EUROPEAN LUNG CANCER CONFERENCE 2016

NSCLC TARGETED THERAPY AND CIRCULATING BIOMARKERS

Proffered Papers session 3

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DISCLOSURE SLIDE

Commercial Research Support: Janssen and Astellas

Honoraria: Merck, Pfizer, Astra Zeneca, Roche, Boehringer Ingelheim, BMS

Abstracts to discuss

- 58O_PR - Clinical and demographic features that influence EGFR mutation detection in plasma from patients with aNSCLC: The ASSESS experience. **Dr. Normanno *et al***

- 134O_PR - Plasma ctDNA analysis for detection of EGFR T790M mutation in patients with EGFR mutation-positive advanced non-small cell lung cancer (aNSCLC) **Dr. Jenkins *et al*** Dr. Yang presenting

- 135O_PR - Plasma genotyping for predicting benefit from osimertinib in patients with advanced NSCLC **Dr. Oxnard *et al***

The liquid Biopsy: Easy access to the primary and resistance phenotype(s)? Or not?

Abstract 580: ASSESS

- Large (n= 1162) multicentre, non-interventional, non comparative diagnostic study evaluating the utility of ctDNA for EGFR mutation testing in patients with NSCLC in Europe and Japan
- Mandatory plasma and tumor at diagnosis (Stage IIIA/B or recurrent after surgery, chemo naïve

- Objectives:
  - Primary: Concordance between tissue/cytology and blood (plasma) Testing
  - Secondary: EGFR Mutation practices

- Presentation of impact of clinical (disease)/patient characterization the ability to detect mutations in plasma

Primary Results:

ctDNA assessment is feasible

Accuracy of Plasma v Tumour

- Concordance 89%
  - **Sensitivity: 46% (Real World Setting)**
    - Sensitivity in plasma increases with disease burden
  - Specificity: 97%
- Presumably a wide array of technologies used for local practice tissue assessment ?
  - Technology for ctDNA? Digital v Non-Digital

- **Increased sensitivity associated with burden of disease (Intuitive and demonstrated previously)**
- **Also in never Smokers**
  - Tseng JS. Dynamic plasma EGFR mutation status as a predictor of EGFR-TKI efficacy in patients with EGFR-mutant lung adenocarcinoma. J Thorac Oncol 2014;10:603–10.
  - Madic J, Pyrophosphorolysis-activated polymerization detects circulating tumor DNA in metastatic uveal melanoma. Clin Cancer Res 2012;18:3934–41.
- **Intriguing findings in relation to clinical characteristics and/or patient demographics on the ability to detect mutations in plasma**
  - **EGFR Mutation detection in plasma higher in patients aged <65 v >65!!!**
  - Overall higher frequency of EGFR mutations in patients >65 but nevertheless detection in plasma higher in younger patients
  - **A window on disease biology as a function of age**
- **Similar sensitivity and PPV comparing Exon 19 Del v L858R**
- **Reassurance of similar trends in IGNITE**

AURA Studies: Technologies

	PHASE 1	PHASE 2
Plasma Assay	BEAMing	Cobas
Comparator Assay	ddPCR or Cobas	miSEQ NGS
Abstract	1350	1340

Abstract 1340: AURA Phase II Studies Osimertinib

- Plasma ctDNA of T790M
- EGFR Roche Cobas® v2
- T790M: Concordance of Cobas® v2 with **NGS** Methodology (miSeq)
- Sensitivity, Specificity and Concordance
  - Tissue
    - Sensitivity: 88.3%
    - Specificity: 97.3%
    - Concordance: 91%
  - Plasma
    - Sensitivity: 91.5%
    - Specificity: 91.1%
    - Concordance: 91.3%

Cobas® Plasma v Cobas® Tissue

Cobas® plasma performance with Tissue as Reference or "Gold Standard"

	L858R	Del Exon 19	T790M
Sensitivity (PPA)	75.6%	85.1%	61.4%
Specificity (NPA)	98.1%	98%	78%
Concordance (OPA)	90.9%	90%	65.4%

- Objective Response Rates (ORR) similar between tissue and plasma
- Similar figures to those seen in Karlovich *et al* Clin Cancer Research 2016*
- T790M Plasma v Tissue: Reflects Tumour Biology and Molecular Heterogeneity in the setting of resistance
- Issue of Negative T790M in plasma arises

* Karlovich et al. Assessment of EGFR Mutation Status in Matched Plasma and Tumor Tissue of NSCLC Patients from a Phase I Study of Rociletinib (CO-1686). Clin Cancer Res. 2016 Jan 8

135O - Plasma genotyping for predicting benefit from Osimertinib in patients with advanced NSCLC AURA Trial

- Sensitivity of plasma genotyping 82-86% for sensitizing mutations
  - But sensitivity is 70% for T790M

- Reassurance of sensitivity for T790M association with sensitizing mutation
  - But T790M- sensitizing Mutation negative is uninformative

When is a False Positive NOT a False Positive?

- **"False Positive' Rate: 3-4% for Sensitizing Mutations BUT 31% for T790M**
  - **Spotlight shone on these false positives (n=18)**
  - **Orthogonal assessment**
  - **14 confirmed, 4 remained discordant, all with very low allele frequency**
    - **Cut off issue**
  - **No false positives for T790M in 100 cases without any sensitizing mutation in EGFR**
- **High ORR in patients with tumour or plasma T790M**

- **Heterogeneity Issue: Provides strong support for concept of ctDNA representing a gestalt situation**
  - **Biopsy alone misses T790M**

- **False Negative T790M an issue**
  - Reflex to tissue
- **Concept of uninformative plasma test is very helpful:**
  - T790M – Sensitizing +
  - T790M - and Sensitizing – (Status Unknown)
- Proposed Paradigm for use of plasma genotyping: See below

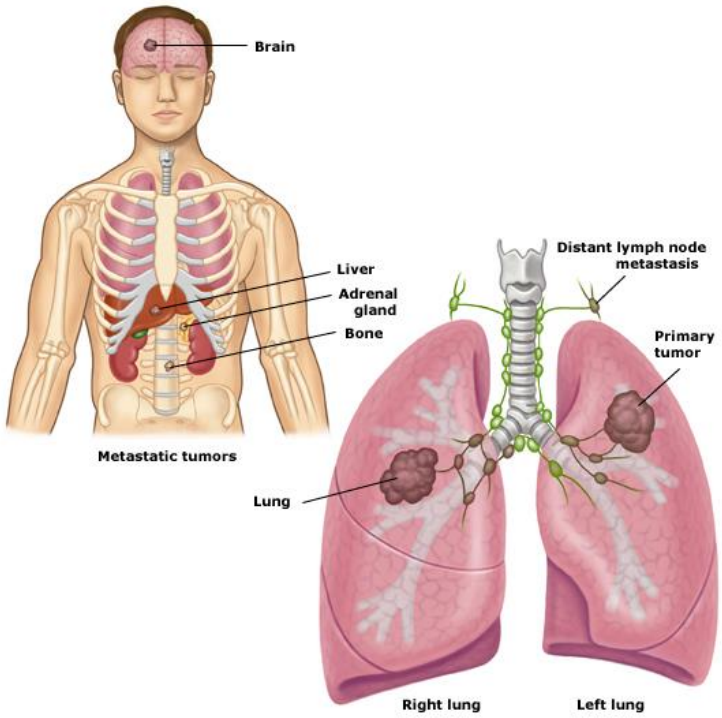
The Liquid Biopsy Centre Stage

Narrow Definition: A blood test that is associated with cytopathological assessment of CTCs

Broader Definition: ctDNA, ctRNA and Exosomes

Appeal of the “Liquid Biopsy”

Diagnosis, Prognosis, Theranostics, Prediction, Biology



Heterogeneity:
Liquid Biopsy as a Gestalt
Accessibility:
Blood, serum, plasma, urine, pleural fluid etc.
Temporal Heterogeneity of Disease:
Serial Access

Tissue V Plasma

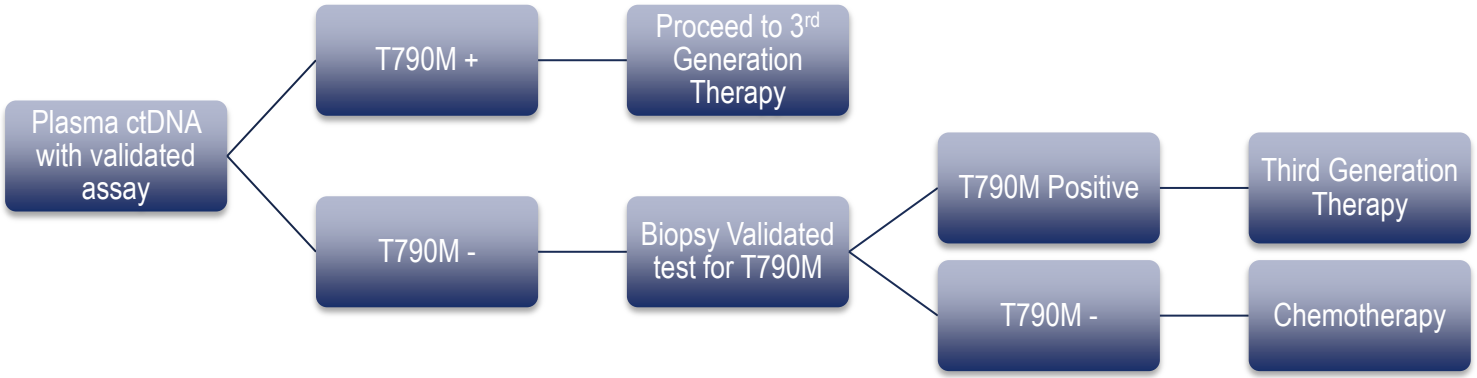
	Tissue Re-biopsy	Plasma ctDNA
Ease of Access/Patient Comfort	X	✔
Serial Access	X	✔
Assessing potential Other Resistance Phenotypes	✔	X
Small Cell Transformation	✔	X
Addresses Heterogeneity	X	✔
Turn Around Time	X	✔

Abstracts: Refine and add granularity to the ctDNA and T790M story

Summary:

- ctDNA feasible and practical at diagnosis and progression
- Especially useful when positive!!
- ctDNA is probably **superior to biopsy alone** as a screen for T790M if followed by a tissue test when T790M- and Sensitizing mutation-
- For T790M many False Positives are True Positives
- Use the sensitizing mutation as a control
- Beware the negative test

Testing Paradigm for acquired resistance to EGFR-TKI

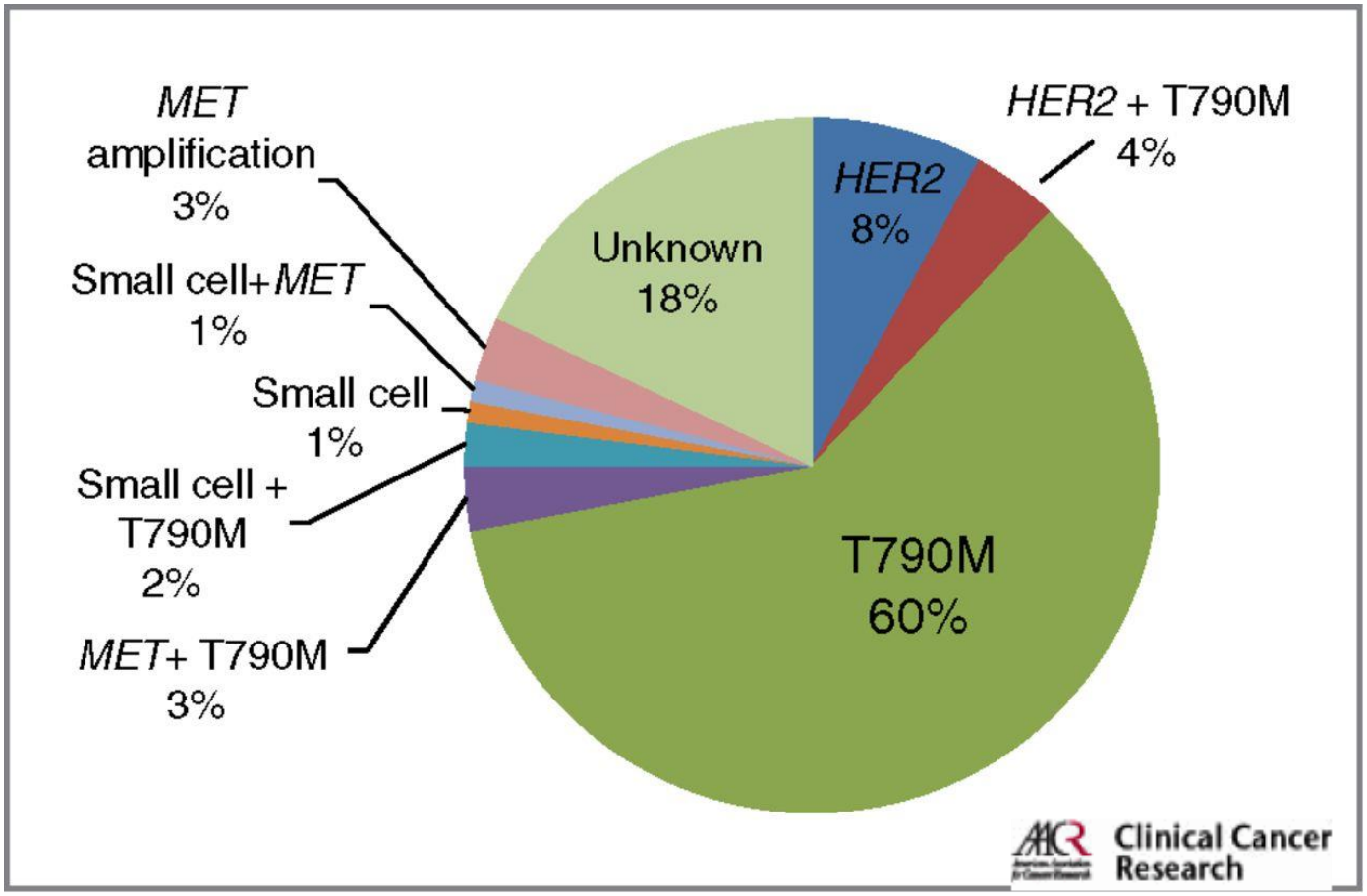


Tissue V Plasma

	Tissue Re-biopsy	Plasma ctDNA
Ease of Access/Patient Comfort	X	✔
Serial Access	X	✔
Phenotypes		
Small Cell Transformation	✔	X
Addresses Heterogeneity	X	✔
Turn Around Time	X	✔

We need to use plasma and tissue together

The relative frequencies of the various mechanisms of acquired resistance.



Yu H A et al. Clin Cancer Res 2013;19:2240-2247

Unanswered Questions

- Technology
  - Non Digital: Cobas®, Therascreen™ ARMS
  - Digital: Droplet Digital PCR, BEAMing
  - NGS
- Focus:
  - T790M burden to monitor disease?
  - Allelle Frequency
  - EGFR sensitizing and resistance mutations only?
  - How to integrate other resistance candidates: Small Cell, PIK3CA, Her2 Amp, IGF1R, Met Amp
  - Resistance to third Generation TKIs? Role of assessment for C797S
  - Assessing T790M C797S cis and trans alleles