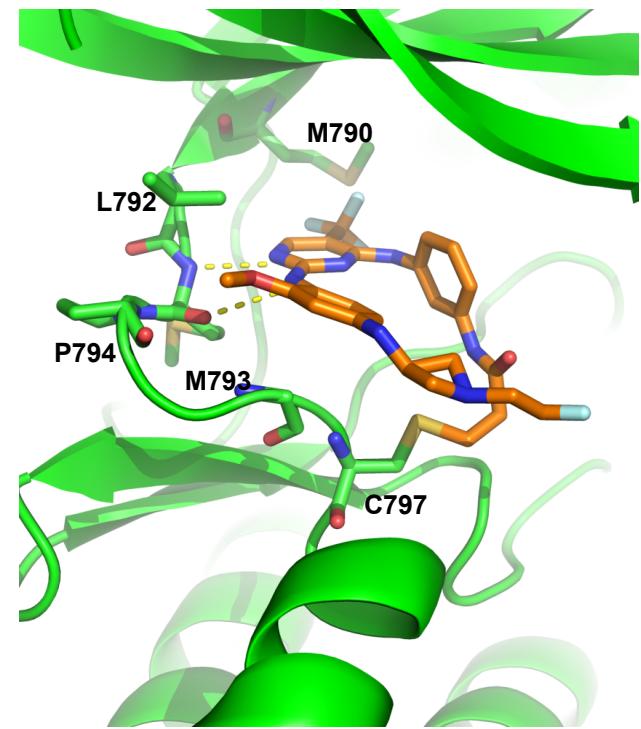
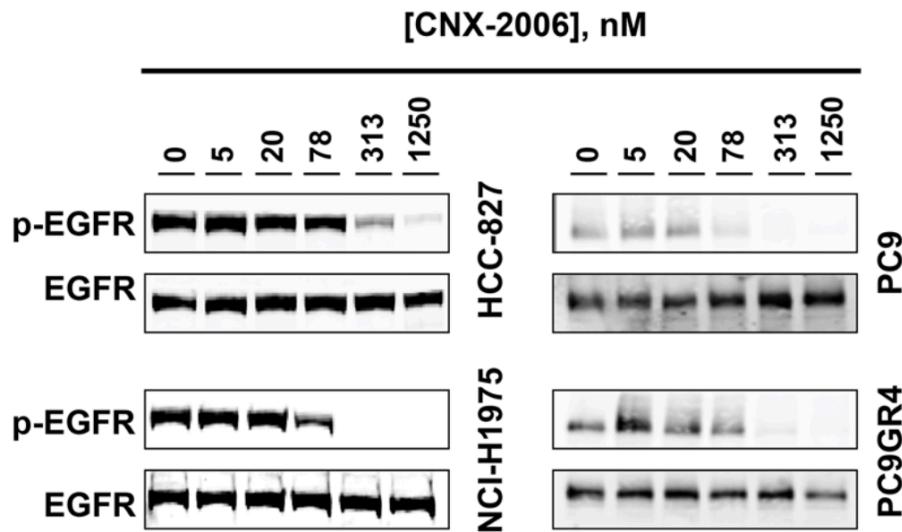
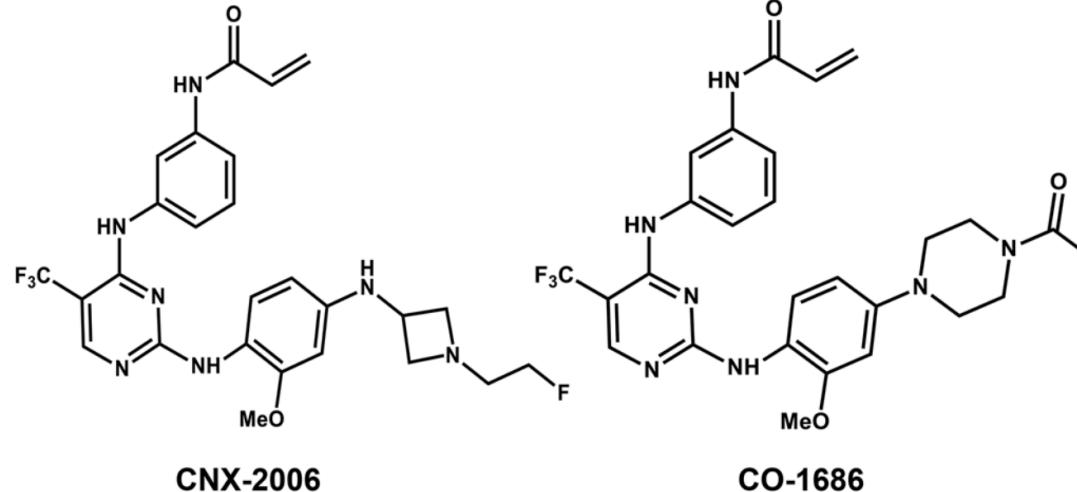
Current treatment paradigm for metastatic EGFR^{mut} NSCLC



Looking for mechanisms underlying resistance to 3rd generation EGFR-TKIs



Our study on CNX-2006, an analogue of rociletinib



Antiproliferative effects

NSCLC cells

EGFR WT

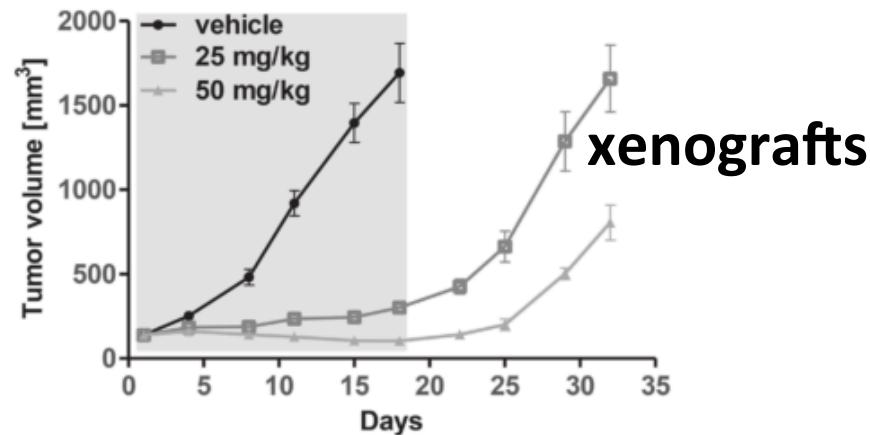
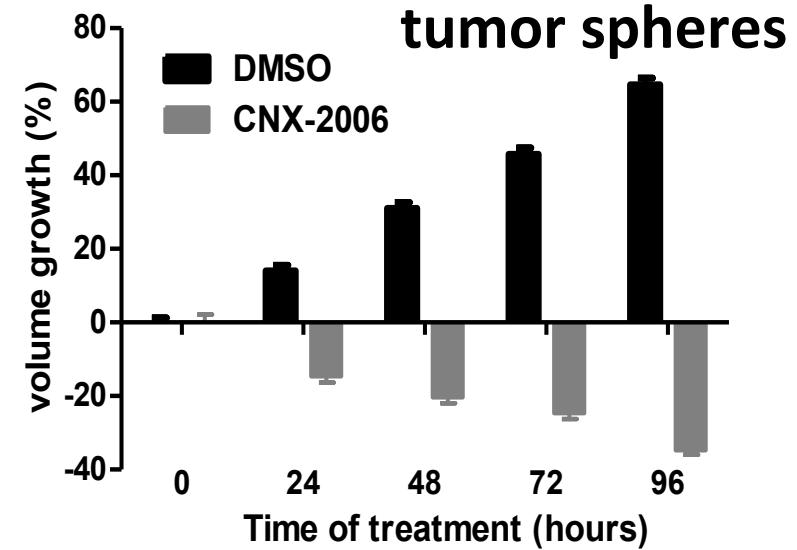
Cell line	Gefitinib IC_{50} μM	CNX-2006 IC_{50} μM
H23	11.2	2.4
H522	13.7	1.5
H1703	8.2	4.3

Activating EGFR-mut

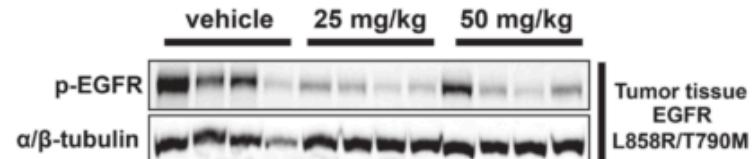
Cell line	Gefitinib IC_{50} μM	CNX-2006 IC_{50} μM
HCC-827	0.01	0.003
H3255	0.02	0.006
PC9	0.04	0.01

EGFR-T790M

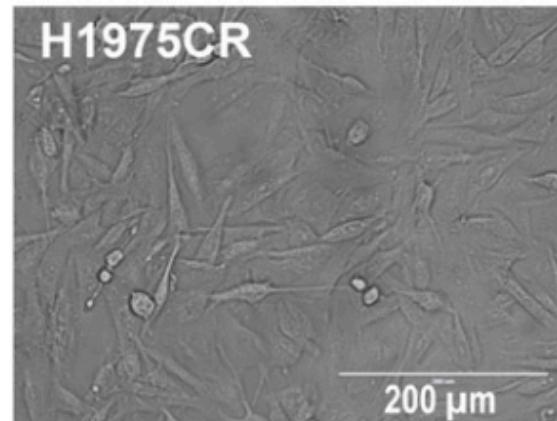
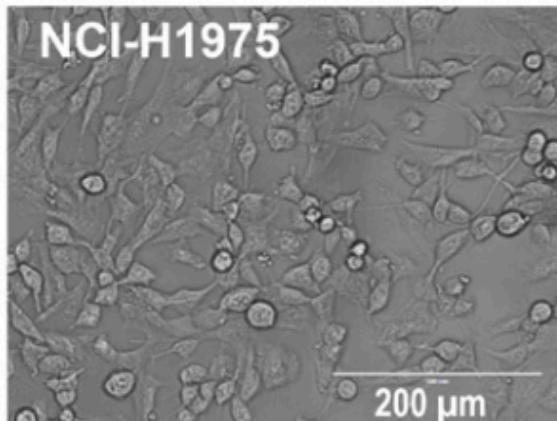
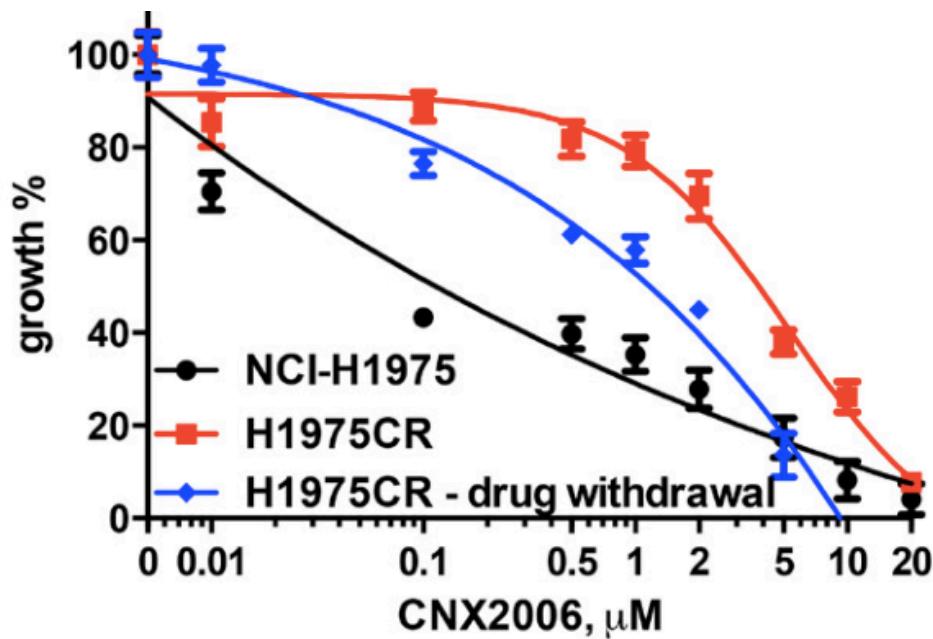
Cell line	Gefitinib IC_{50} μM	CNX-2006 IC_{50} μM
H1975	10.0	0.07
PC9GR4	2.1	0.008
PC9DR1	7.4	0.006



B

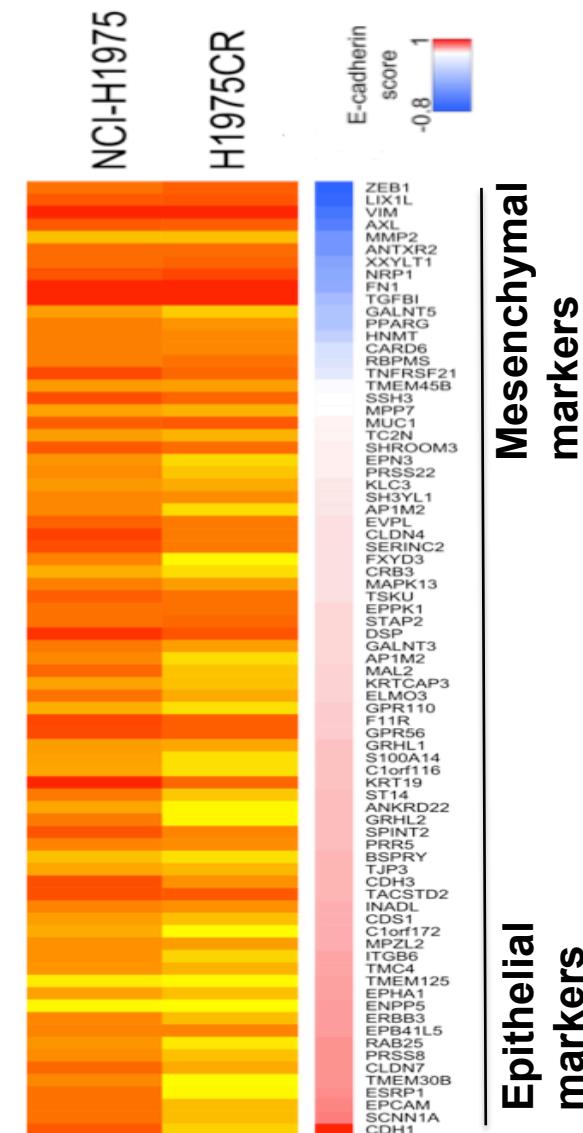
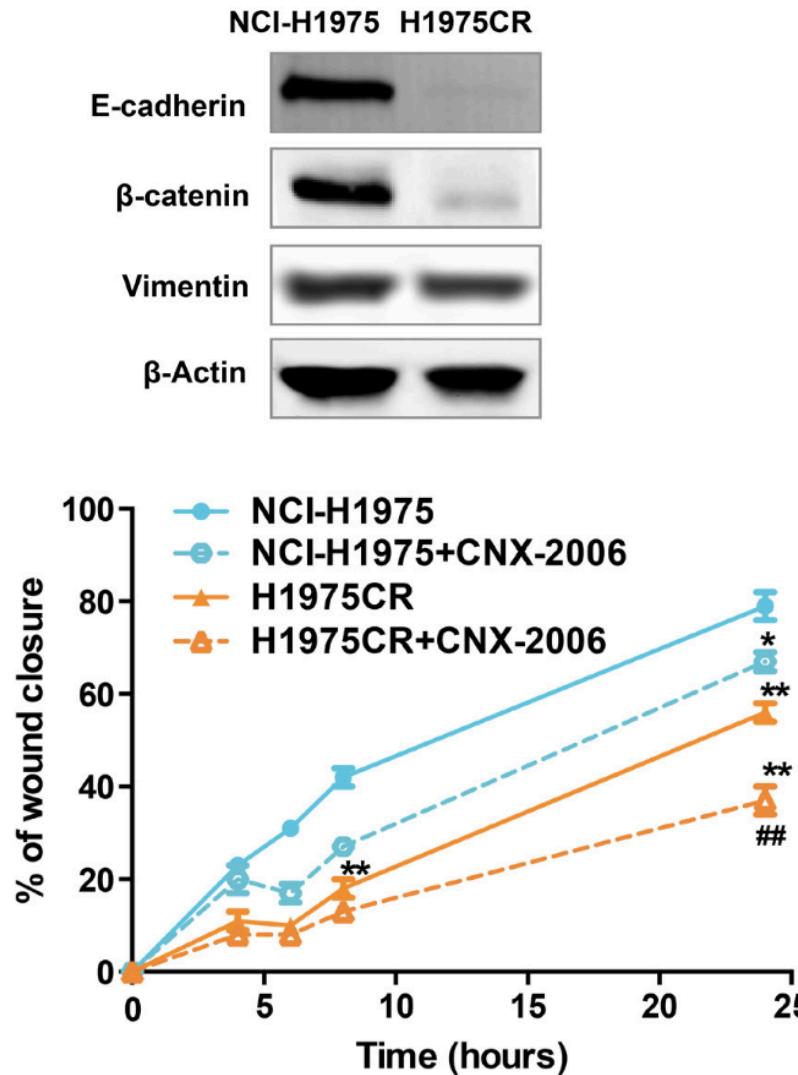


Creation of a resistant clone to CNX-2006

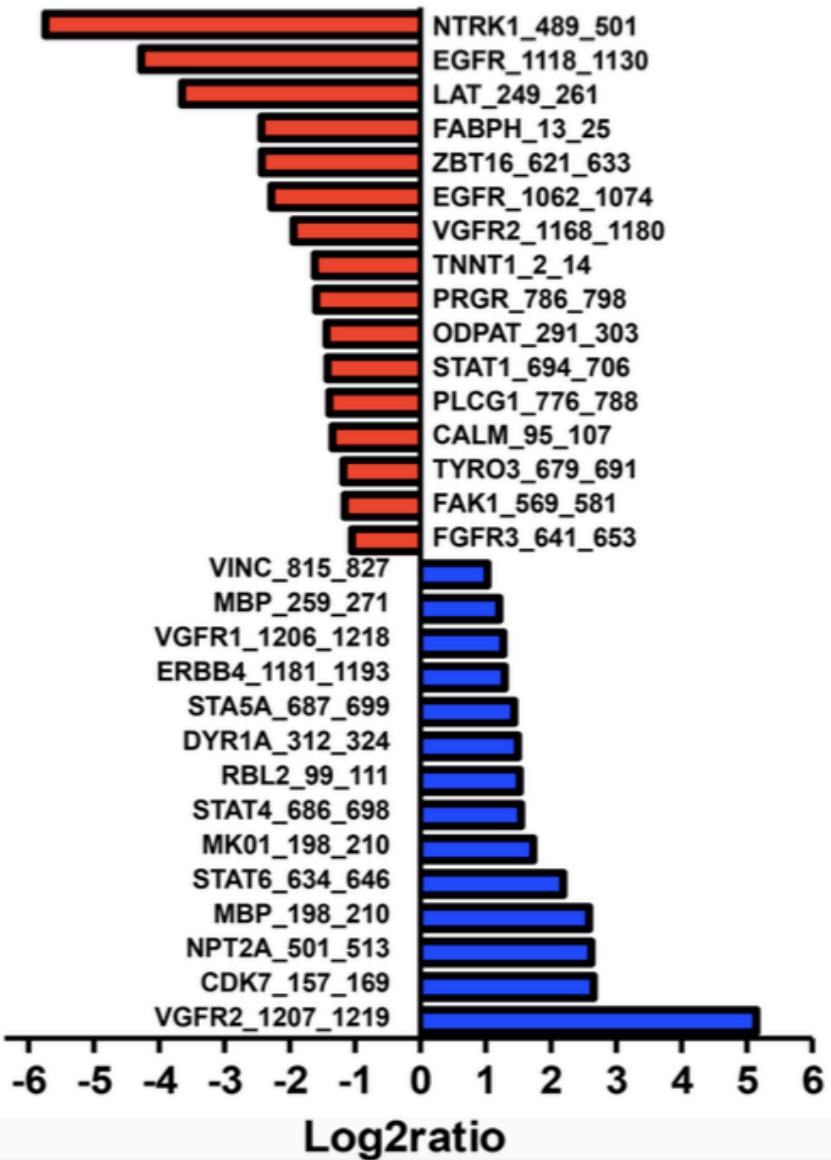
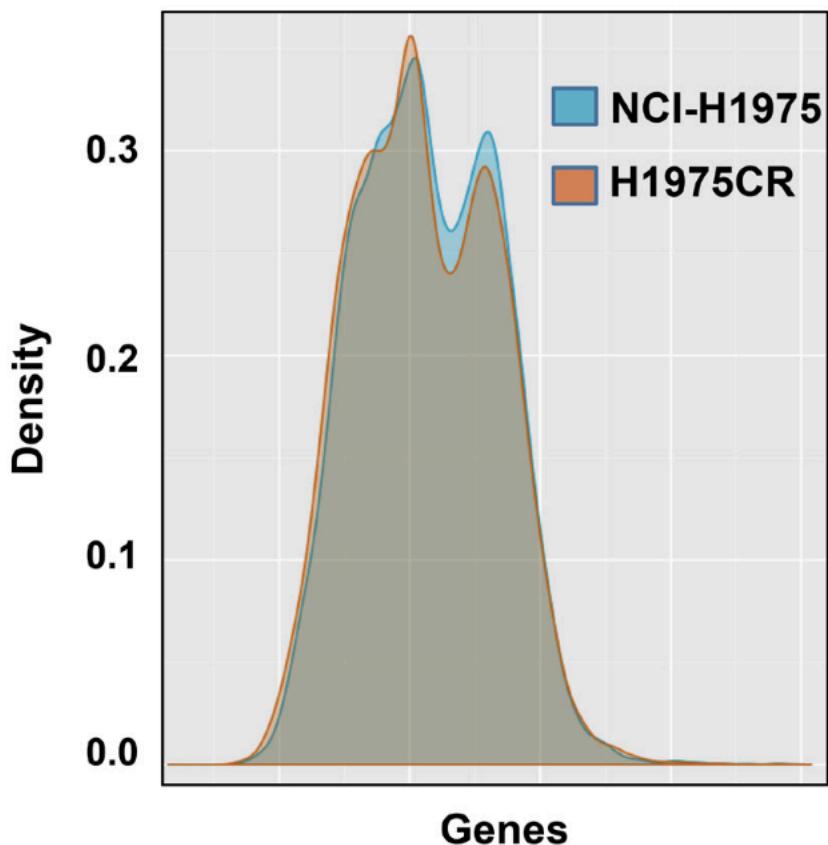


Controversial role of EMT

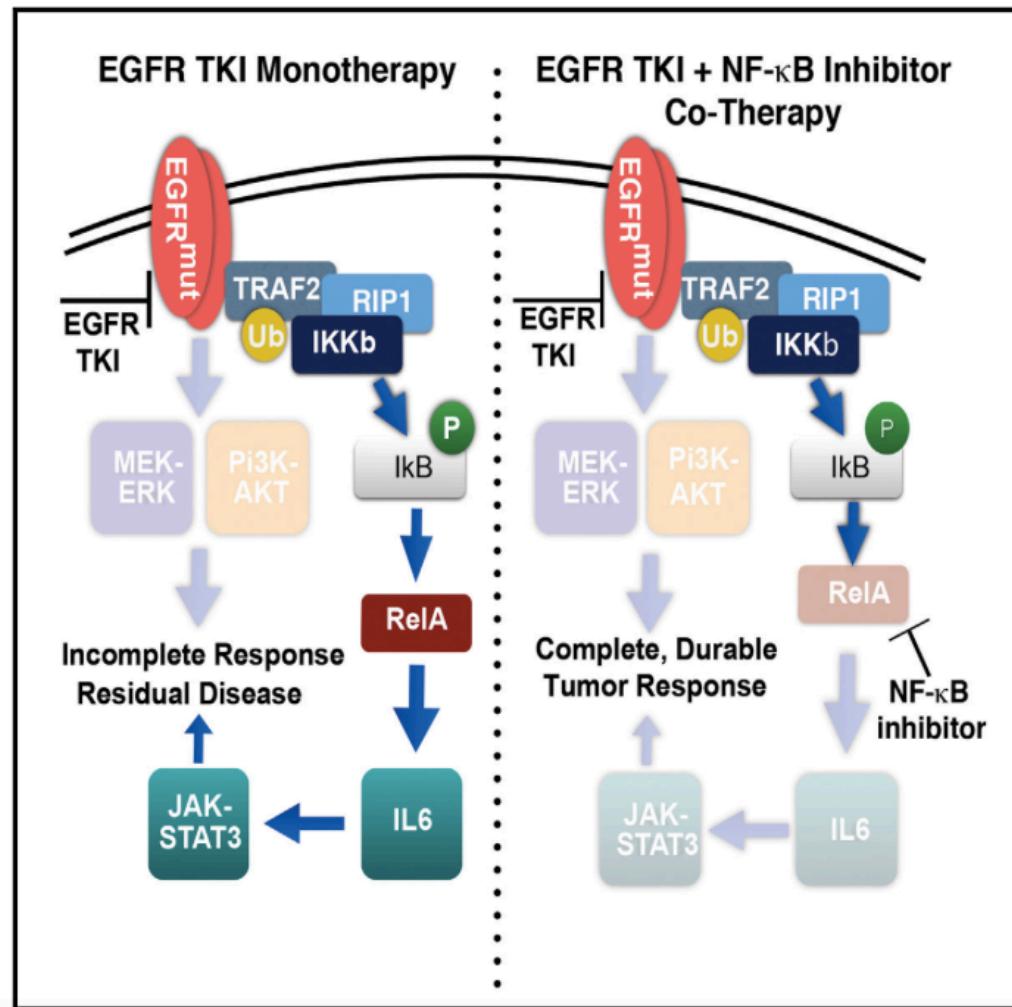
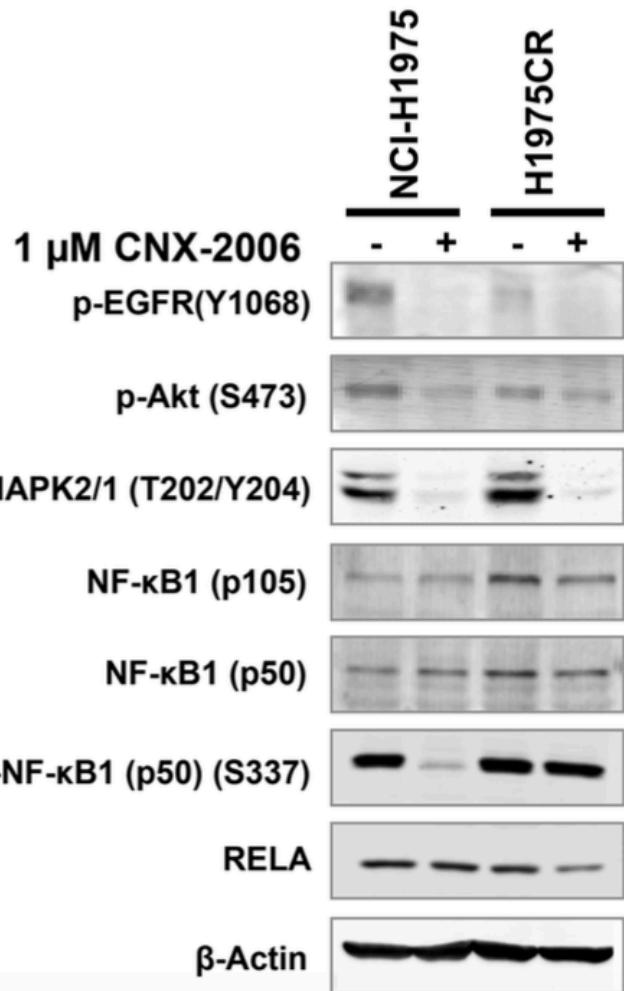
Cells resistant to CO-1686 showed signs of Epithelial-to-Mesenchimal Transition (EMT) (Walter et al., Cancer Discov 2014), but...



NGS and kinase array

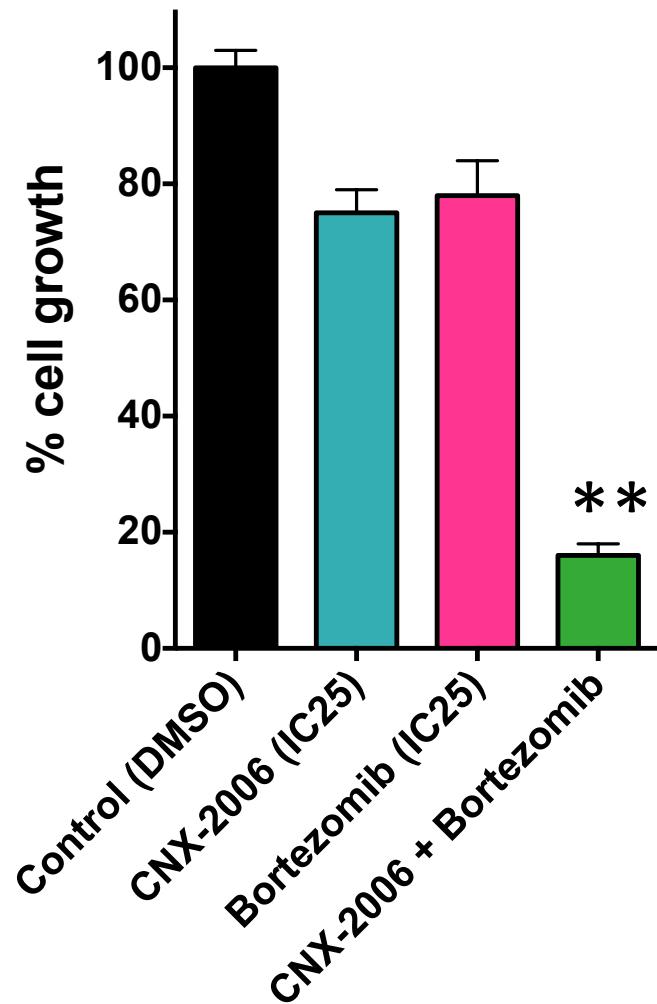
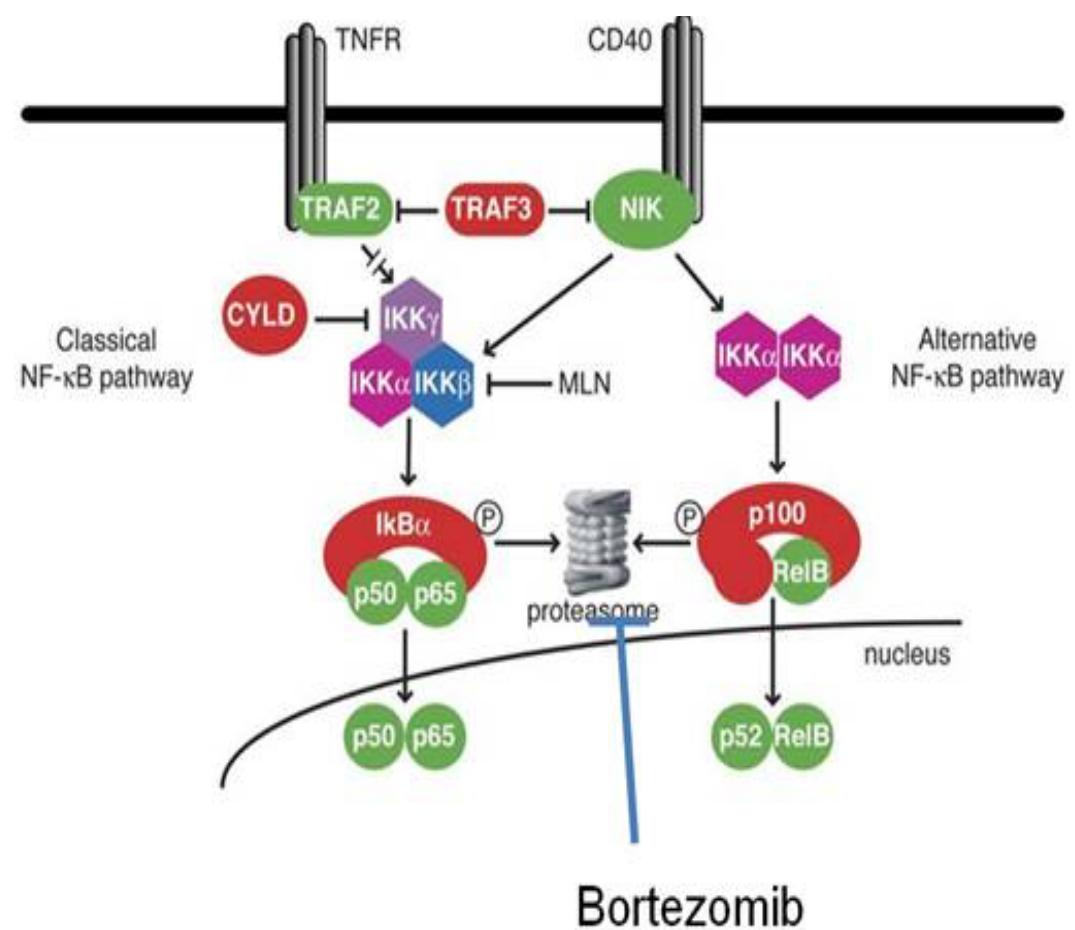


Role of NF-κB signaling



Blakely et al., Cell Rep 2015

Combination with bortezomib

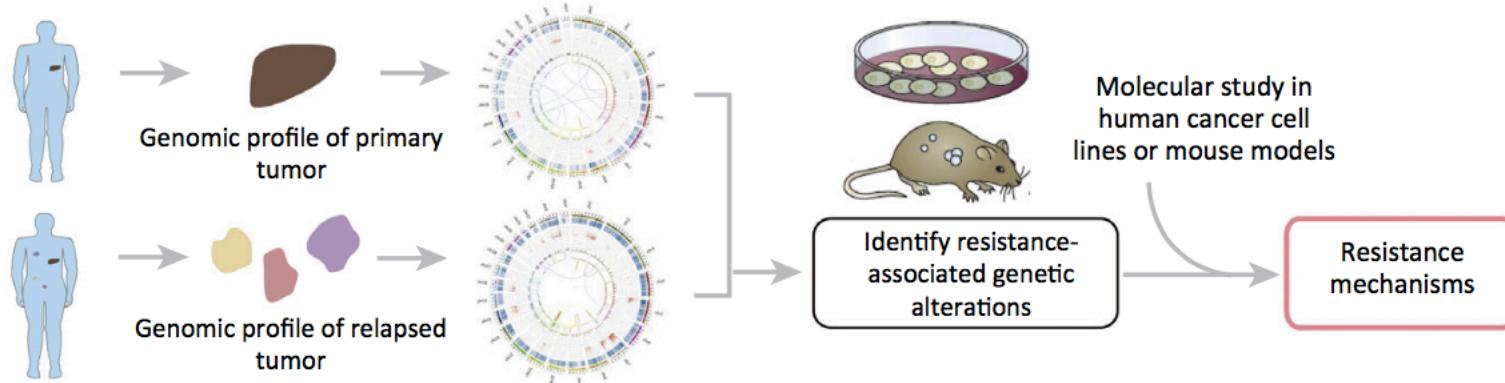


In conclusion

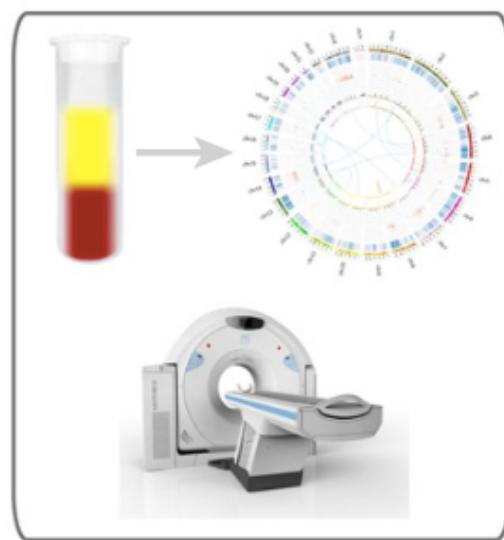
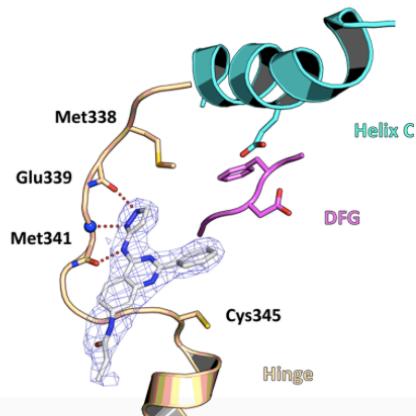


Future strategies to overcome resistance

1. -OMICs profiling & molecular preclinical studies to identify resistance mechanisms

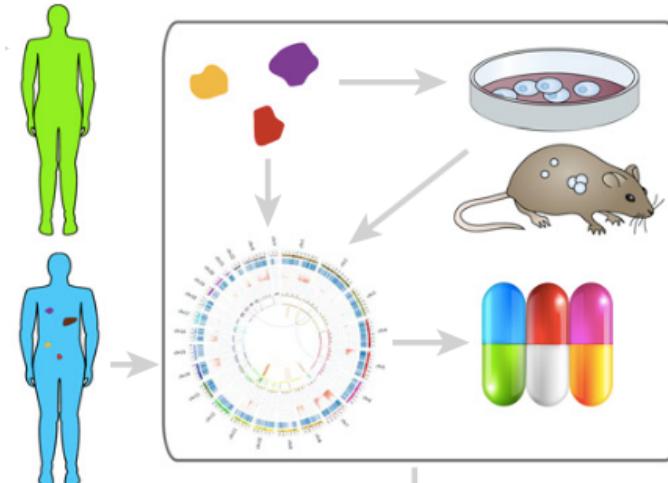


2. Design better & more selective compounds



3. Non-invasive monitoring of relapse

4. Adapt combination therapy on tumor longitudinal profiling and preclinical studies



Acknowledgments

- **CNX study**

Prof. GJ Peters

Dr. E Galvani

Dr. LG Leon

Dr. EF Smit

Prof. R Bernards

Prof. W Pao

- **New EGFR-TKIs/cMet review**

Prof. C Rolfo

Dr. I Garajova

- **Studies on bortezomib**

Dr. G Jansen

Dr. J Cloos



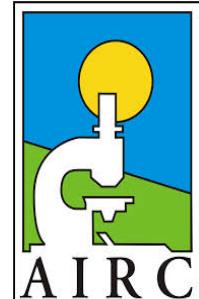
EORTC
European Organization for Research
and Treatment of Cancer



MARIE CURIE



Nederlandse Organisatie voor
Wetenschappelijk Onderzoek



AIRC