Update on Regulation of Liquid Biopsy

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Outline

- Background
  - Liquid Biopsy as Companion Diagnostics
    - Recent FDA approval
    - Assay Performance Considerations
- NGS Oncology Panels (patients diagnosed with cancer)

Liquid Biopsy

- Circulating tumor DNA (ctDNA) or cell-free tumor DNA (cfDNA) in plasma
- Testing for tumor DNA using a blood sample
  - ctDNA / cfDNA shed from tumors into the blood
  - non-invasive method

  Incorporated into numerous drug development programs

Liquid Biopsy
FDA-AACR Workshop

- FDA-AACR Liquid Biopsies in Oncology Drug and Device Development Public Workshop: July 19, 2016
  - http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides

Outline

- Background

  - Liquid Biopsy as Companion Diagnostics

    Recent FDA approval

    Assay Performance Considerations

- NGS Oncology Panels

FDA Approval of a Liquid Biopsy Test

cobas EGFR Mutation Test v2 (using plasma specimens)

Roche Molecular Systems, Inc.

- First "liquid biopsy test" approved for NSCLC
- Approved on June 1, 2016, as a companion diagnostic to identify patients eligible for treatment with Tarceva (erlotinib).
- Approved on September 28, 2016, as a companion diagnostic to identify patients eligible for treatment with Tagrisso (osimertinib).
- Test was previously approved for same indication using FFPE tissue specimens.

Analytical Performance

- Test = Specimen to Result (validate all steps)
- Pre-analytic steps are part of assay
  - e.g., plasma processing, cfDNA isolation
- Validation with the intended specimen type, using clinical specimens from the intended population
- All studies should follow protocol in labeling
- Studies should demonstrate robustness at clinical cut-off, as needed
- Analytical validation precedes clinical validation

Validation Studies

Analytical Performance Studies

- Limit of Detection
- Precision
- Accuracy
- Lot Interchangeability
- Interference
- Contrived Sample Commutability*
- Reproducibility
- Comparator Method Validation*
- Robustness
- Stability

Practical Considerations for Liquid Biopsy (LB) Tests

- Pre-analytical: Every step from blood draw, plasma processing, to storage can greatly affect sample quality and ctDNA yield.
- Analytical validation issues: Clinical specimens representing the intended use population may be limiting
- Lack of reference method / standards
- LB to Tissue concordance: Relevance to clinical outcomes, not just analytical status, should be demonstrated

Procured LB ↔ Tissue?

- Key factors impacting circulating vs. tissue status (e.g., tumor type, stage) observed in cohorts outside of therapeutic trials

- Potential inflated concordance if “easier” distribution and/or frequency of analytes, in specimen cohort

Clinical Validation

- A commercial drug and companion diagnostic test (denoted as CDx) are validated via pivotal clinical trial(s) (e.g. phase III clinical trial)
  - Drug and CDx are validated in the same pivotal clinical trial and CDx is used for determining patient marker status at patient enrollment *[recommended approach]*
  - Drug and CDx are validated in the same pivotal clinical trial. However a clinical trial assay (denoted as CTA) is used for patient enrollment. Enrolled patient samples based on CTA are retested by CDx i.e. bridging study
  - Drug and CDx are not validated in the same pivotal clinical trial (some follow-on companion diagnostic devices)

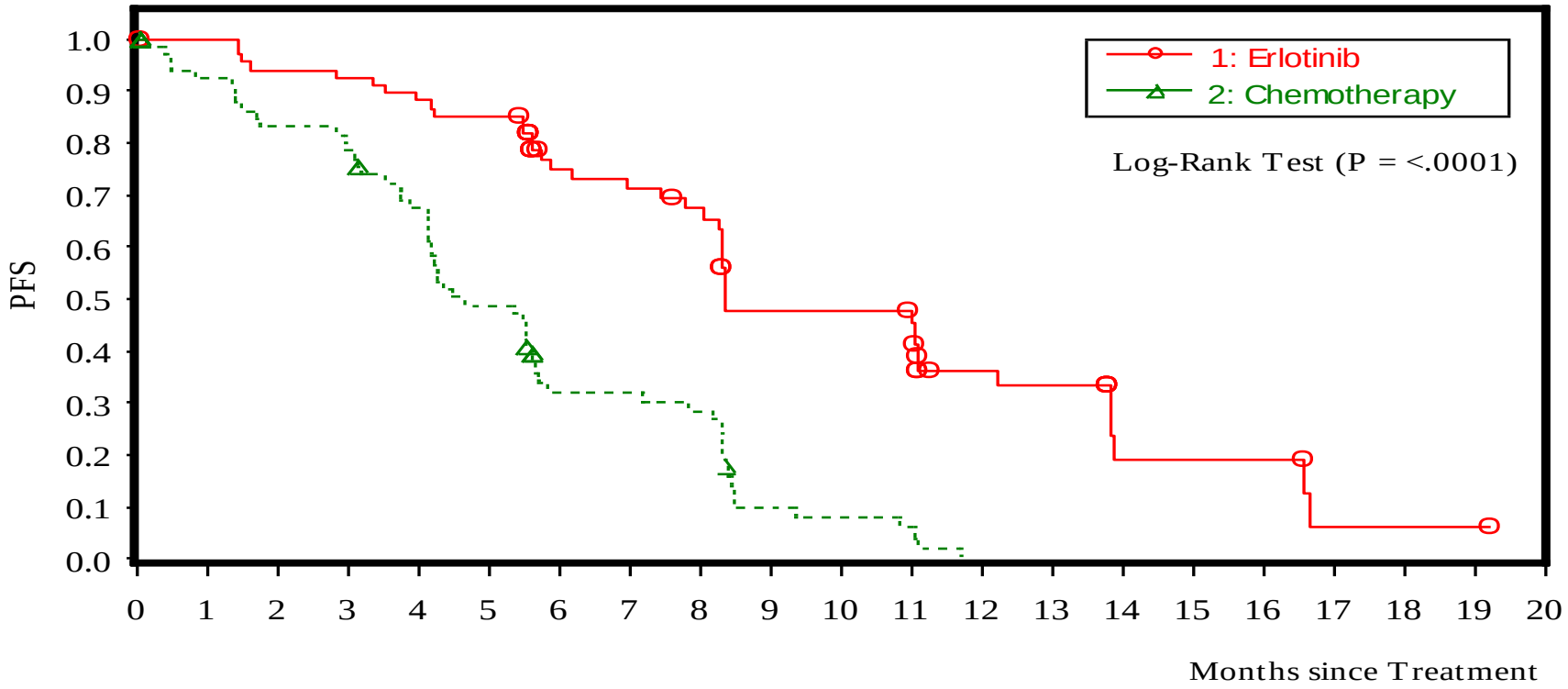
Clinical Validation: P150047

Cobas EGFR mutation test using plasma for Tarceva

Clinical Performance Studies

- Clinical Bridging Study
- Correlation between Plasma and Tissue
  - ENSURE Phase III study of erlotinib vs. cisplatin in combination with gemcitabine as first-line therapy for stage IIIb/IV NSCLC
  - Patients were enrolled based on detection of EGFR activating mutations (exon 19 deletions or L858R mutations) in FFPE tissue specimens by the cobas EGFR Tissue Test v1
  - Available plasma samples evaluated and bridged to FFPET

Clinical Bridging Study: Kaplan-Meier Plot of PFS by treatment for patients with mutation detected by the cobas® EGFR Test in both plasma and tissue



N at Risk

1	68	67	63	62	59	57	40	38	35	23	23	22	12	11	4	4	4	1	1	1	0
2	69	60	54	51	43	31	18	18	16	5	4	3	0								

Correlation between Plasma and Tissue: Agreement between Plasma Test & Tissue Test for Detection of EGFR Mutation (with 2.0 mL Plasma Sample)

		cobas® Tissue Test v1		
		EGFR+ (MD)	**EGFR(-) (NMD)**	**Total**
cobas® Plasma Test v2	**EGFR+ (MD)**	161	4	165
	EGFR(-) (NMD)	49	217	266
	Total	210	221	431
With only Valid Result	**PPA (95% CI)**	**76.7%** (70.5%, 81.9%)		
	NPA (95% CI)	**98.2%** (95.4%, 99.3%)		

Clinical Validation

Cobas EGFR mutation test using plasma for Tarceva

- Clinical Bridging Study
- PFS benefit in patients who are tissue positive whether plasma positive or negative
- Observed drug efficacy of tissue test: HR 0.34 (0.21, 0.54)
- Observed drug efficacy of plasma test: HR 0.29 (0.19, 0.45)
- Correlation between Plasma and Tissue
- High NPA for exon 19 deletions or L858R mutations in plasma compared to tissue.
- In 76.7% of tissue-positive cases, plasma was also positive
- In 98.2% of tissue-negative cases, plasma was also negative

P150047 Approval June 1st

- "Reflex" companion diagnostic - Patients with positive test results are eligible for treatment with TARCEVA. Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.

Intended Use – P150047 Approval June 1st

The cobas® EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in non-small cell lung cancer (NSCLC) patients. Defined EGFR mutations are detected using DNA isolated from formalin-fixed paraffin-embedded tumor tissue (FFPET) or circulating-free tumor DNA (cfDNA) from plasma derived from EDTA anti-coagulated peripheral whole blood.

The test is indicated as a companion diagnostic to aid in selecting NSCLC patients for treatment with the targeted therapies listed in Table 1 below in accordance with the approved therapeutic product labeling:

Table 1

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	Exon 19 deletions and L858R	Exon 19 deletions and L858R
TAGRISSO™ (osimertinib)	T790M	

Patients with positive cobas® EGFR Mutation Test v2 test results using plasma specimens for the presence of EGFR exon 19 deletions or L858R mutations are eligible for treatment with TARCEVA® (erlotinib). **Patients who are negative for these mutations by this test should be reflexed to routine biopsy and testing for EGFR mutations with the FFPET sample type.**

Clinical Validation: P150044

Cobas EGFR mutation test using plasma for Tagrisso

Clinical Performance Studies

- Clinical Bridging Study
- Correlation between Plasma and Tissue
  - Patient specimen cohorts from two AstraZeneca clinical studies: The AURA1 Ext Phase 1 study and the AURA2 Phase II study enrolled patients with advanced or metastatic NSCLC who had progressed following an EGFR-TKI
  - Patients were enrolled based on T790M substitution mutation result in FFPE tissue specimens by the cobas EGFR Tissue Test v1
  - Available plasma samples evaluated and bridged to FFPET

Clinical Validation

Cobas EGFR mutation test using plasma for Tagrisso

- **Clinical Bridging Study**
  - The ORR as determined by the BICR in the AURA2 study was 61% (128/210) (T790M+ by the cobas® EGFR Tissue Test v1).
  - Among the patients with evidence of T790M mutation by the EGFR Plasma Test v2 who were enrolled in AURA2, the ORR was also 61% (72/117).
  - Conclusion: In patients with a known T790M substitution mutation in a FFPET specimen, which also had a T790M positive plasma result, had clinical benefit similar to those treated with TAGRISSO™ (osimertinib) based on a tissue result.
  - Since patients with a "tissue negative/plasma positive" result for T790M were not enrolled in AURA2, the response rate in this population is unknown.

Correlation between Plasma and Tissue: Agreement between Plasma Test & Tissue Test for Detection of EGFR T790M Mutation (with 2.0 mL Plasma Sample)

		cobas® Tissue Test v1		
		T790M+	**T790M(-)**	**Total**
cobas® Plasma Test v2	**T790M+**	131	**22**	153
	T790M(-)	92	89	181
	Total	223	111	334
With only Valid Result	**PPA (95% CI)**	**58.7%** (52.2%, 65.0%)		
	NPA (95% CI)	**80.2%** (71.8%, 86.5%)		

LB ↔ Tissue Discordance

- LB-/Tissue+ → reflex to tissue
- LB+/Tissue- → less likely to be referred, underestimated in tissue+ trials?
- Impact of selecting altered intended use population, especially LB+/tissue-

Clinical Validation

Cobas EGFR mutation test using plasma for Tagrisso

- Correlation between Plasma and Tissue
- In 58% of tissue-positive cases, plasma was also positive
- In 80% of tissue-negative cases, plasma was also negative
- Poor Agreement led to the following drug labeling implications:
- Confirm the presence of a T790M EGFR mutation in tumor or, in the absence of tumor, plasma specimens prior to initiation of treatment with TAGRISSO
- Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained.
- If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing.

Intended Use – P150044 Approval Sep 28th

*The efficacy of TAGRISSO™ (osimertinib) has not been established in the EGFR T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore **testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained**.

Drug safety and efficacy have not been established for the following EGFR mutations listed in Table 2 below that are also detected by the **cobas**® EGFR Mutation Test v2:

Table 2

Drug	FFPET	Plasma
TARCEVA® (erlotinib)	G719X, exon 20 insertions, T790M, S768I and L861Q	G719X, exon 20 insertions, T790M, S768I and L861Q
TAGRISSO™ osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q

Recommendation for Postmarketing Commitments

- Since there is some uncertainty regarding the clinical outcomes in patients selected for osimertinib treatment solely using the EGFR Plasma Test v2
  - FDA requested that the data on overall response rate with osimertinib from one or more "real-world" cohorts who have been selected for treatment on the basis of an EGFR T790M mutation positive result from plasma (ctDNA) using the cobas® EGFR Mutation Test v2 be submitted and
  - potentially support further modification of the labeling regarding use of the EGFR Plasma Test

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NGS Oncology Panels

Increasingly employed for use in oncology applications

One Test, Multiple Variants/Allele Representation, Different Genes, Multiple Indications, Multiple Drugs

- Intended to be used as companion diagnostic devices for the clinical management of previously diagnosed oncology patients, and
- Alternative therapeutic management for patients who have already been considered for all appropriate therapies

Current Thinking

- Entire test system validation
  - From specimen collection & sample preparation to the steps in the sequencing pipeline and the generation of a result report
- Analytical Validation: Representative variant approach should cover all relevant variant types with consideration to size, genomic context, etc.
- Markers intended to guide therapy with a corresponding drug – Analytical and clinical validation required.
- Validation for a follow-on claim should be comparable to that of the original companion diagnostic
- If clinical validity of mutations from cell free DNA to select patients for therapy has not yet been demonstrated,
  - clinical outcome data to support the Companion Diagnostic claims for these mutations is needed.
- Appropriate validation for modifications to an approved panel

Resources

- FDA website on companion diagnostics: http://www.fda.gov/companiondiagnostics
- FDA companion diagnostic guidance: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf
- FDA-AACR: Liquid Biopsies in Oncology Drug and Device Development (7/19/2016): http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/pages/fda-aacr-liquid-biopsies-in-oncology-drug-and-device-development.aspx#bypslides
- FDA Public Workshop: NGS-Based Oncology Panels (2/25/2016): http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm480046.htm
- cobas EGFR Mutation Test v2 – SSED
- http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150047B.pdf
- http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150044B.pdf

- FDA Draft guidance on Principles for Codevelopment of an In Vitro Companion diagnostic device with a therapeutic product.
- http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm510824.pdf

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Questions?

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