Novel definition of TKI resistance: Clinical versus molecular

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Disclosures

- Consulting fees from AstraZeneca, Boehringer-Ingelheim, Clovis, Genentech, Sysmex
- I will discuss off-label and investigational use of products developed by the above parties

Outline

- **Can we predict TKI resistance based on molecular testing?**

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- Can we diagnose TKI resistance using molecular testing?

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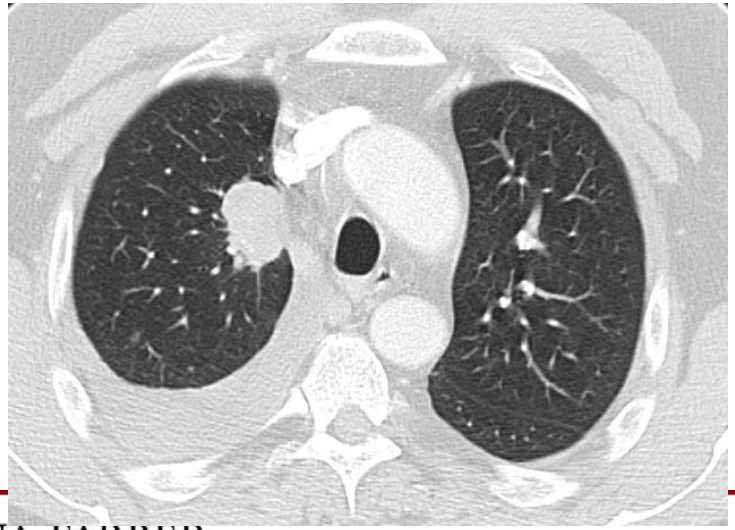
- Can we diagnose TKI resistance using molecular testing?
- Can we monitor TKI resistance using plasma genotyping?

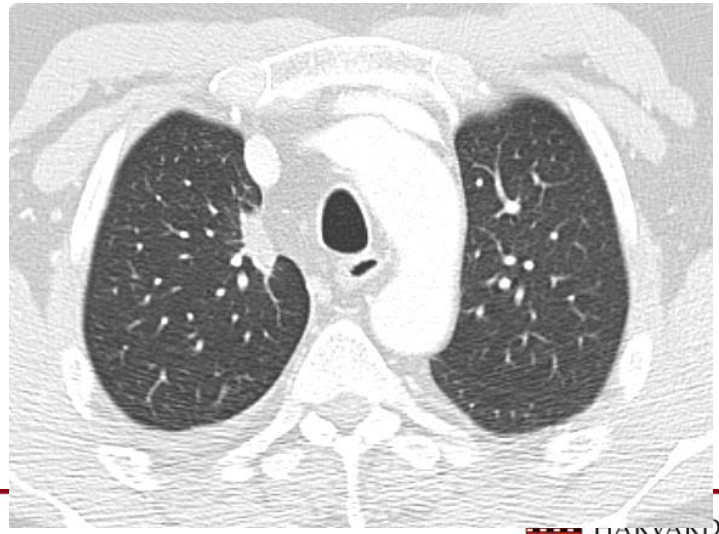
A case

- **55 y/o male never-smoker with NSCLC metastatic to bones**
  - **Biopsy of lung mass shows *EGFR* L858R**
  - **Responds to first-line erlotinib**

Baseline



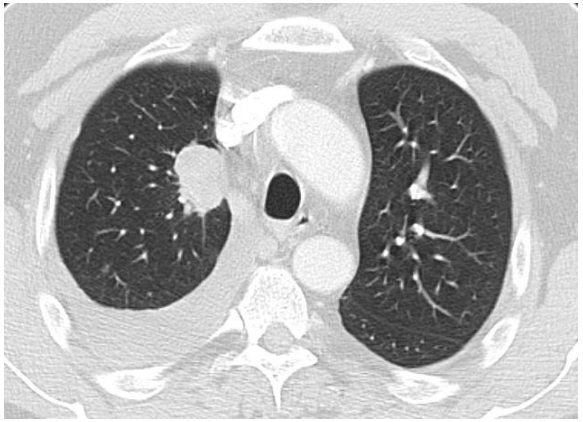
2 months



A case

- **55 y/o male w EGFR-mutant NSCLC**
  - **Develops re-growth of lung mass after 12 months on erlotinib, is asymptomatic**
  - **What do you recommend?**

Baseline



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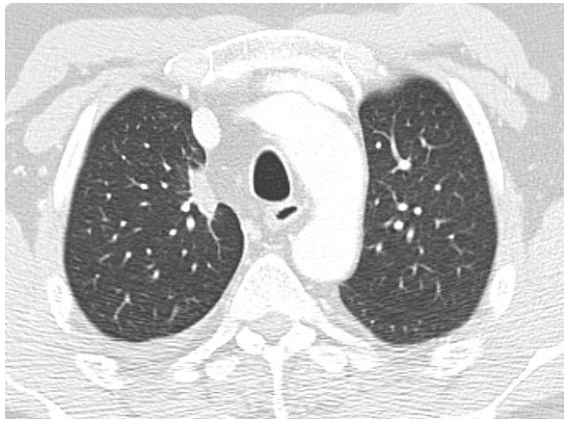

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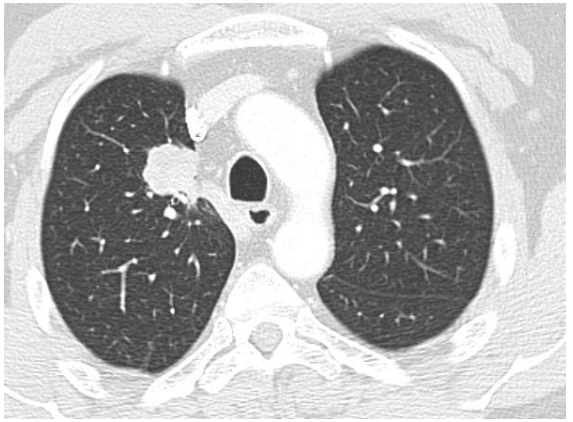

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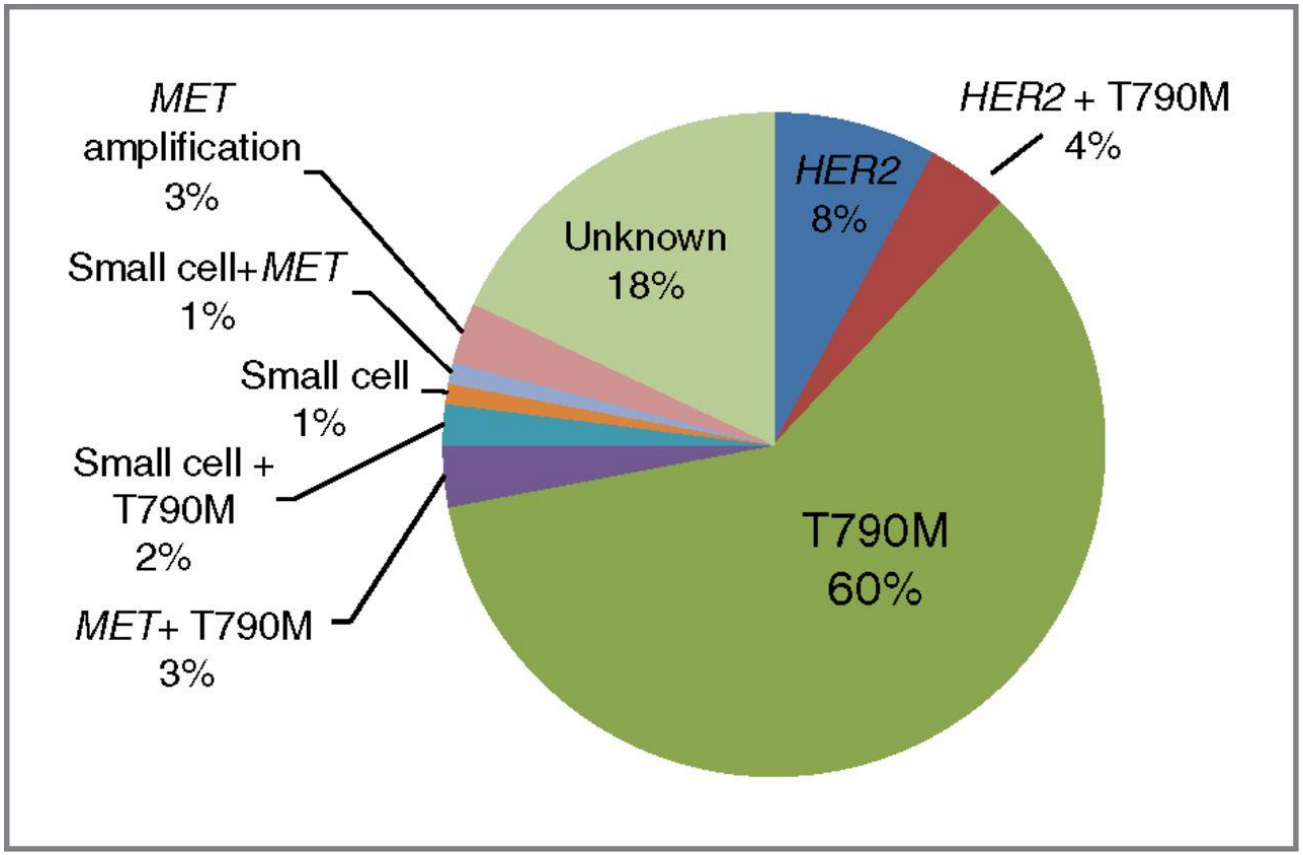
  - **Progression after initial benefit**
- **"Baseline resistance" or "refractory" to a drug**
  - **Progression despite presence of a mutation associated with benefit**
- **"Not sensitive" to a drug**
  - **No expectation of response (e.g. KRAS mutant lung cancers)**

Acquired resistance

- **Mechanisms of resistance to EGFR TKI**



Yu et al, CCR, 2013

Acquired resistance

- **Mechanisms of resistance to EGFR TKI**
  1. **Clinically relevant**

  2. **Biologically interesting**

Acquired resistance

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  1. **Clinically relevant**
     - **Small cell transformation**
     - ***EGFR* T790M**
     - ***MET* amplification**
  2. **Biologically interesting**

Acquired resistance

- **Mechanisms of resistance to EGFR TKI**
  1. **Clinically relevant**
     - **Small cell transformation**
     - ***EGFR* T790M**
     - ***MET* amplification**
  2. **Biologically interesting**
     - ***HER2* amplification**
     - ***BRAF* V600E**
     - **AXL, CRKL, etc**

Oxnard et al, ASCO, 2013

Predicting resistance

- **Does molecular testing allows us to predict baseline resistance to TKI?**
  - **Yu et al studied 13 patients with baseline EGFR T790M & L858R or 19 del**
  - **Detected with standard clinical genotyping assays (sequencing, PCR, Sequenom)**
  - **8% RR, 1.5m median PFS**

Yu et al, Ann Oncol, 2014

Predicting resistance

- **Some have found that T790M does not indicate resistance**
  - **Maheswaran et al, NEJM, 2008**
  - **Rosell et al, CCR, 2011**
  - **Su et al, JCO, 2012**
- **All used highly sensitive investigational assays which detected T790M in >30% of cases at baseline**
- **Recent concern for risk of false positives using highly sensitive assays on FFPE**
  - **Ye et al, JTO, 2013**

Predicting resistance

- **Baseline MET amplification plus EGFR mutation can also cause resistance**
- **31 year-old female with exon 19 deletion and high MET amplification on NGS**
  - **Clear progression of cervical LN on erlotinib**

Diagnosing resistance

1. **67 yo Asian male with advanced NSCLC, EGFR L858R, metastatic to bone**
   - **Receives palliative radiation to spine mets**
   - **Starts on erlotinib**
   - **Initial CT shows slightly decreased lung mass, enlarging pleural effusion, new bone mets**
   - **Complains of fatigue, pain, shortness of breath**

Does he have resistance?

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   - **Complains of fatigue, pain, shortness of breath**
   - **NGS of pretreatment biopsy shows L858R, no other resistance mechanism**

Does he have resistance?

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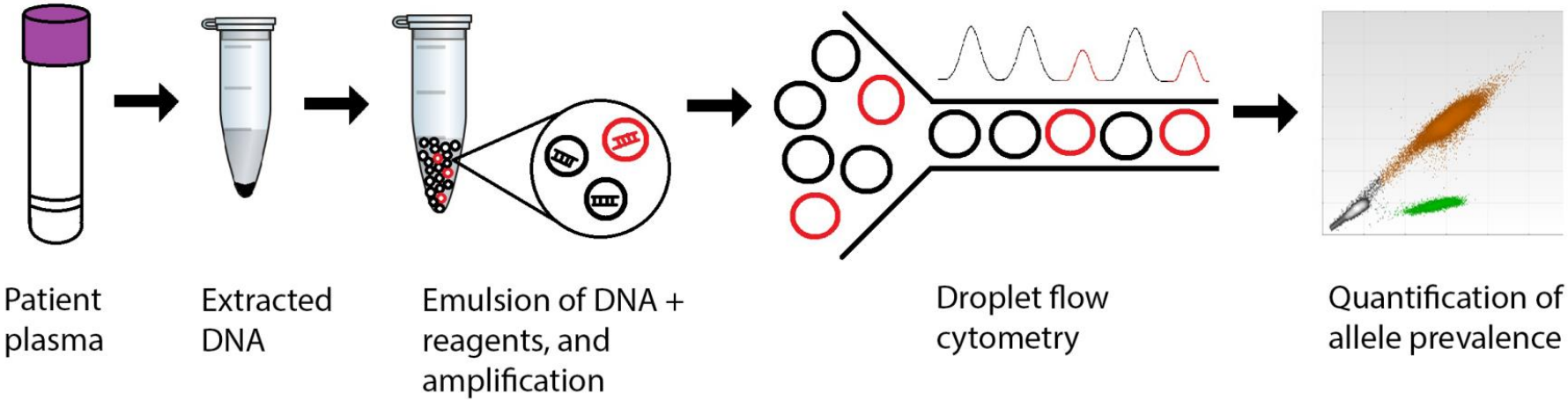
   - Feeling OK on dose reduced afatinib (20mg)
   - Chest CT shows poorly visualized liver lesions, possibly enlarged from prior

Does he have resistance?

Plasma genotyping

- **Droplet digital PCR (ddPCR) allows quantitative detection of EGFR mutations in cell free DNA (cfDNA)**



- **For clinical use, must have no false positives**

Oxnard et al, CCR, 2014

Diagnosing resistance

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2. After early progression on erlotinib, he goes on to receive chemotherapy x2 years
3. Then is started on afatinib and has a response lasting 8 months
   - Feeling OK on dose reduced afatinib (20mg)
   - Chest CT shows poorly visualized liver lesions, possibly enlarged from prior
4. Plasma ddPCR is performed and is positive for L858R and <u>T790M</u>

Diagnosing resistance

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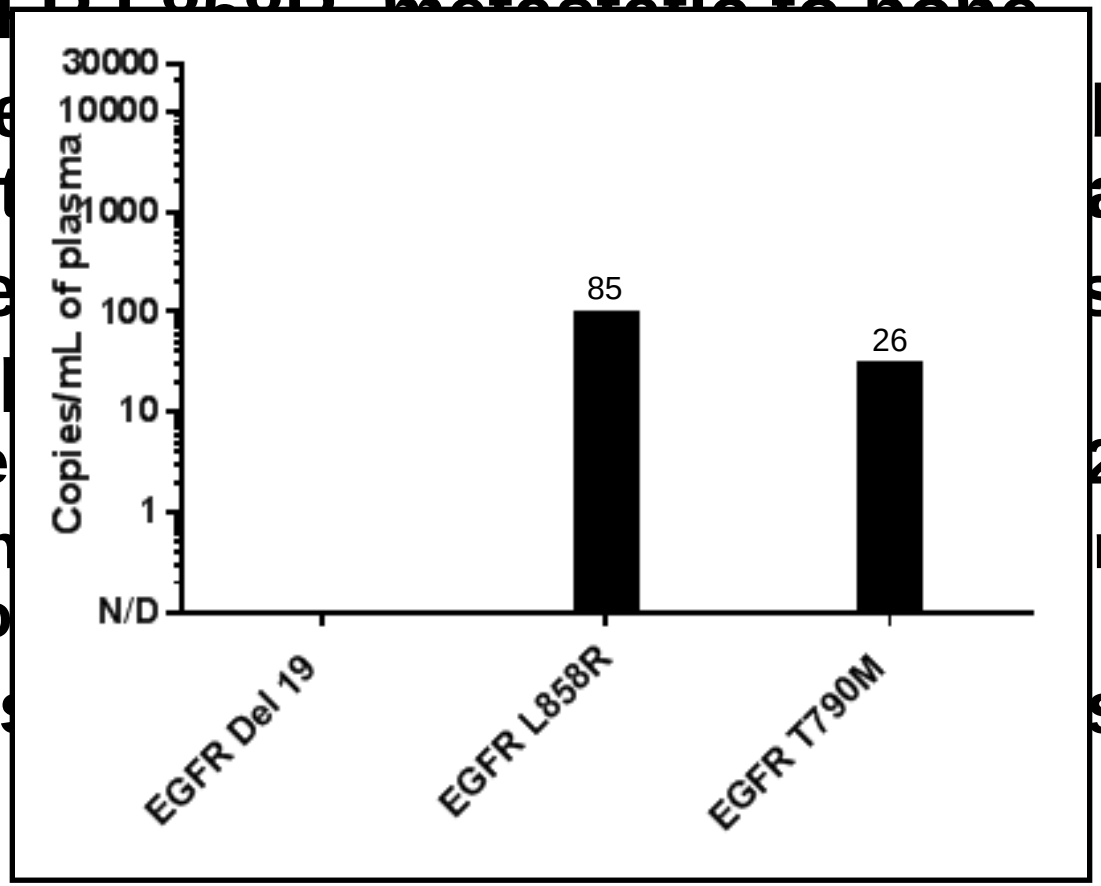
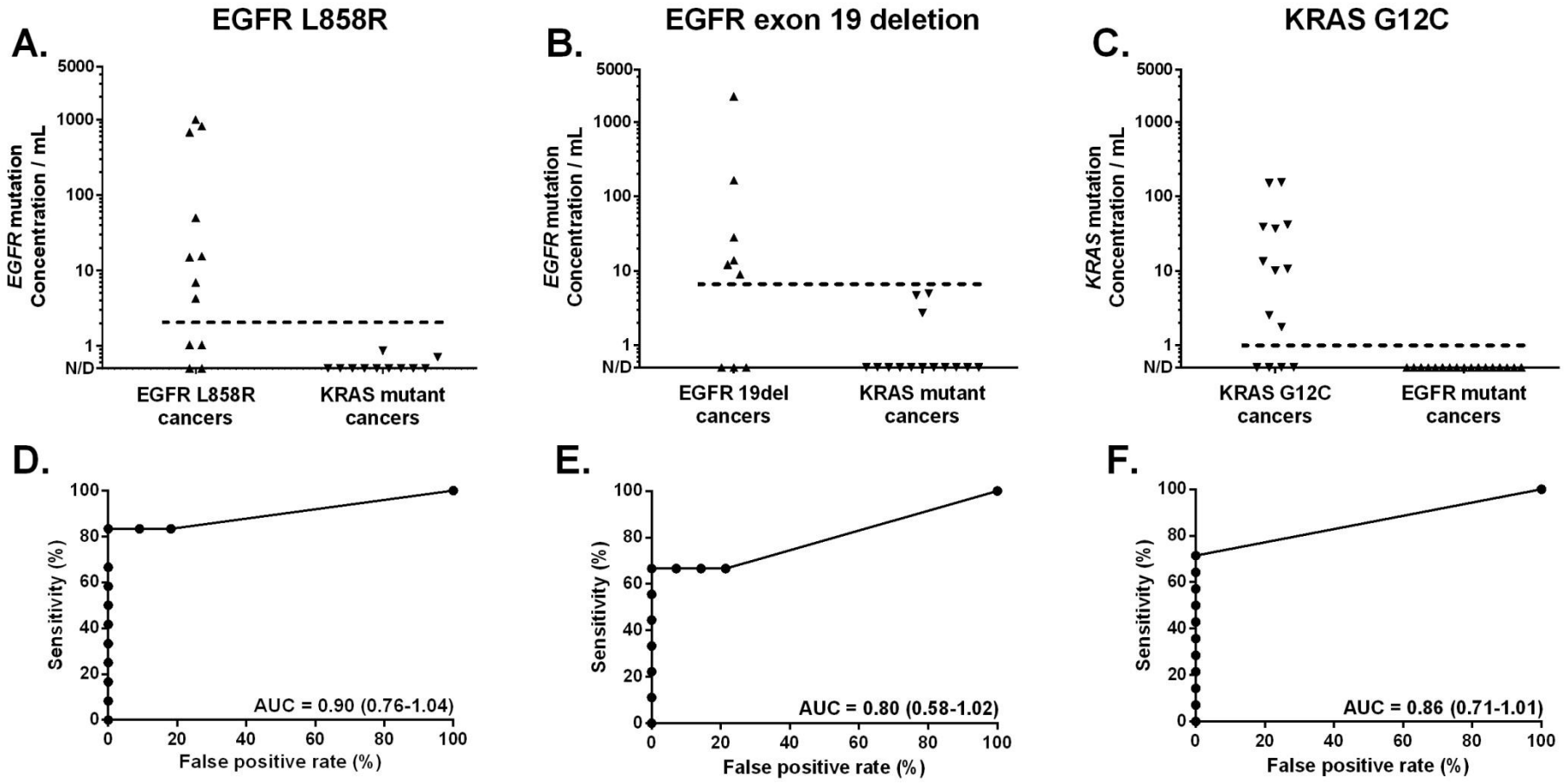


Plasma genotyping



Oxnard et al, CCR, 2014

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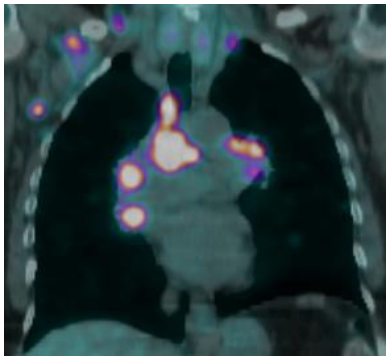

DAY 0:
CT shows marked progression on erlotinib, plasma drawn

DAY 1:
cfDNA genotyping detects 806 copies/ml of *EGFR* T790M

DAY 25:
Report from rebiopsy genotyping shows *EGFR* T790M

DAY 31:
Patient starts treatment with AZD9291

DAY 73:
CT with radiographic response

Diagnosing resistance

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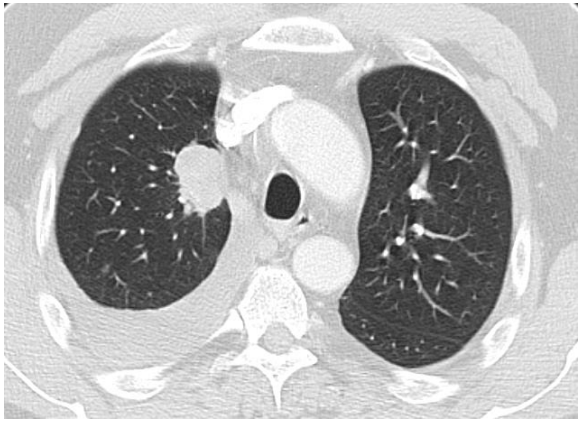
  - **Develops re-growth of lung mass after 12 months on erlotinib, is asymptomatic**

Baseline



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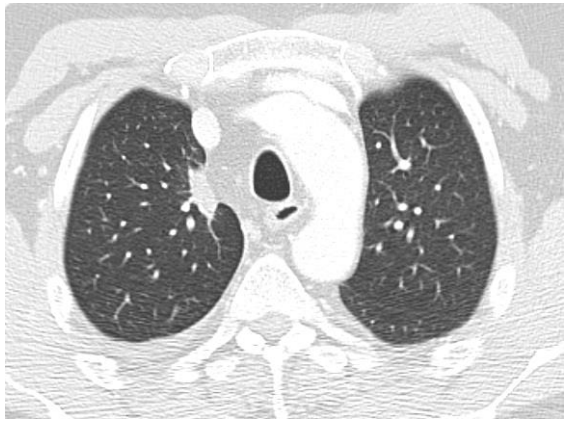

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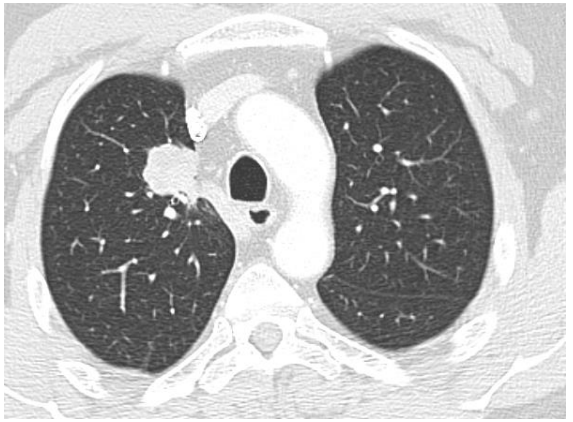
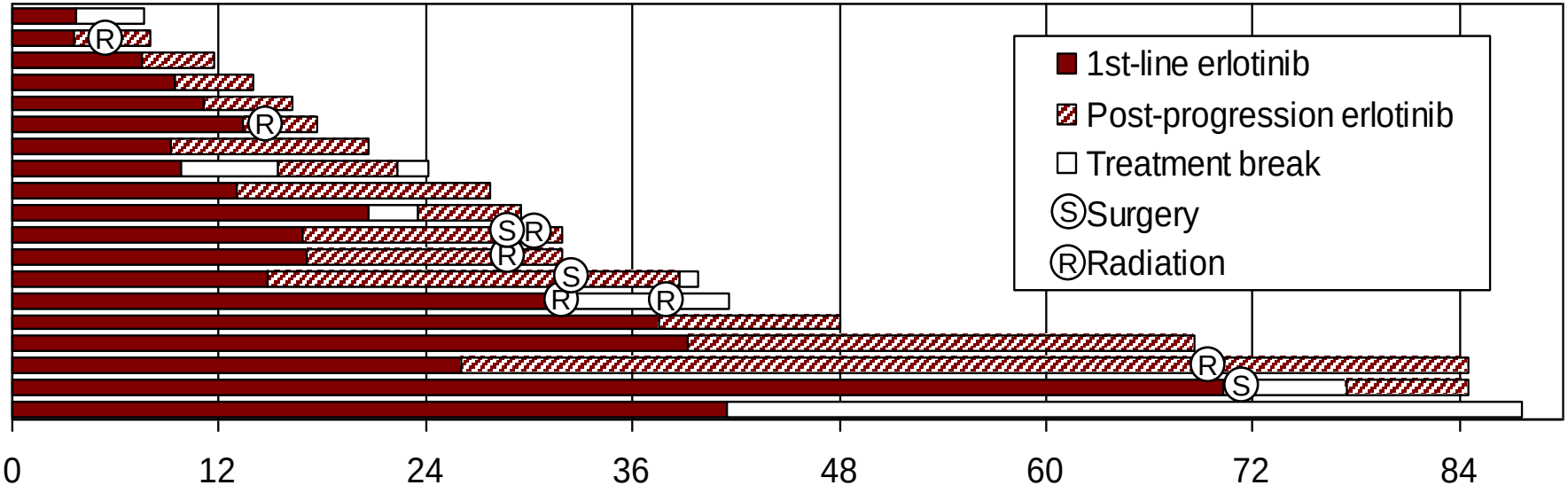


  - **No detectable mutations on plasma genotyping with ddPCR**

Diagnosing resistance

- **Remember, patients can stay on TKI after PD**
  - **Studied 42 pts with EGFR-mutant NSCLC receiving 1st-line erlotinib on 3 clinical trials**
  - **45% of pts delayed change of therapy >3 months after RECIST progression**

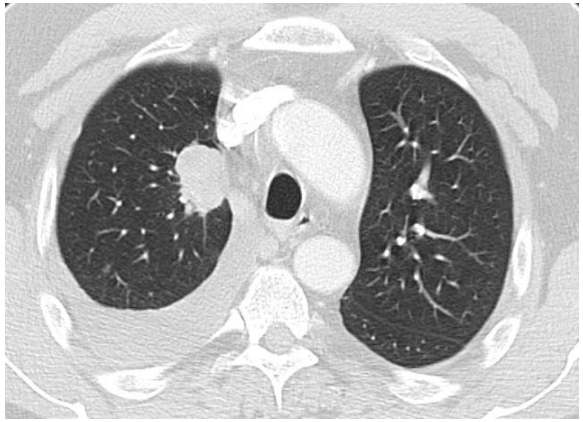


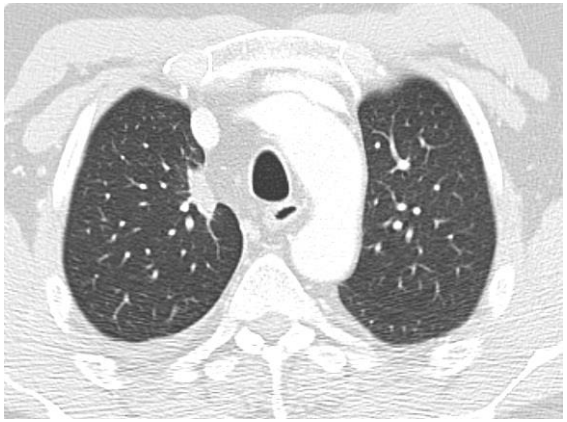
Oxnard et al, ASCO, 2012

Monitoring resistance

- **55 y/o with acquired TKI resistance**
  - **Continues erlotinib 6 more months**

Baseline





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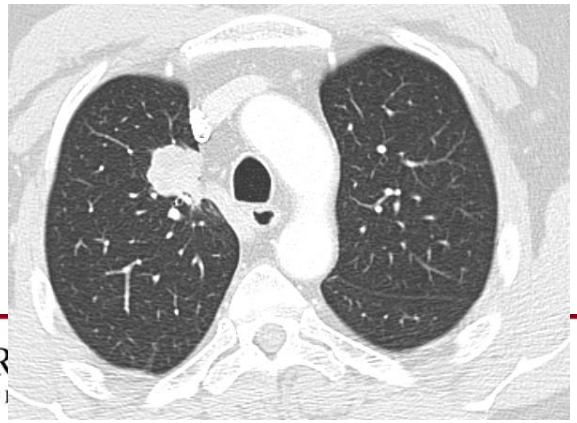
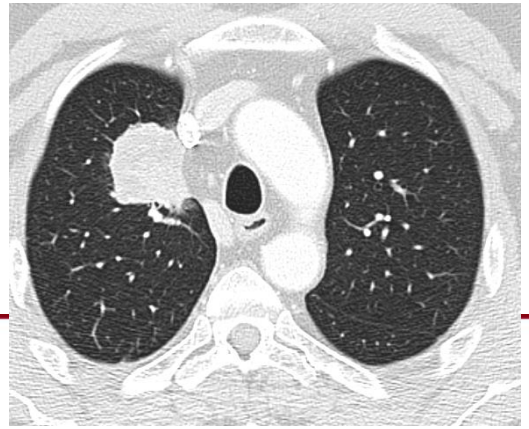
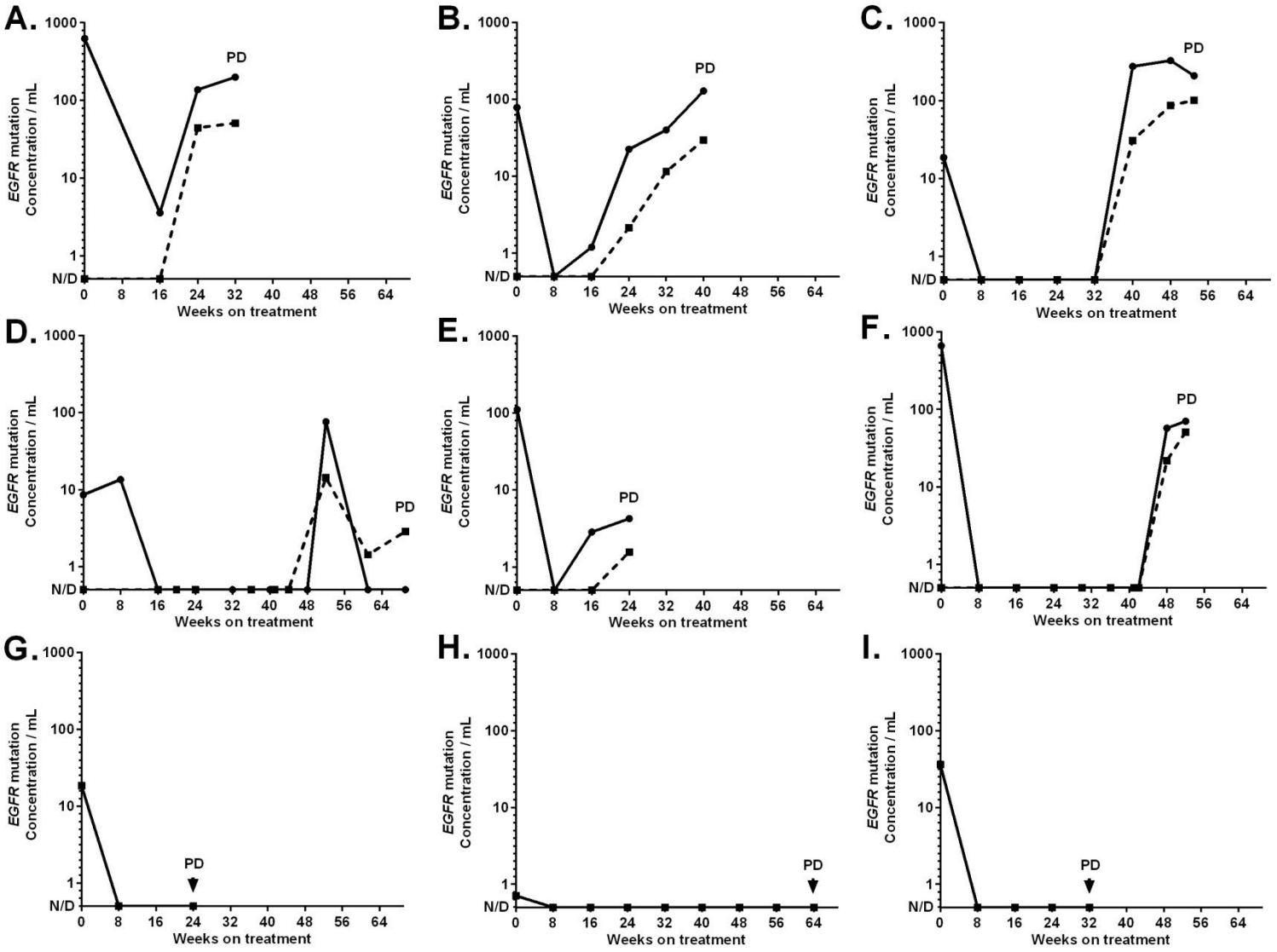




18 months

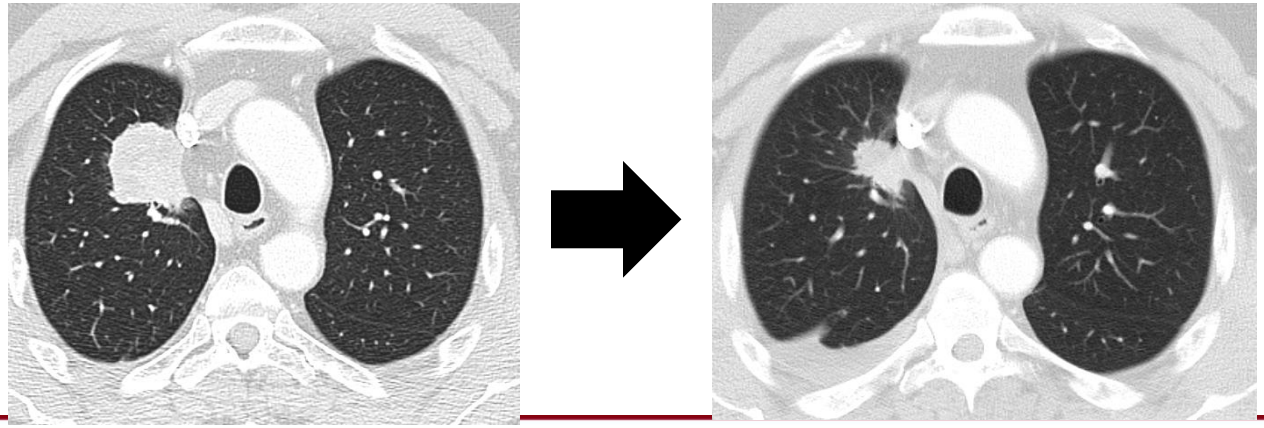
Monitoring resistance



Oxnard et al, CCR, 2014

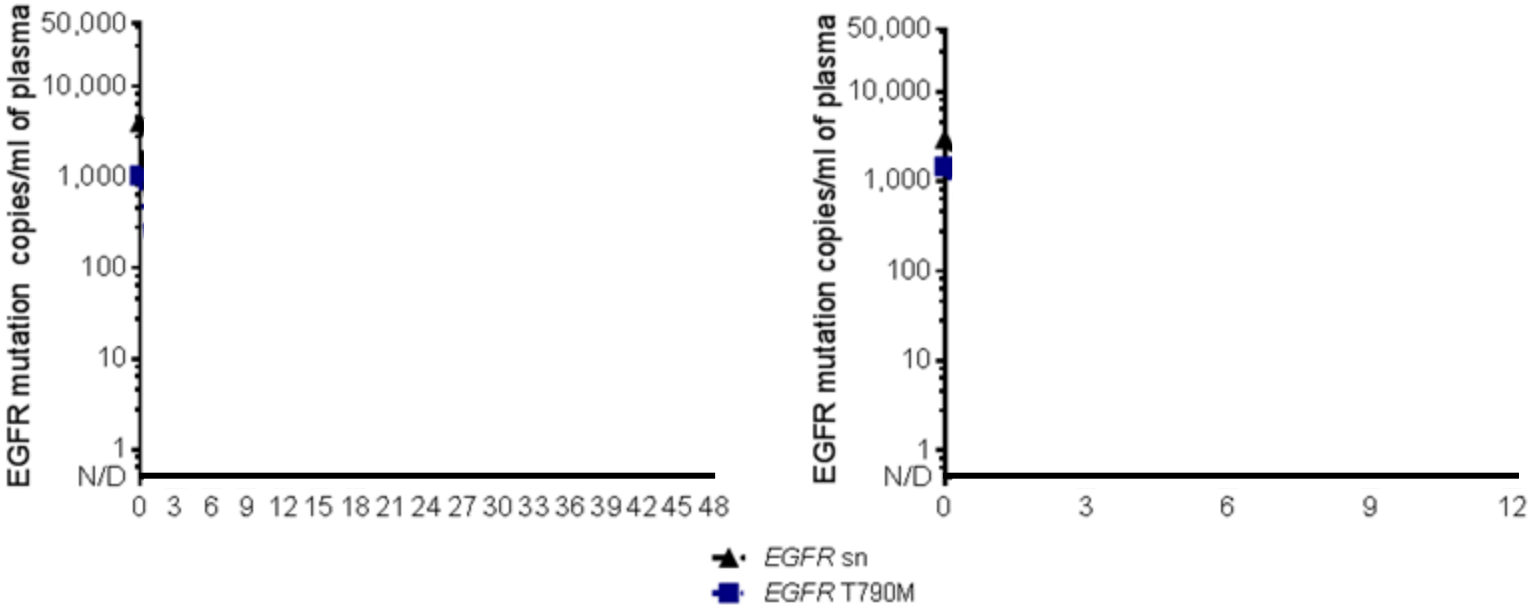
Monitoring resistance

- 55 y/o with acquired TKI resistance
  - Develops further growth, cough
  - Plasma shows L858R & T790M
  - Biopsy confirms T790M
  - Starts on clinical trial of AZD9291



Monitoring resistance

- **Serial plasma genotyping to follow response and progression**



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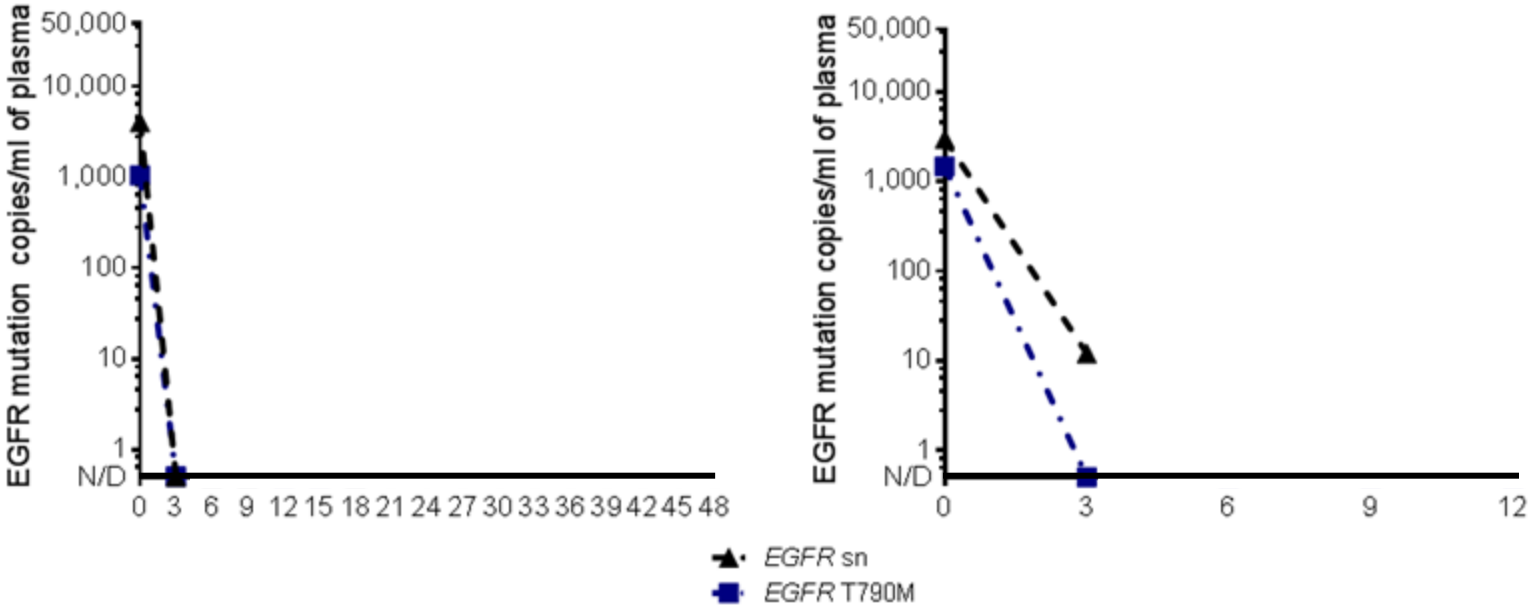

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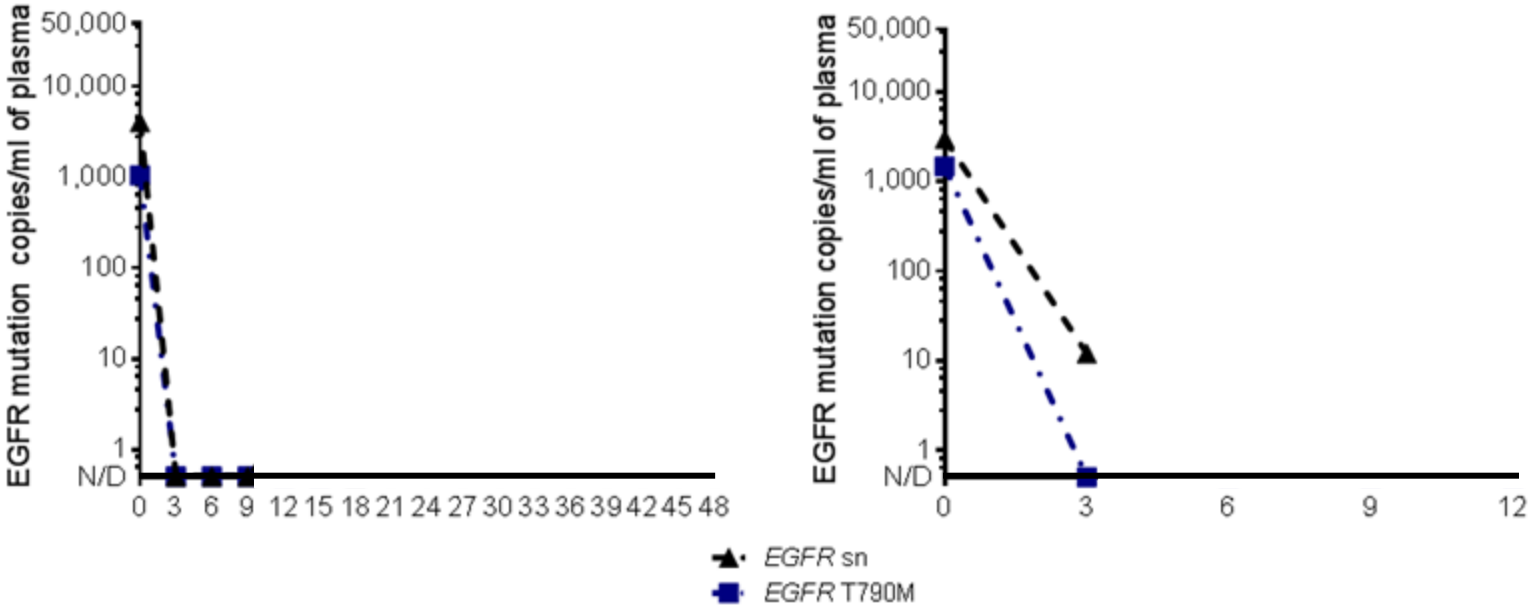

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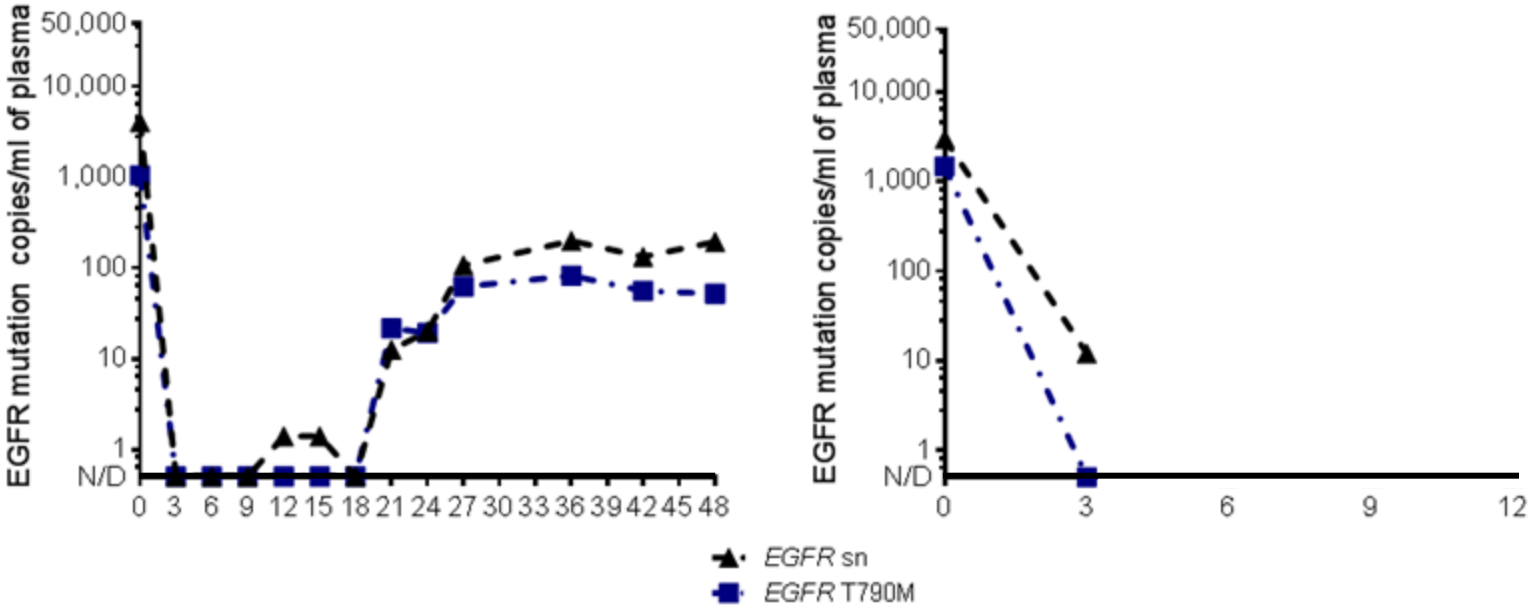

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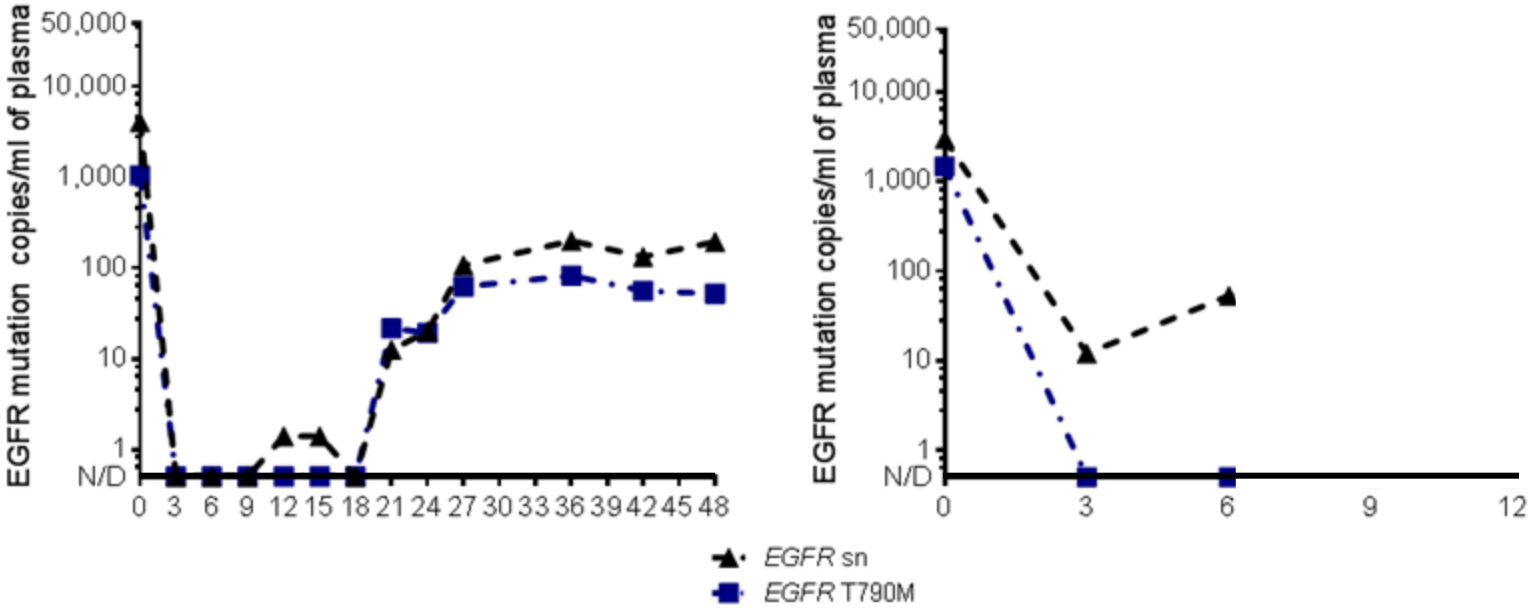

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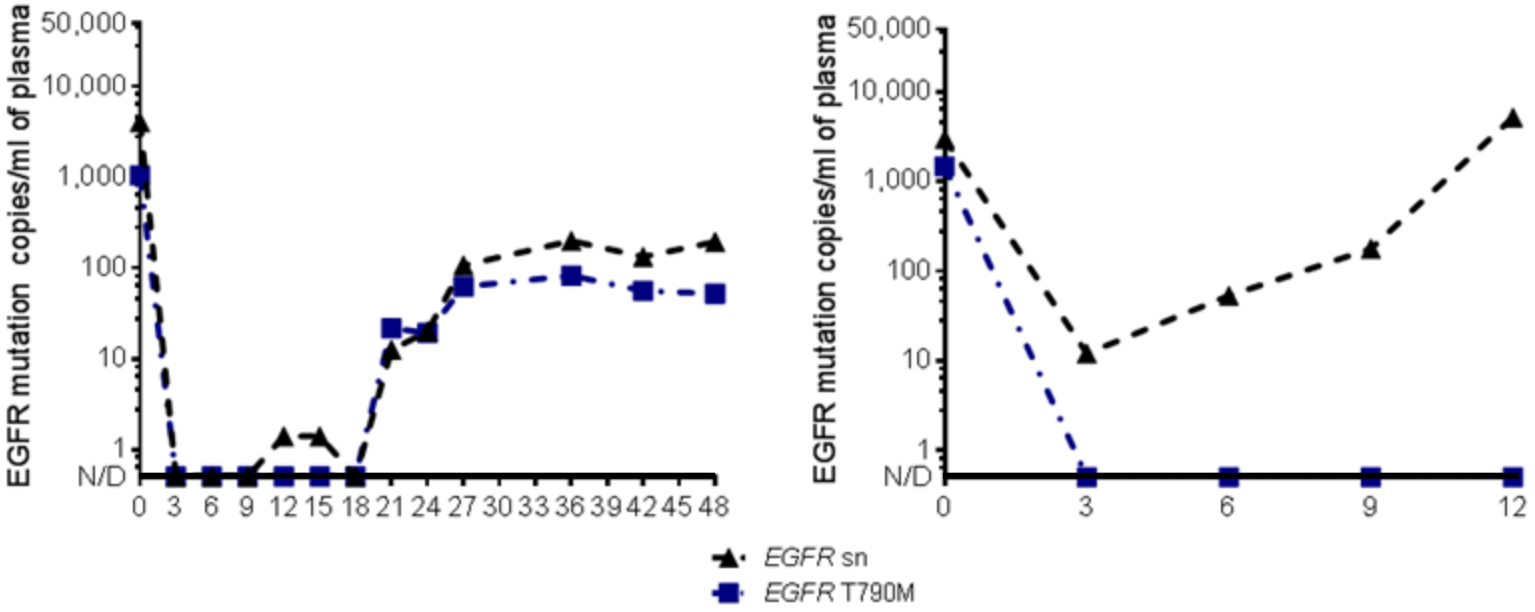

Summary

1. Resistance mutations like *EGFR* T790M represent a molecular criteria for resistance
2. Not all patients with resistance require immediate treatment change
3. Tumor and liquid biopsies have potentially complementary roles for characterizing the biology of resistance
4. Serial monitoring of plasma genotyping on therapy represents a compelling tool for understanding resistance

Acknowledgements

- US Department of Defence
- Stading-Younger Foundation
- Phi Beta Psi Sorority

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