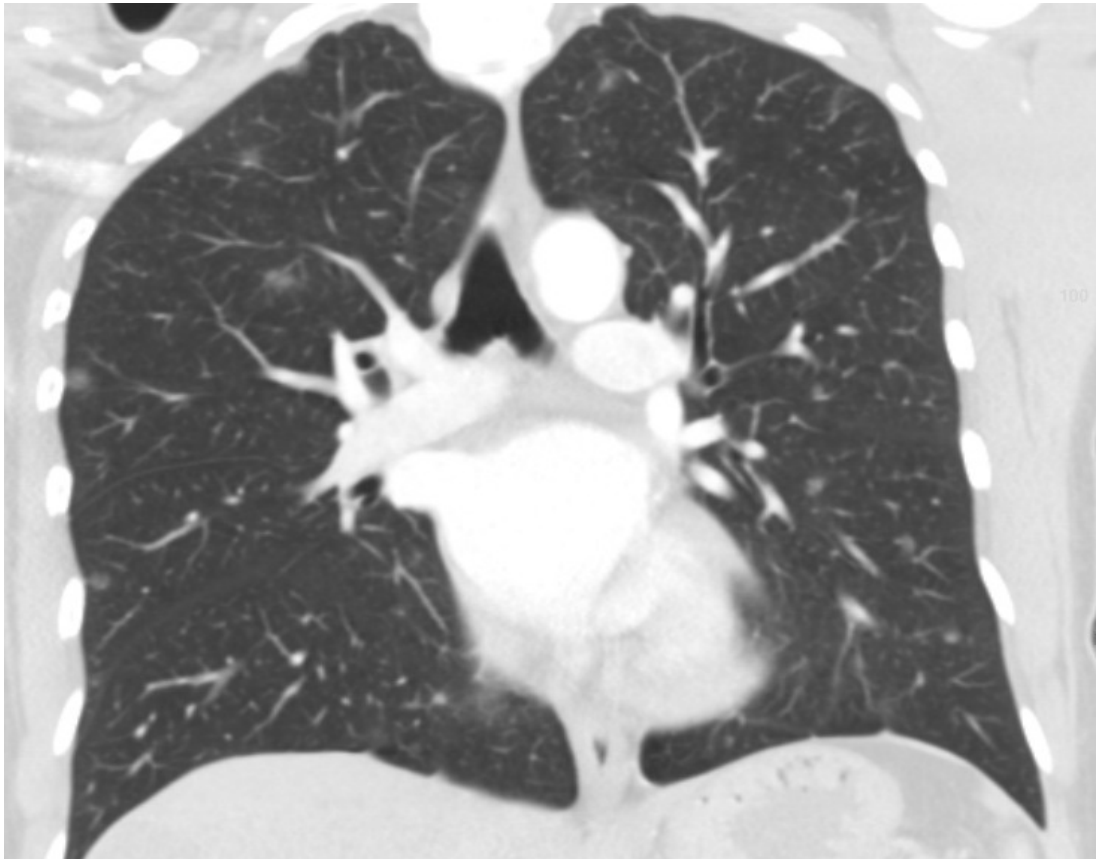
Testing for T790M in EGFR-mutant NSCLC with acquired resistance

Geoffrey R. Oxnard, MD
Damon Runyon-Gordon Family Clinical Investigator
Assistant Professor of Medicine
Dana-Farber Cancer Institute

Case

- 53-year-old F never-smoker incidentally found to have lung nodules on abdominal CT:

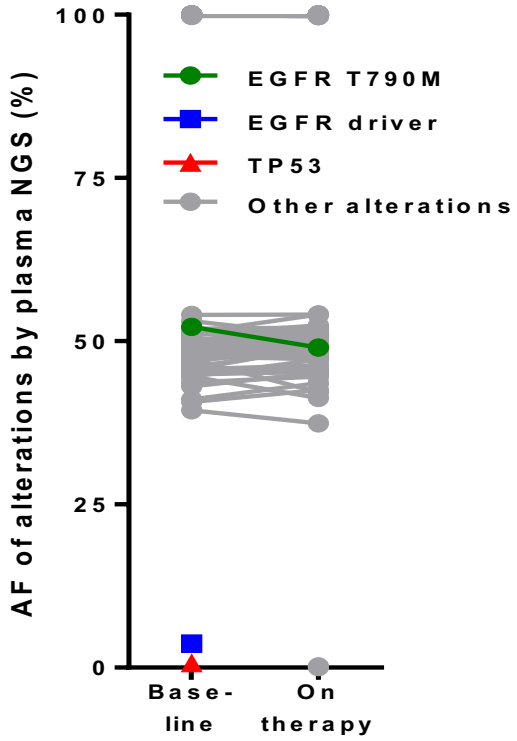


Case

- 53-year-old F never-smoker incidentally found to have lung nodules on abdominal CT:
  - FNA suggests multifocal BAC. PET is negative. She is asymptomatic. Lost to follow-up.
  - Re-presents 4 years later with growing lung nodules. Staging shows brain and liver metastases. Brain biopsy reveals metastatic adenocarcinoma, positive for *EGFR* L858R.
  - She starts erlotinib, but develops dyspnea and cough. Initial follow-up scans show progression of lung nodules.

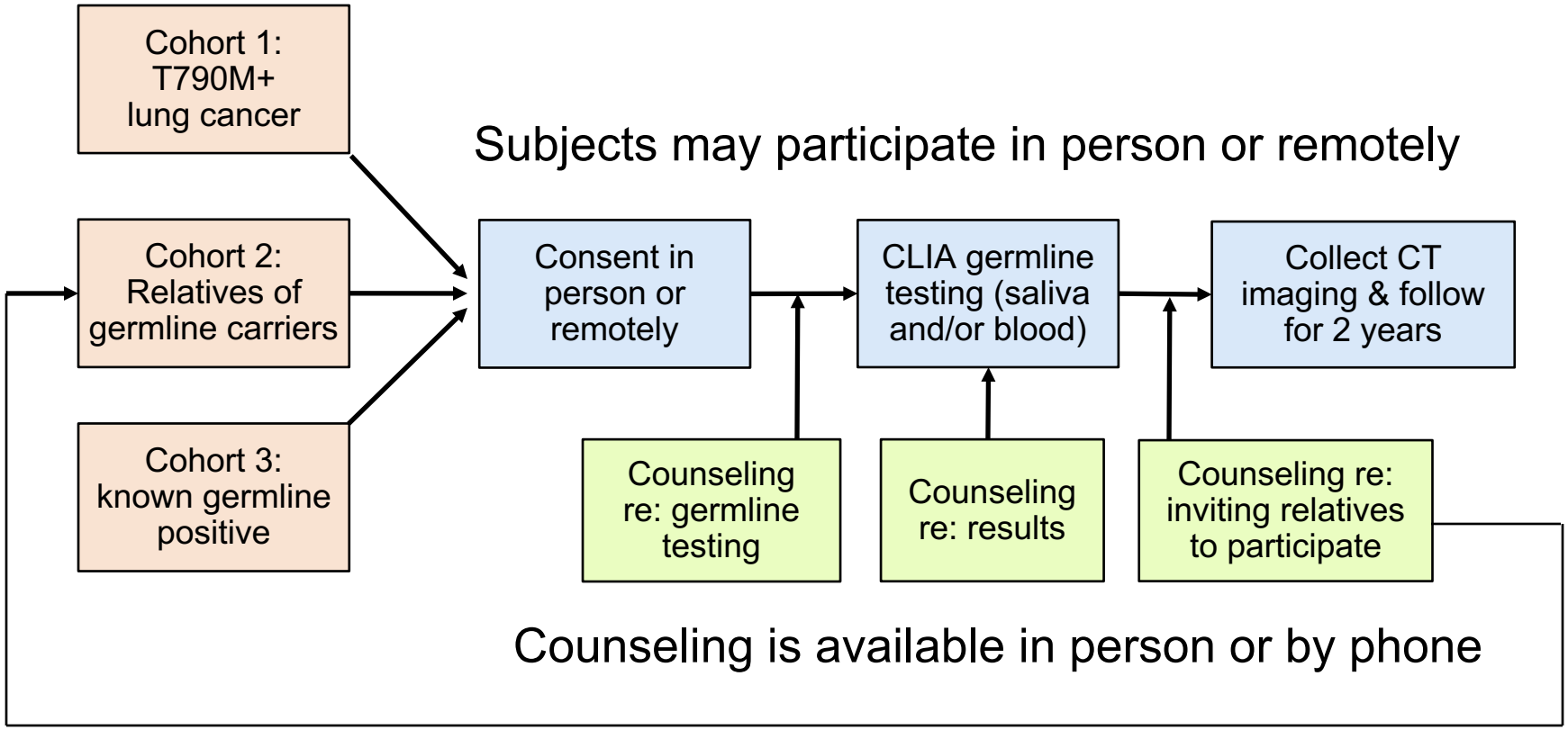
Case

- 53-year-old F never-smoker with stage IV EGFR-mutant NSCLC refractory to erlotinib:
  - Tumor NGS done on pretreatment tumor:
    - EGFR L858R at 79% AF
    - EGFR T790M at 81% AF
  - Plasma NGS is sent for testing:
    - Low level L858R (1% AF)
    - High level T790M (50% AF)



INHERIT EGFR study

- Free-germline EGFR testing and counseling



Case

- 53-year-old F never-smoker with stage IV NSCLC positive for EGFR L858R and T790M:
  - Germline EGFR sequencing positive
  - Working to invite appropriate relatives to receive germline testing on study
  - She has initiated osimertinib and tolerated it well with durable response

Testing for T790M in EGFR-mutant NSCLC with acquired resistance

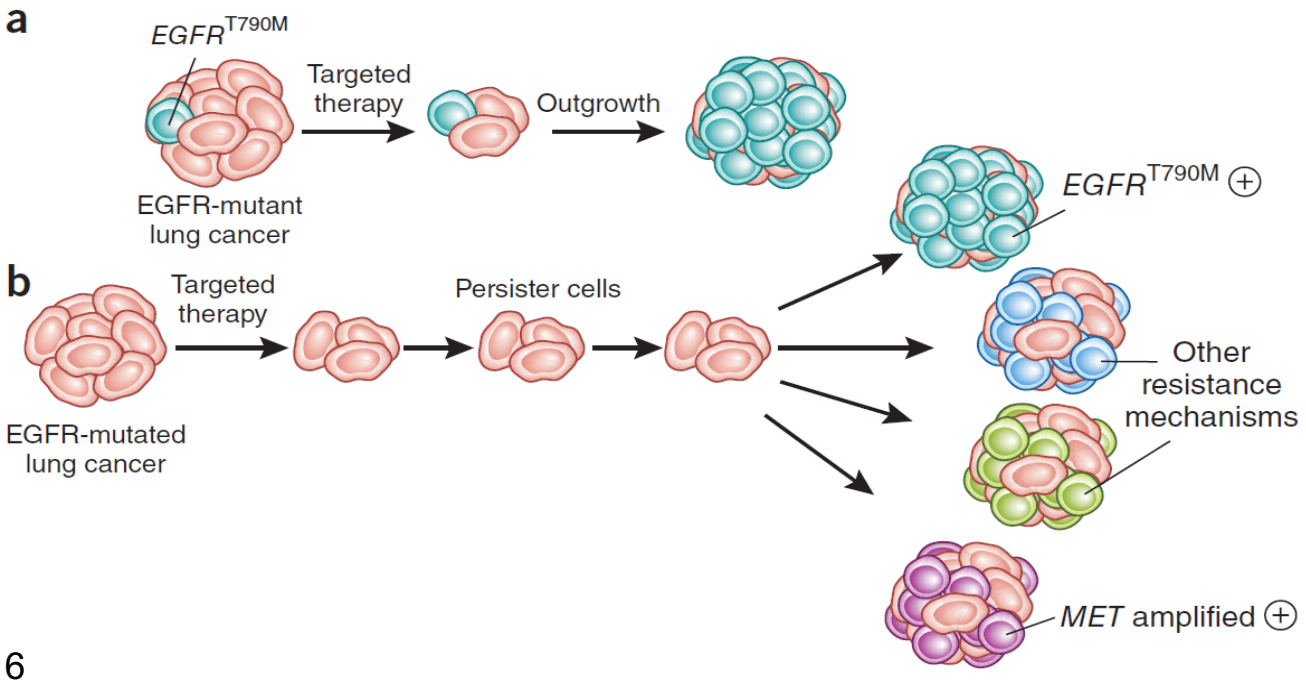
Geoffrey R. Oxnard, MD
Damon Runyon-Gordon Family Clinical Investigator
Assistant Professor of Medicine
Dana-Farber Cancer Institute

Disclosures

- Consulting fees from Ariad, AstraZeneca, Boehringer-Ingelheim, Genentech, Inivata, Novartis, Takeda
- Honoraria from AstraZeneca, Boehringer-Ingelheim, Chugai

T790M testing

- With the regulatory approval of osimertinib, T790M testing has now become SOC
- Development of T790M cannot be predicated using pretreatment biopsy:



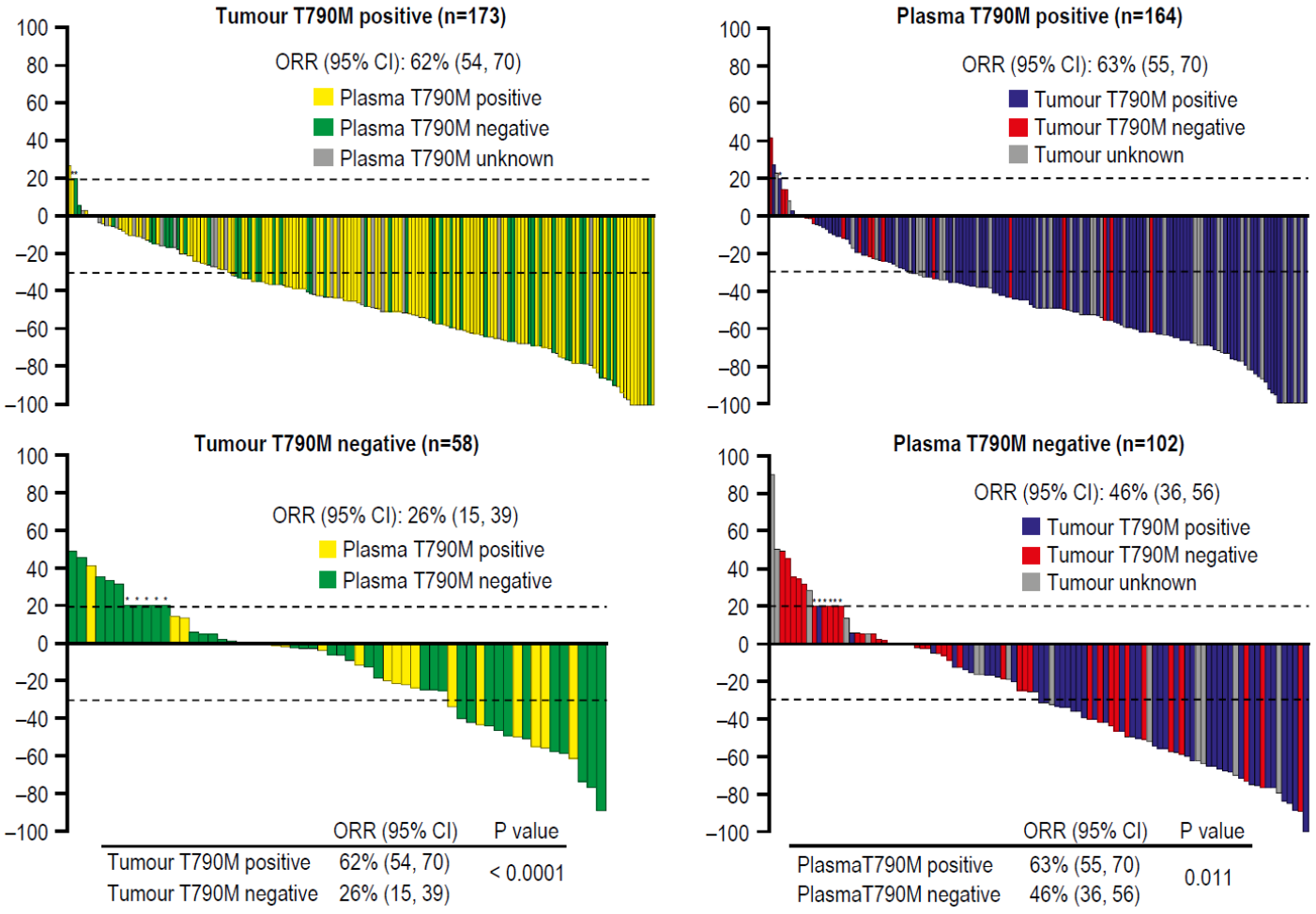
Hata et al, Nat Med, 2016
Ramirez et al, Nat Comm, 2016
Oxnard, Nat Med, 2016

T790M testing

	Tissue genotyping	Plasma genotyping
Scope	Comprehensive: histology, genomics, FISH, IHC, etc.	Limited: DNA only, best established for EGFR
Sensitivity	Reference standard but may miss due to heterogeneity	50%-70% because not all cancers shed DNA
Invasiveness	Usually invasive, sometimes infeasible	Just a blood test
Turnaround time	Biopsy, path, and molecular can take weeks	Days to weeks
Cost	High if you consider the biopsy and possible complications?	High if you consider the possible need for a biopsy if negative?

T790M and outcome

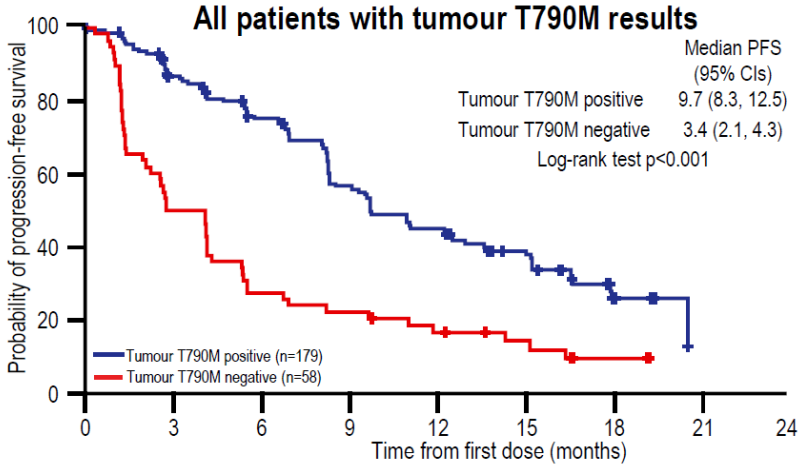
- Osimertinib is highly active in T790M+

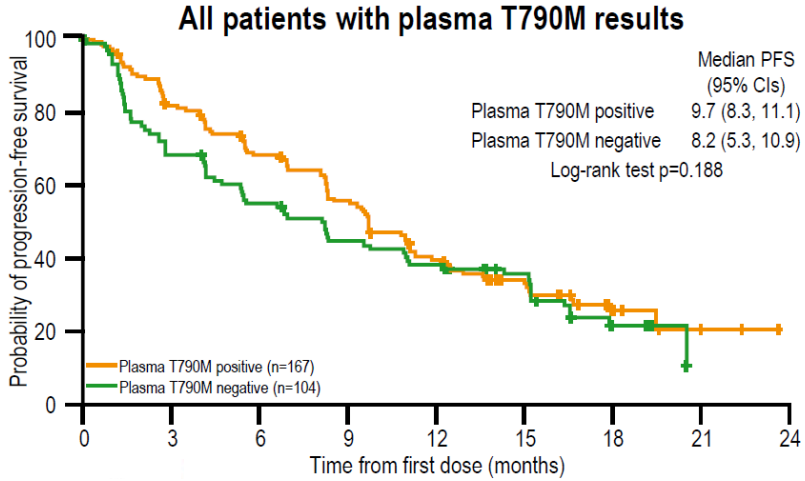


Oxnard et al. ELCC 2016; Oxnard et al. JCO 2016.

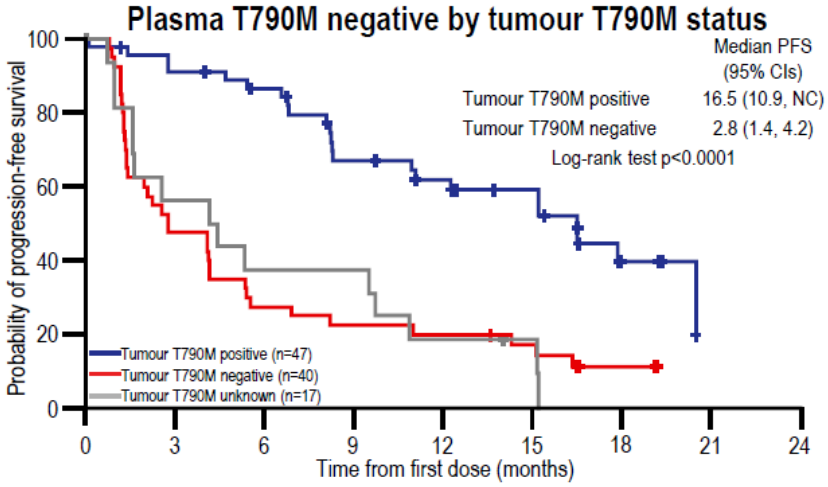
T790M and outcome

- Osimertinib is highly active in T790M+





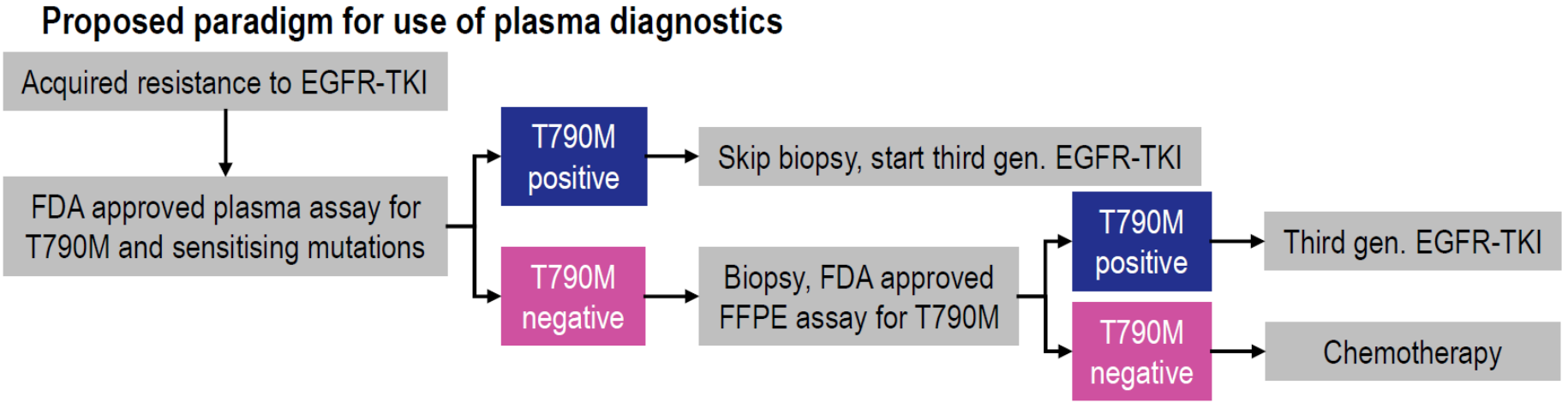
- For plasma T790M- cases, tumor genotyping can identify cases of missed T790M that do well on osimertinib



Oxnard et al. ELCC 2016; Oxnard et al. JCO 2016.

T790M testing in practice

- FDA has approved plasma genotyping for T790M in cases where tumor genotyping is unavailable
- Data would also support rapid plasma genotyping as a screening test prior to planned biopsy for resistance

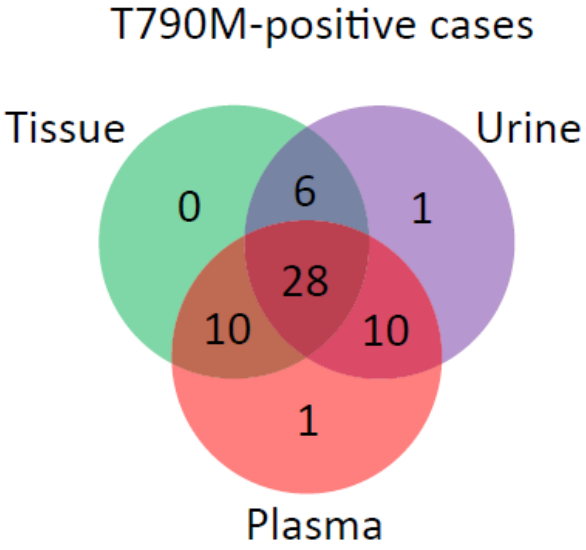


Oxnard et al. ELCC 2016; Oxnard et al. JCO 2016.

T790M in urine

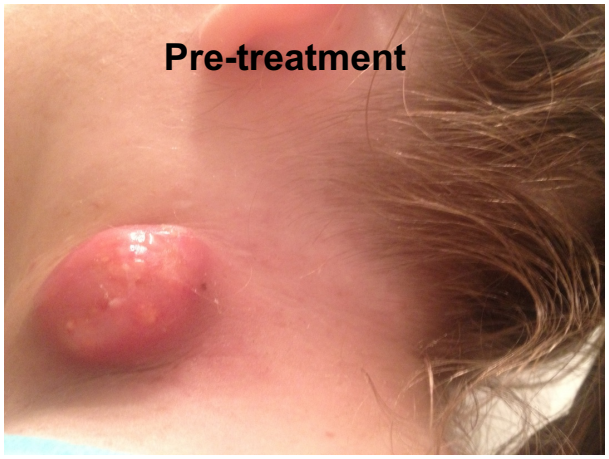
- Reckamp et al studied urine cfDNA genotyping in 63 patients with EGFR-mutant NSCLC treated on TIGER-X
  - Urine genotyping had a sensitivity of 67%-75% for EGFR mutations when compared to tumor genotyping
  - Plasma genotyping in this cohort had a sensitivity of 87%-100%
  - In ~20 cases with >90 ml of urine, sensitivity was 80%-93%

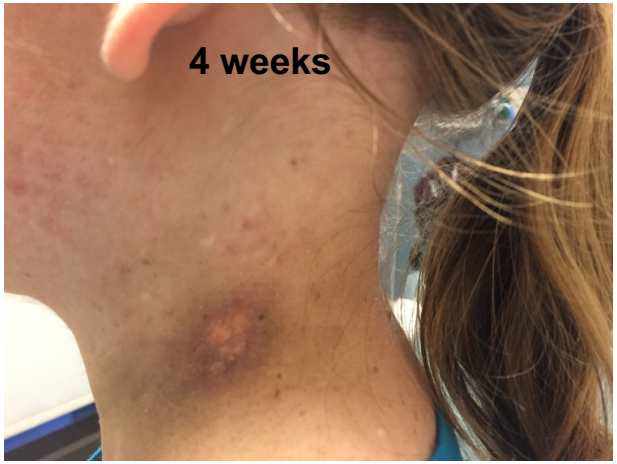
- Urine genotyping may be a useful alternative to plasma genotyping for some patients



Non-T790M resistance

- Patients negative for T790M may have other targeted therapy options available:
  - EGFR mutant / MET amplified with response to osimertinib & savolitinib (TATTON trial)





  - ~9 combinations of EGFR TKI & MET TKI currently under investigation

False positives

- Assay validation can be variable:
  - 57-year-old Asian male presents with NSCLC, and plasma genotyping is sent

SUMMARY:

EGFR Mutations (Del19, L858R, T790M):

Alteration	Result	Percent Mutant Allele	Mutant Copy Number
T790M	Detected	0.2% mutation frequency of T790M over EGFR wild-type.	1
L858R	Not Detected	N/A	N/A
Del19	Detected	7.6% mutation frequency of Del19 over EGFR wild-type.	65

  - Has dramatic response to erlotinib lasting ~12 months, at which time biopsy is T790M-neg
  - In hindsight, the low level T790M at diagnosis was likely a false positive

Summary

- T790M testing has become a fundamental biomarker in the care of EGFR-mutant NSCLC
- Tumor and plasma genotyping likely have complementary roles
- Germline EGFR T790M should be suspected in setting of:
  - T790M presence pretreatment
  - High level T790M in plasma
  - Family history of lung cancer in non-smokers