



# Resistance to Afatinib and Cetuximab Combination Therapy in *EGFR*-mutant Lung Adenocarcinoma

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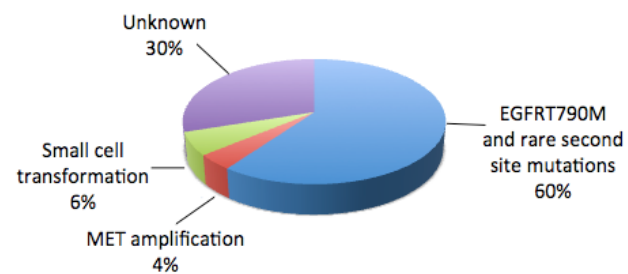
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Abstract #A38

## BACKGROUND

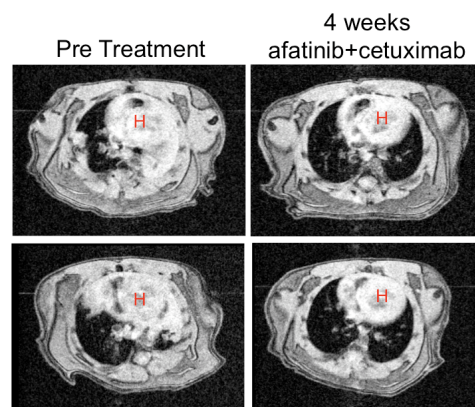
### Mechanisms of resistance to EGFR TKIs



Modified from Oxnard GR et al, Clin Cancer Res, 2010

The Epidermal Growth Factor Receptor (EGFR) T790M mutation confers acquired resistance to tyrosine kinase inhibitors (TKIs) in approximately 50% of drug-resistant EGFR mutant lung adenocarcinomas.

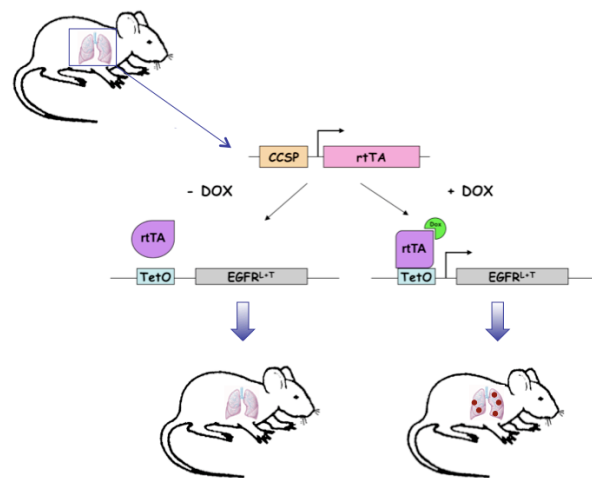
### The combination of afatinib and cetuximab induces tumor regression of mouse lung tumors driven by *EGFR*<sup>L858R+T790M</sup>



Experiments using genetically engineered mouse models of EGFR mutant lung cancer have revealed that T790M-mediated resistance can be overcome using a second generation TKI, afatinib, in combination with the anti-EGFR antibody, cetuximab. This drug combination is currently in clinical trials in patients with TKI-resistant tumors and is showing a promising ~ 40% response rate. Nevertheless, cases of afatinib+cetuximab resistance are beginning to emerge.

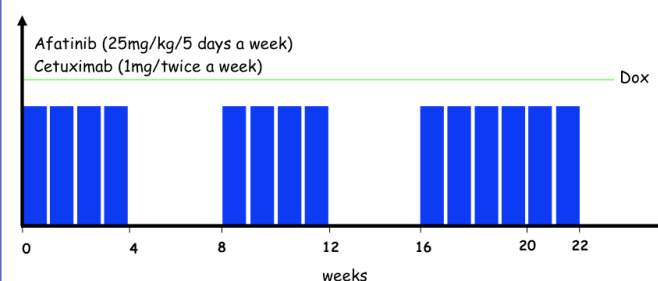
## STRATEGY

### Tetracycline-inducible mouse model of *EGFR*<sup>L858R+T790M</sup>-dependent lung cancer



Mice receiving doxycycline develop lung adenocarcinomas that are dependent on the continued presence and activity of the mutant receptor for survival.

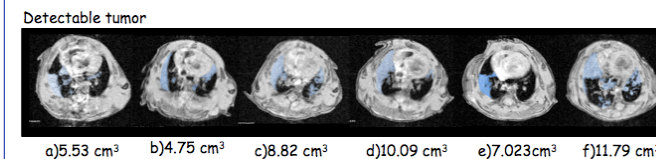
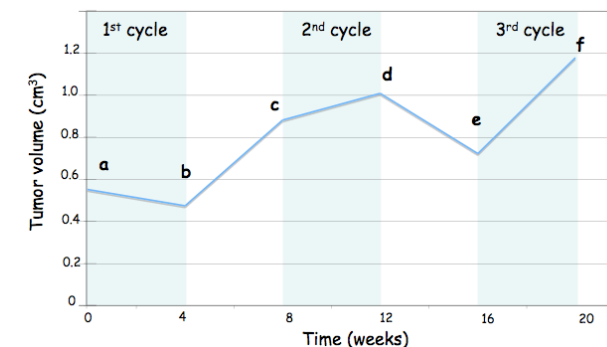
### Intermittent drug dosing protocol is used to generate afatinib+cetuximab resistant tumors



Mice harboring lung tumors are treated with afatinib (25mg/kg/5 days a week) and cetuximab (1mg/twice a week) for four weeks. Drug-treatments are then interrupted for one month. This on/off drug treatment regimen is repeated until the lung tumor no longer responds to treatment. The mouse is then maintained on the drug regimen for an additional 2 weeks to document whether the tumor volume increases despite the presence of drug.

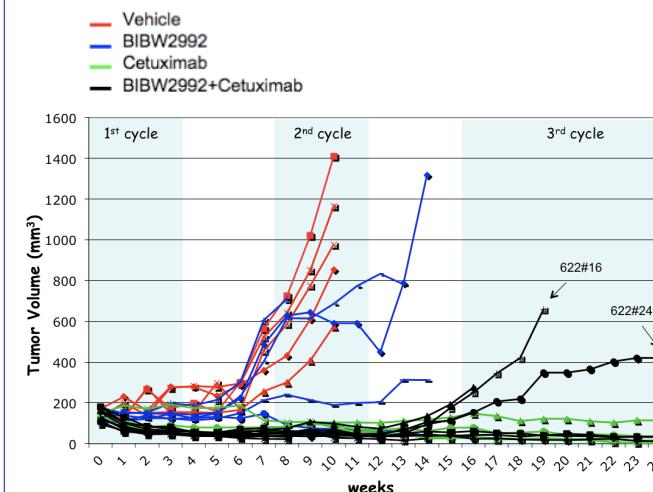
## RESULTS

### *EGFR*<sup>L858R+T790M</sup> mice develop resistance to afatinib+cetuximab treatment

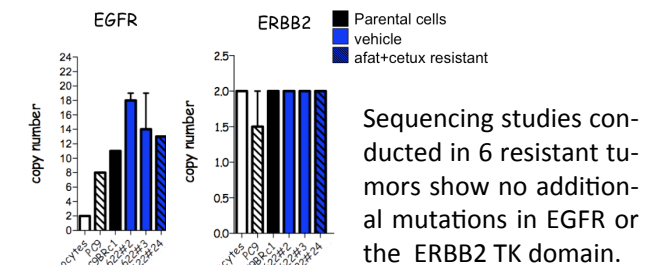


Magnetic resonance images of lungs are taken at the beginning and at the end of every drug cycle and tumor volume is calculated. In this case, the tumor volume increased despite the presence of the drugs during the final treatment cycle. The tumor area is highlighted in blue. Twelve mice have developed resistance to afatinib+cetuximab treatment.

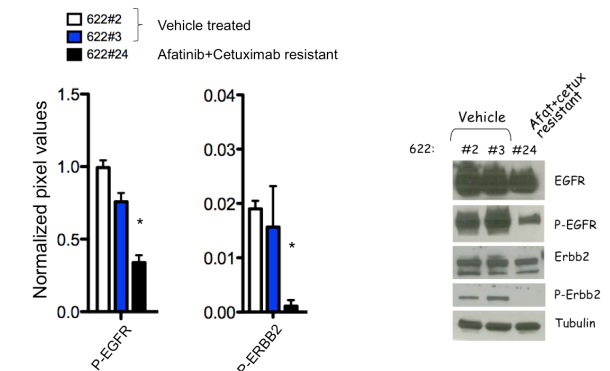
### Xenografts of human lung adenocarcinoma cells expressing *EGFR*<sup>Del19+T790M</sup> develop resistance to afatinib+cetuximab treatment



### Increased copy number of *EGFR* or *ERBB2* is not present in drug-resistant tumors



### Afatinib+cetuximab resistant tumors show decreased phosphorylation of EGFR and ERBB2



## Ongoing studies

Identification of mechanisms of drug resistance

Transgenic and xenograft afatinib+cetuximab resistant tumors

Genomic studies:

Signaling Pathway Activation:

Mutation and Expression studies:

Whole exome capture

Western Blot; Phospho-RTK array

EGFR; ERBB2; KRAS; MET

Validation on human samples that developed progressive disease to afatinib+cetuximab therapy

## Funding

National Cancer Institute

UNITING AGAINST Lung Cancer UALC

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