Overcoming Resistance to EGFR Tyrosine Kinase Inhibitors in EGFR Mutant Lung Cancer

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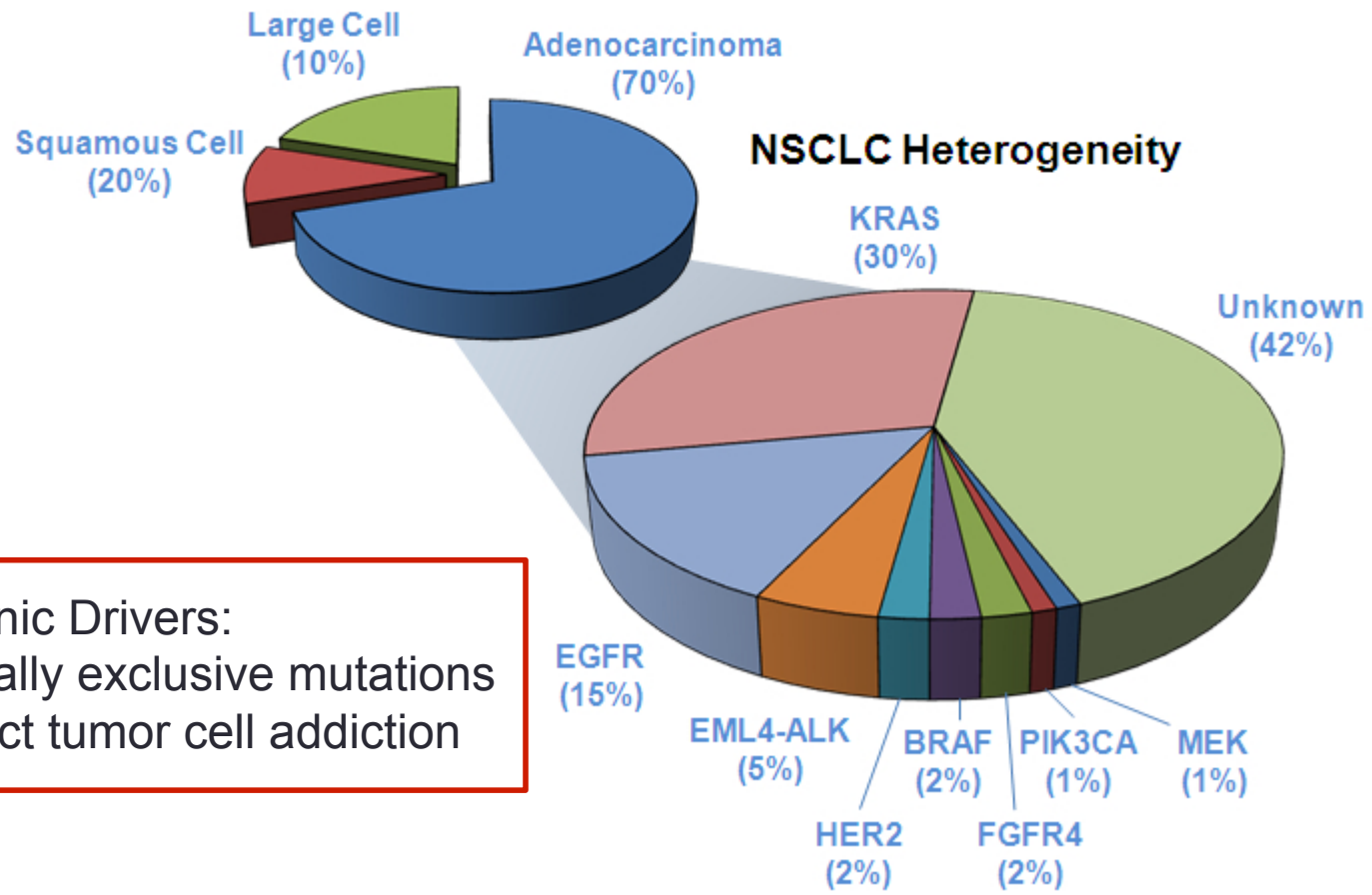
Lung Cancer

- Leading cause of cancer mortality for both men and women in the United States
- More than 220,000 individuals diagnosed annually
- 5 year survival for advanced disease < 15%
- Histologically and molecularly heterogeneous disease
  - contemporary therapy for advanced disease is based on identification & targeting of oncogenic drivers

Histologic and Molecular Subtypes of Non-Small Cell Lung Cancer



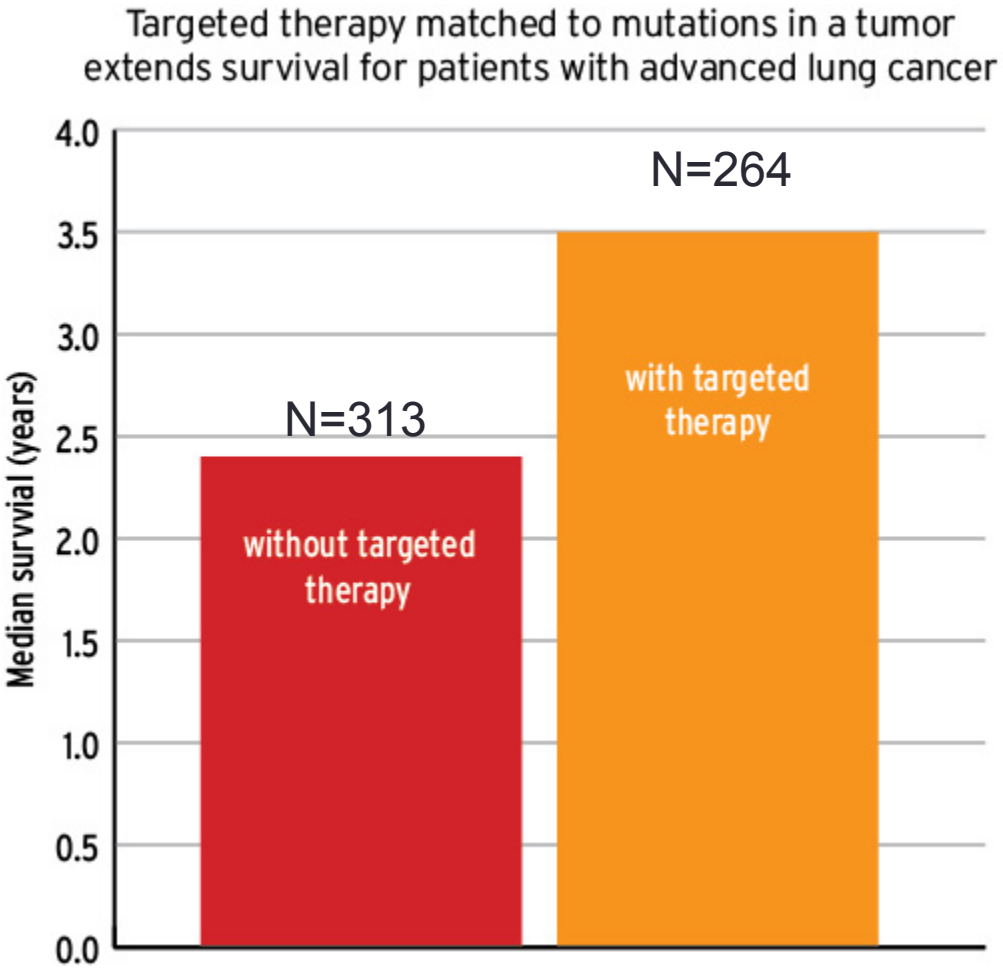
Oncogenic Drivers:

- Mutually exclusive mutations
- Reflect tumor cell addiction

Precision Medicine in NSCLC Treatment

- In about 60% of lung adenocarcinomas, a specific oncogenic driver mutation can be identified
- Drugs that target these oncogenic drivers are selectively toxic to malignant cells
- Targeted therapies offer better-tolerated disease modifying treatment options in patient populations defined by relevant oncogene mutations
- Successful implementation requires robust biomarker assays; rapid turn-around time; menu of targeted therapies; access to targeted agents

Precision medicine extends NSCLC survival

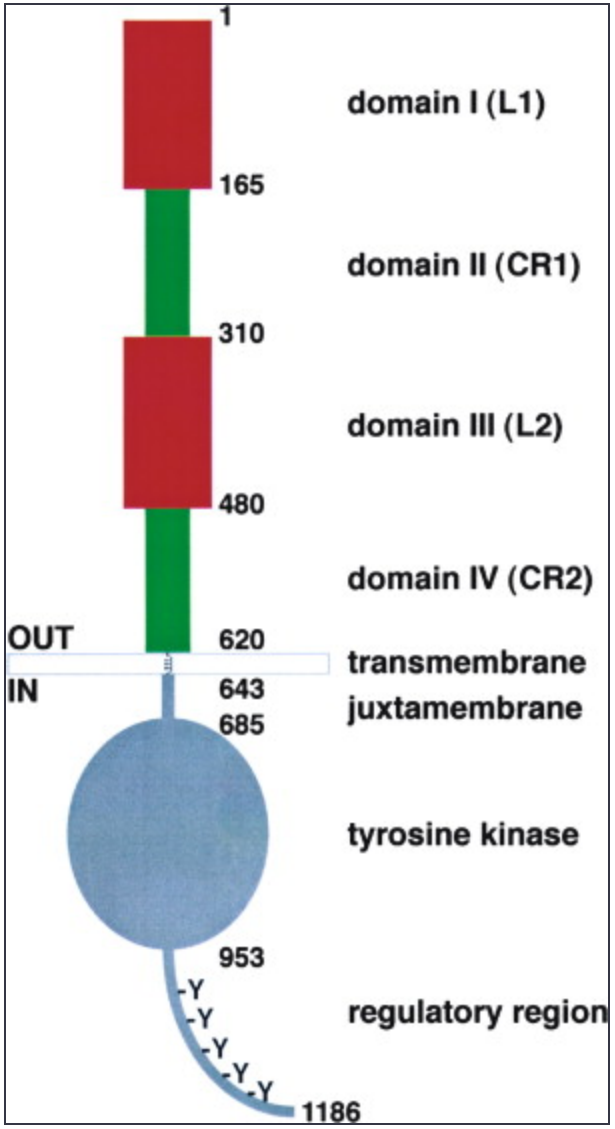


*all patients had a targetable lesion

Mark Kris, MD

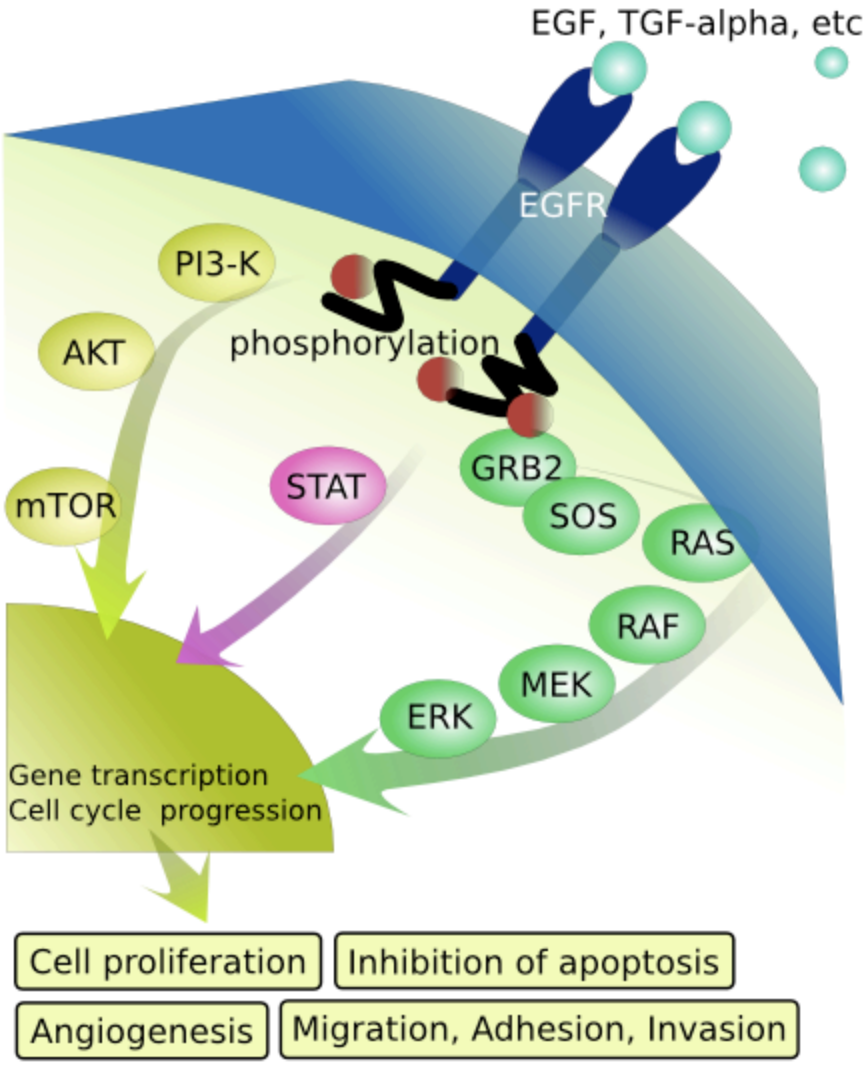
EGFR Structure

- Receptors exist on the surface of cells and contain an extracellular, transmembrane, and intracellular domain.
- Each domains is responsible for a different aspect of signaling
  - Extracellular Domain
    - Ligand binding
    - Receptor dimerization
  - Intracellular Domain
    - Tyrosine kinase
    - Regulatory region



*Burgess AW, Cho HS, Eigenbrot C, et al. *Mol Cell*. 2003;12:541-542

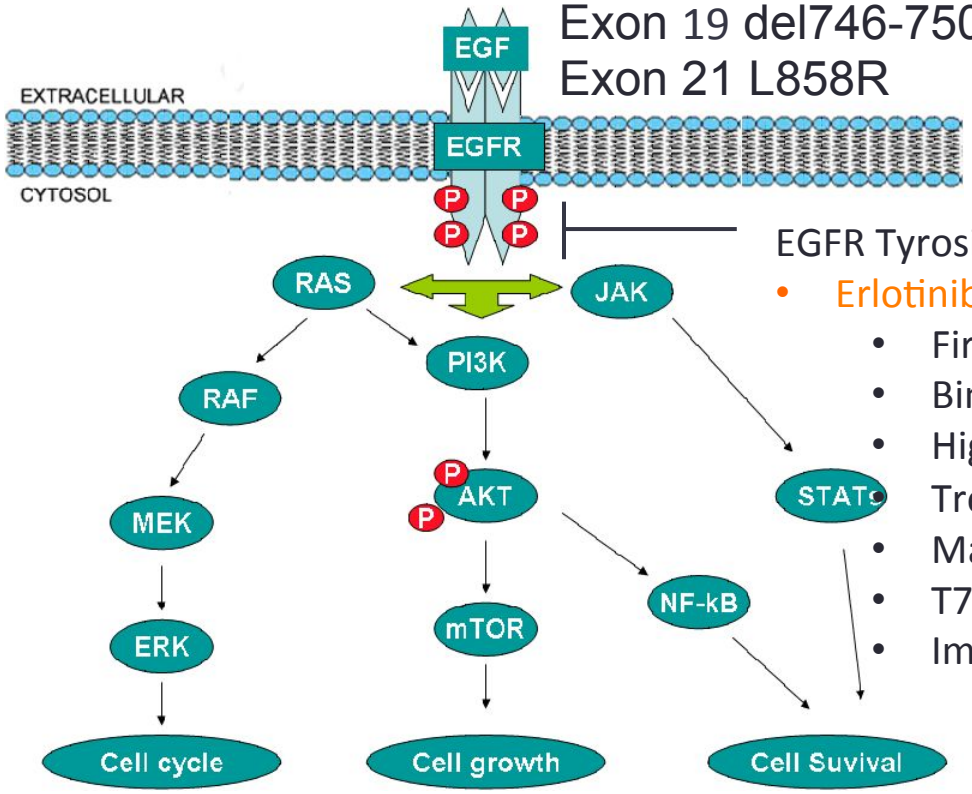
EGFR downstream signaling



EGFR Gene Mutations in NSCLC

- Activating *EGFR* gene mutations identified in 15% of lung adenocarcinoma cases in the United States
  - higher rate of mutation in Japan, Korea
- TK domain commonly mutated
  - L858R point mutation in exon 21
  - Exon 19 deletion (near ATP binding site)
  - Mutations stabilize the “activated” conformation of the TK domain
- In mouse models, presence of mutated *EGFR* is necessary and sufficient to induce lung tumors

EGFR Tyrosine Kinase Inhibitors for Treatment of Advanced EGFR Mutant NSCLC



EGFR Tyrosine Kinase Inhibitors

- Erlotinib: FDA Approved, First Line Therapy
  - First generation inhibitor
  - Binds reversibly to TK domain of EGFR
  - High rate of initial response (70%)
  - Treatment failure within 1 year
  - Majority of resistance due to EGFR T790M
  - T790M Lies within the ATP/drug binding cleft of EGFR
  - Improves ATP binding, making erlotinib less effective

Osimertinib

- Oral, irreversible inhibitor selective for EGFR sensitizing mutations and the EGFR T790M resistance mutation
- Wild-type sparing (does not bind wildtype EGFR)
- Osimertinib demonstrates efficacy in Phase II AURA2 trial
  - When delivered *after* EGFR TKI failure, osimertinib has an objective response rate of 70%
  - Complete responses were observed in 3% of patients
  - Responses were durable, average of 11.4 months
- FDA approved for patients with EGFR T790M mutant NSCLC who have progressed on or after EGFR TKI therapy

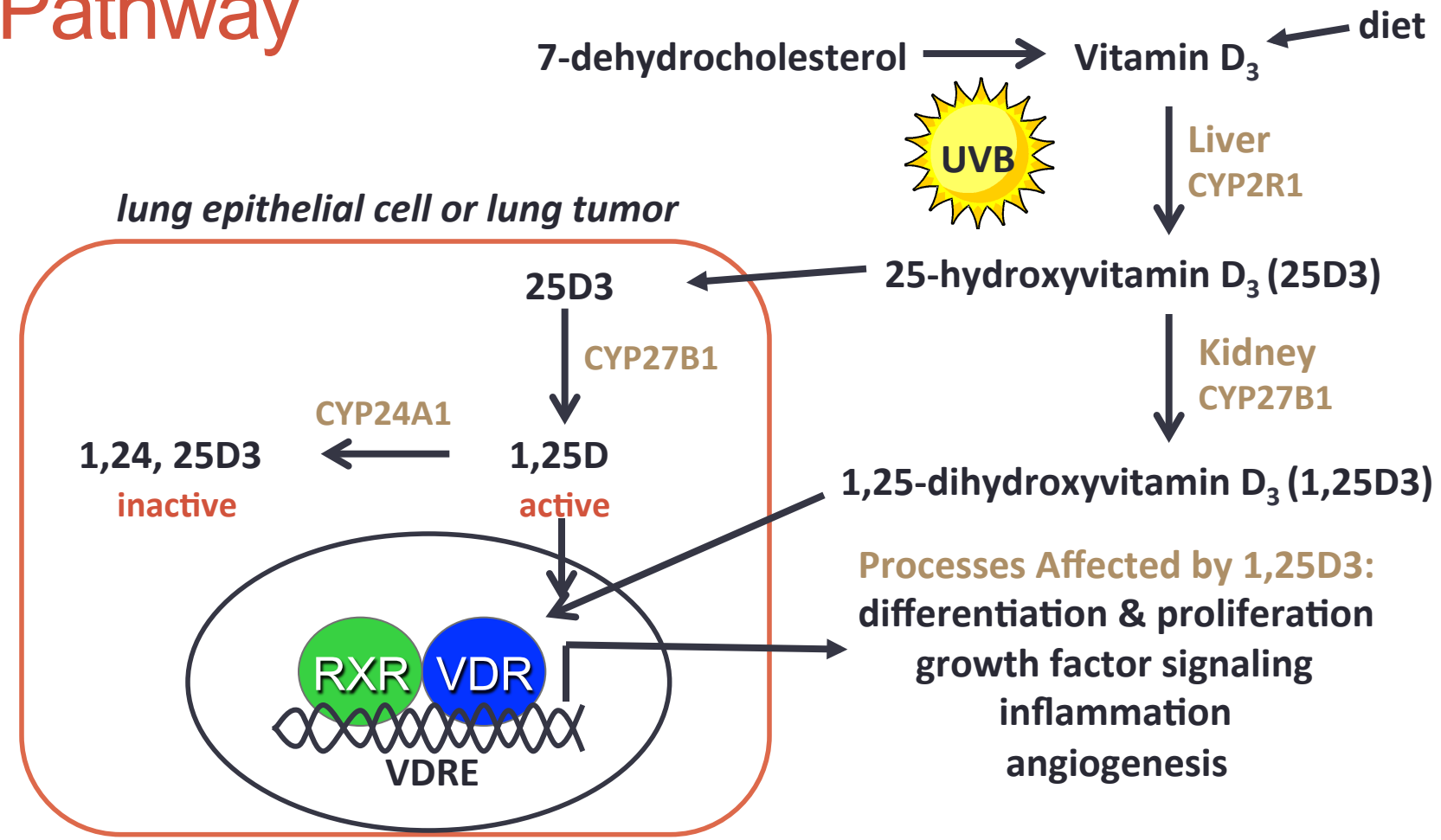
The Question

- Pre-clinical and epidemiologic studies support a role for vitamin D3 metabolites in reducing lung cancer risk

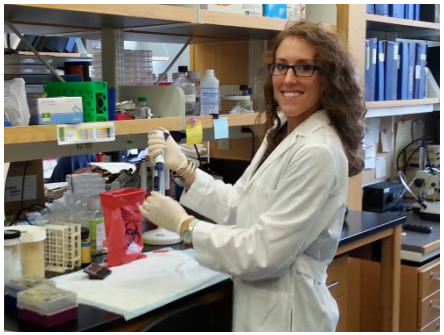
- Impact of vitamin D3 metabolites on lung cancer survival is variably reported
  - TY Cheng and ML Neuhouser (2012) Cancer Causes Control 23:1557
    - no overall association between 25(OH)D_3 and lung cancer mortality in NHANESIII cohort
    - lifetime never smokers with lung cancer significantly less likely to die from their disease if 25(OH)D_3 ≥44 nmol/L vs. <44 nmol/L

- **Might lung cancers that develop in never smokers be preferentially affected by vitamin D3 metabolites?**

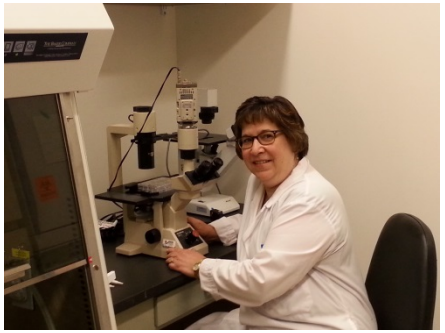
Vitamin D Metabolism and Signaling Pathway



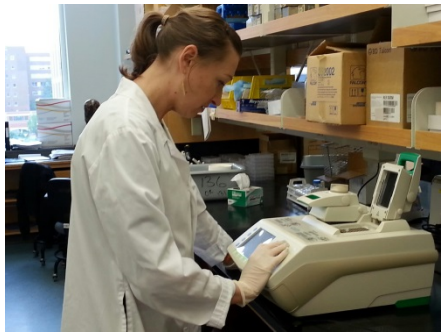
Acknowledgements



Alissa Verone, PhD



Sue Shoemaker



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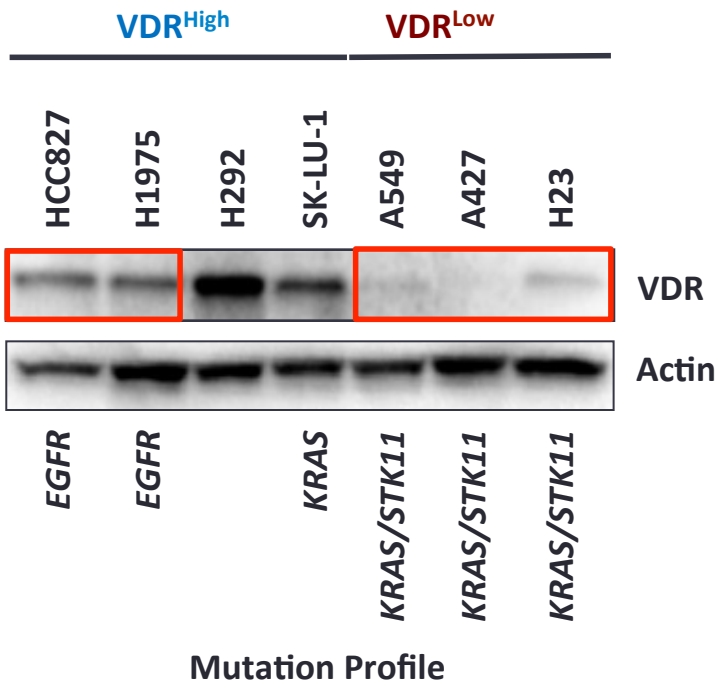
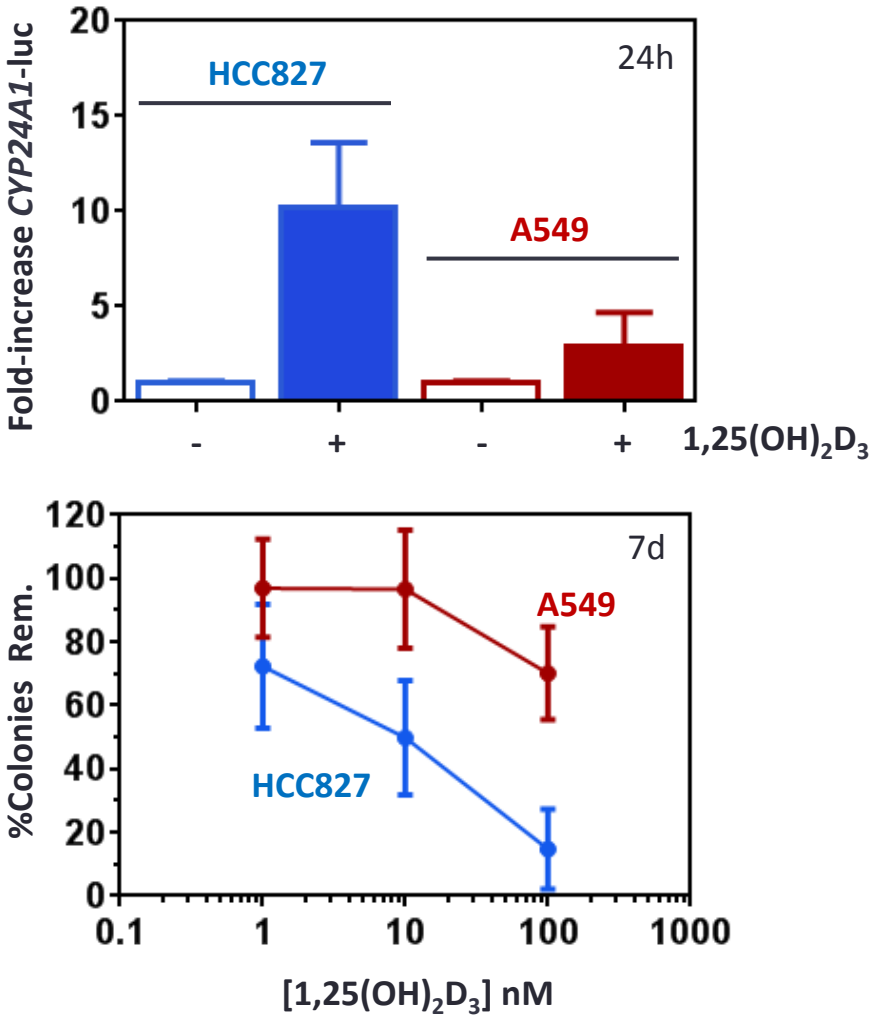
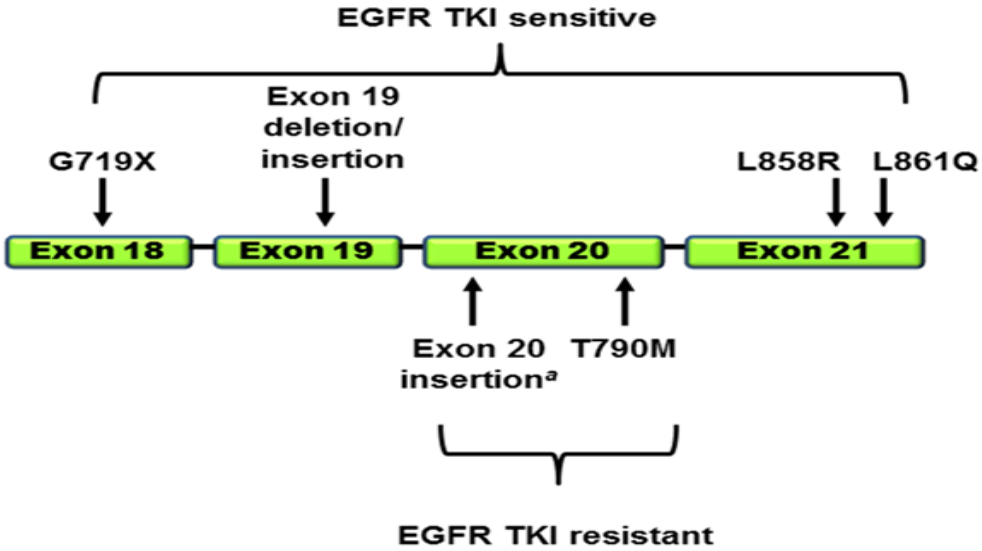
NSCLC cells with *EGFR* mutations are preferentially sensitive to $1,25(OH)_2D_3$





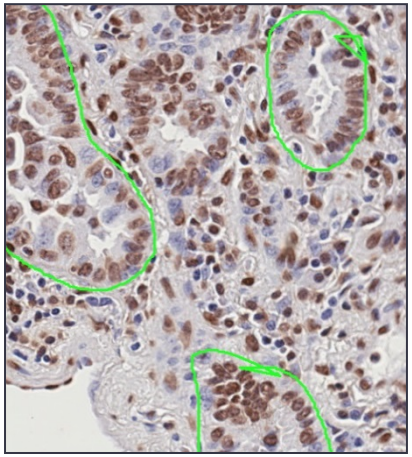
VDR is expressed in human lung tumors that harbor activating *EGFR* mutations



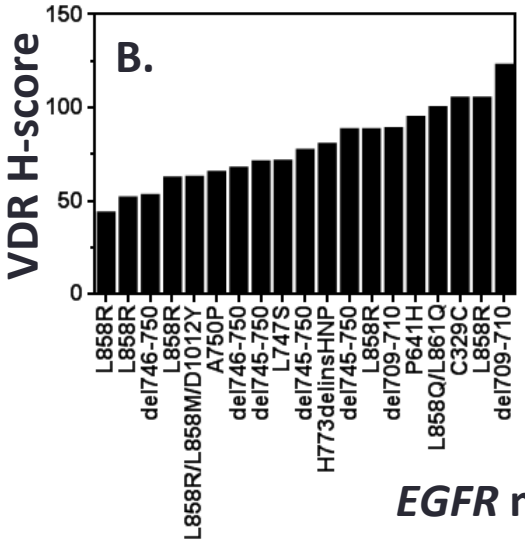
EGFR TKI activity

EGFR mt	RR (%)	OS (mo)
del746-750	70-100	26-30
L858R	20-67	8-17

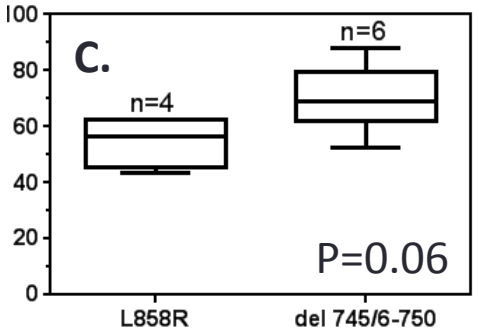
A.



VDR IHC

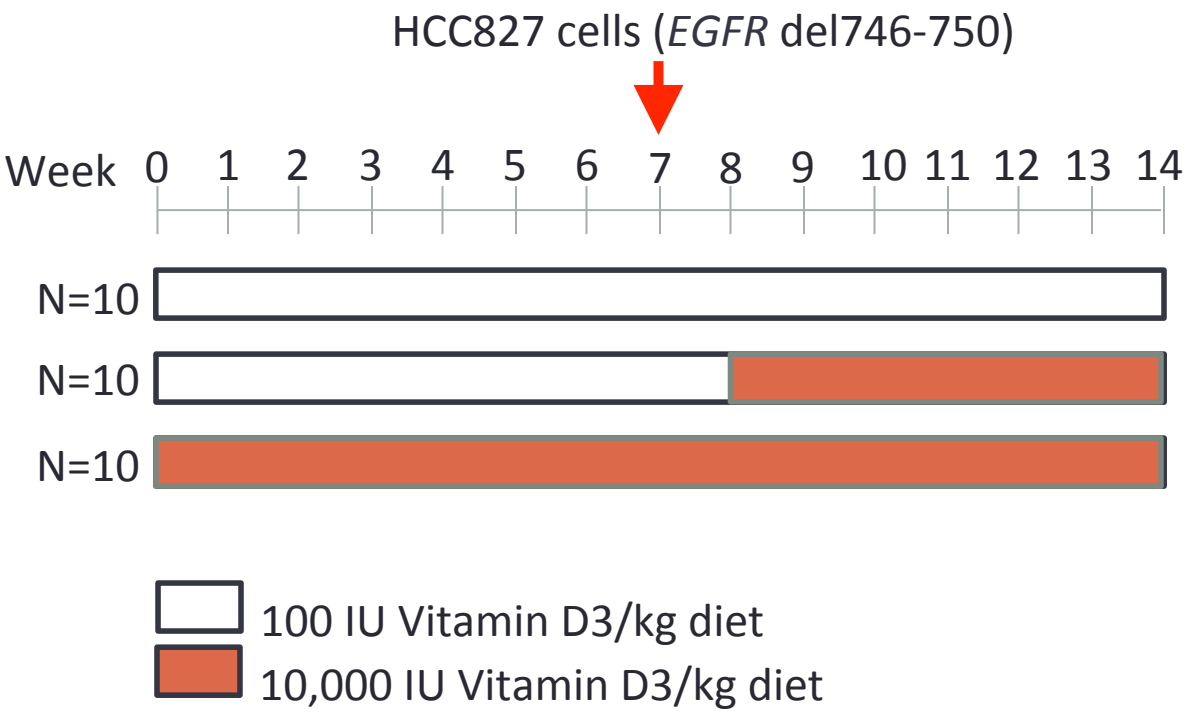


EGFR mutation

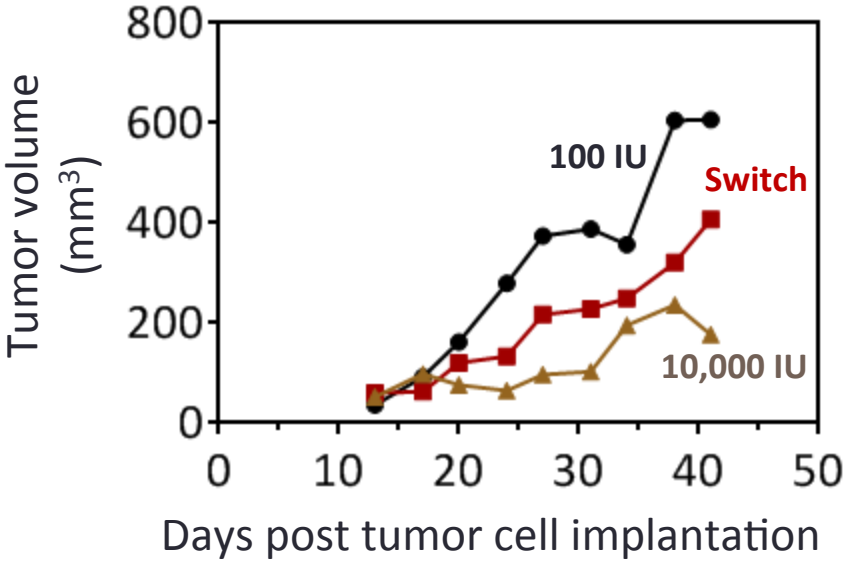


AR Verone-Boyle, et al. (2016) Oncotarget 7:995

Effect of modulating dietary vitamin D3 intake on growth of *EGFR* mutant NSCLC xenografts



Dietary vitamin D3 intake modifies growth of HCC827 human lung tumor xenografts



Growth rate (d13-d27)

Comparison	P-value
100 IU vs switch	0.011
10,000 IU vs switch	0.359
100 IU vs 10,000 IU	0.001

Fold-increase in tumor volume

Diet Group	Final TV/Initial TV
100 IU vitamin D3/kg	16
Switch diet	7
10,000 IU vitamin D3/kg	3

Fraction below 100 mm^3 at study termination

Diet Group	Fraction
100 IU vitamin D3/kg	2/10
Switch diet	5/10
10,000 IU vitamin D3/kg	7/10

AR Verone-Boyle, et al. (2016) Oncotarget 7:995