Clinical utility of comprehensive cell-free DNA (cfDNA) analysis to identify genomic biomarkers in newly diagnosed metastatic non-small cell lung cancer (mNSCLC)

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Disclosures

- Advisory board: Nektar Therapeutics, AstraZeneca, Arrys Therapeutics, Merck, LOXO Oncology, Araxes Pharma, F Hoffman-La Roche, Janssen Research Foundation, Bristol-Myers Squibb, Clovis Oncology, Eli Lilly, Novartis, Takeda, Abbvie, TRM Oncology, Tesaro, Exelixis, Nektar, Gritstone, Arrys, Guardant Health.
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Background

- Clinical practice guidelines advocate for genotyping in all patients with newly diagnosed metastatic non-small cell lung cancer (mNSCLC)
- There is general consensus across guidelines that alterations in up to 7 genes need to be assessed to appropriately guide treatment with FDA approved therapies or therapies currently in development
  - *EGFR* mutations, *ALK* fusions, *ROS1* fusions, *BRAF* V600E mutation, *RET* fusions, *MET* amplification and *MET* exon 14 skipping variants, and *ERBB2* (HER2) mutations
- Real-world studies of clinical practice have demonstrated that only 8% of patients with mNSCLC are tested for all of the guideline-recommended biomarkers[1]
- We aimed to demonstrate the non-inferiority of comprehensive cfDNA, relative to physician discretion standard of care (SOC) tissue genotyping, to identify guideline-recommended genomic biomarkers in patients with newly diagnosed mNSCLC

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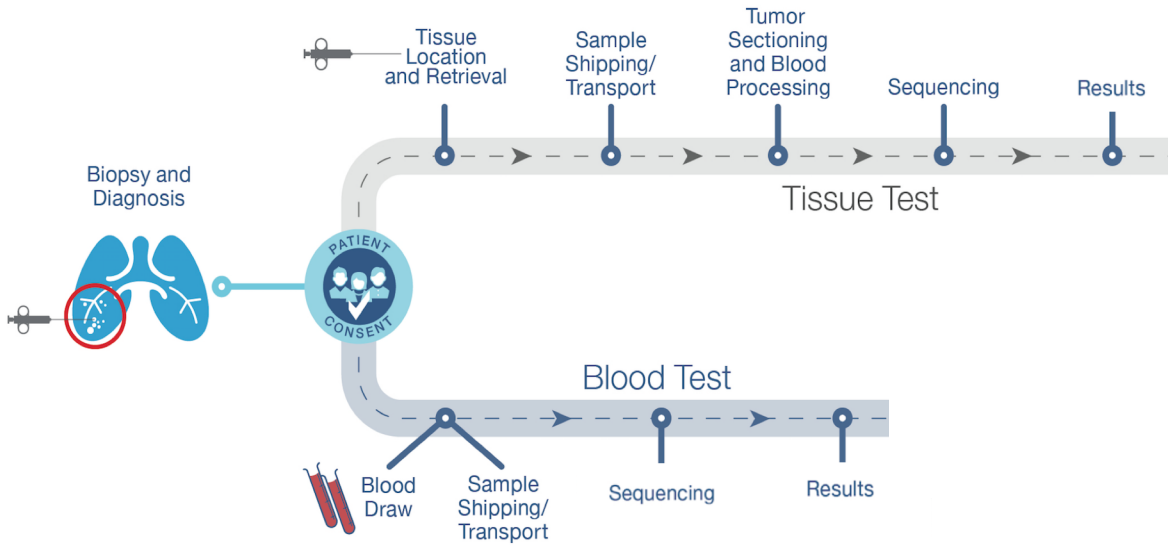
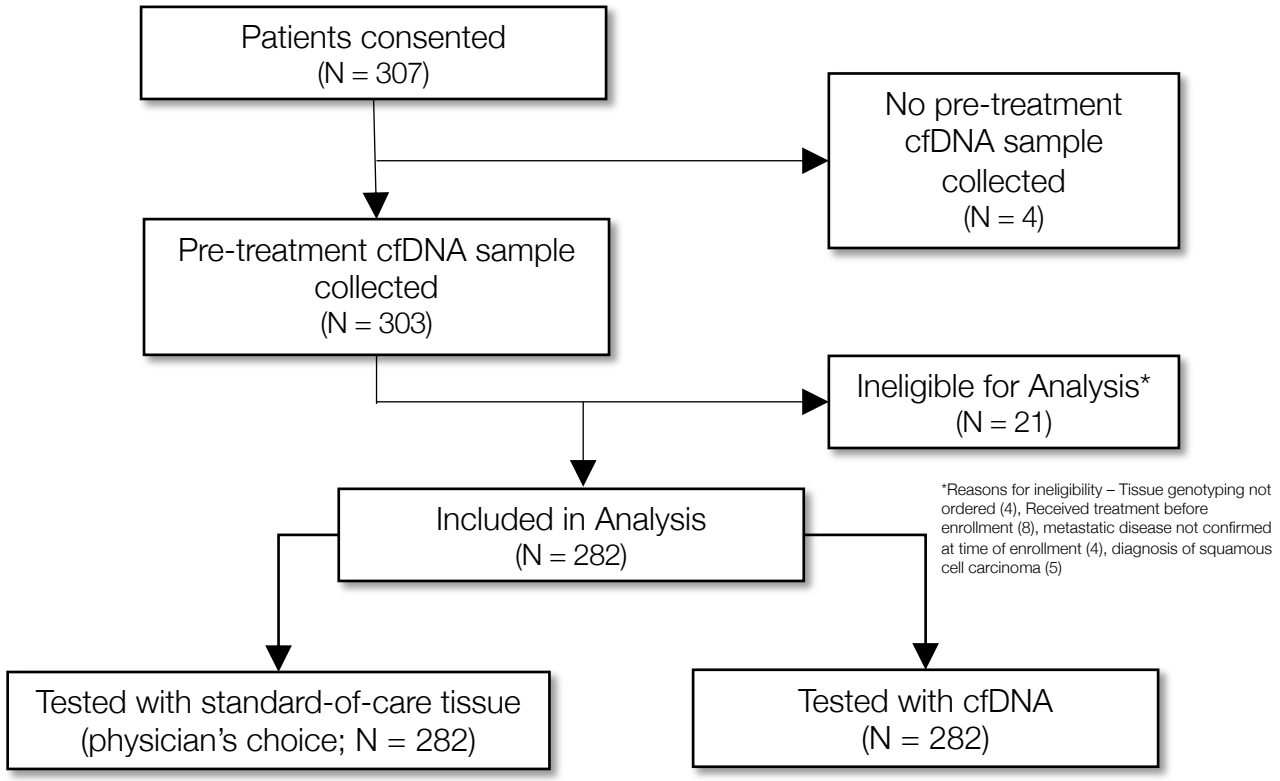
[1]Gutierrez, et al. 2017. Clinical Lung Cancer

Methods

- Between July 2016 and April 2018, patients with newly diagnosed non-squamous mNSCLC, undergoing physician discretion SOC tissue genotyping were prospectively recruited from 28 North American centers
- Patients underwent cfDNA testing utilizing a validated clinically available assay



Study Cohort



Primary Objective

- Detection of guideline recommended biomarkers

Clinical follow-up at one year or at disease progression

		Number	Percentage (%)
Gender	Female	153	54.3
	Male	129	45.7
Median Age at diagnosis (range) in years		69 (26 – 100)	
Race	Asian	17	6.0
	Black or African American	18	6.4
	Native Hawaiian or other Pacific Islander	1	0.4
	White	231	81.9
	Other	8	2.8
	Unknown	7	2.5
Ethnicity	Hispanic	23	8.2
	Non-Hispanic	259	91.8
ECOG status at enrollment	0	71	25.2
	1	151	53.5
	2	36	12.8
	3	12	4.3
	Unknown/missing	12	4.3
History of prior chemotherapy for early stage NSCLC	Yes	45	16.0
	No	237	84.0
Stage of NSCLC at enrollment	IIIb	7	2.5
	IV	275	97.5
Type of NSCLC at enrollment	Adenocarcinoma	271	96.1
	Large cell carcinoma	5	1.8
	Other*	6	2.2
Smoking History	Non-smoker	61	21.4
	Previous Smoker	153	54.4
	Current Smoker	61	21.7
	Unknown	7	2.5

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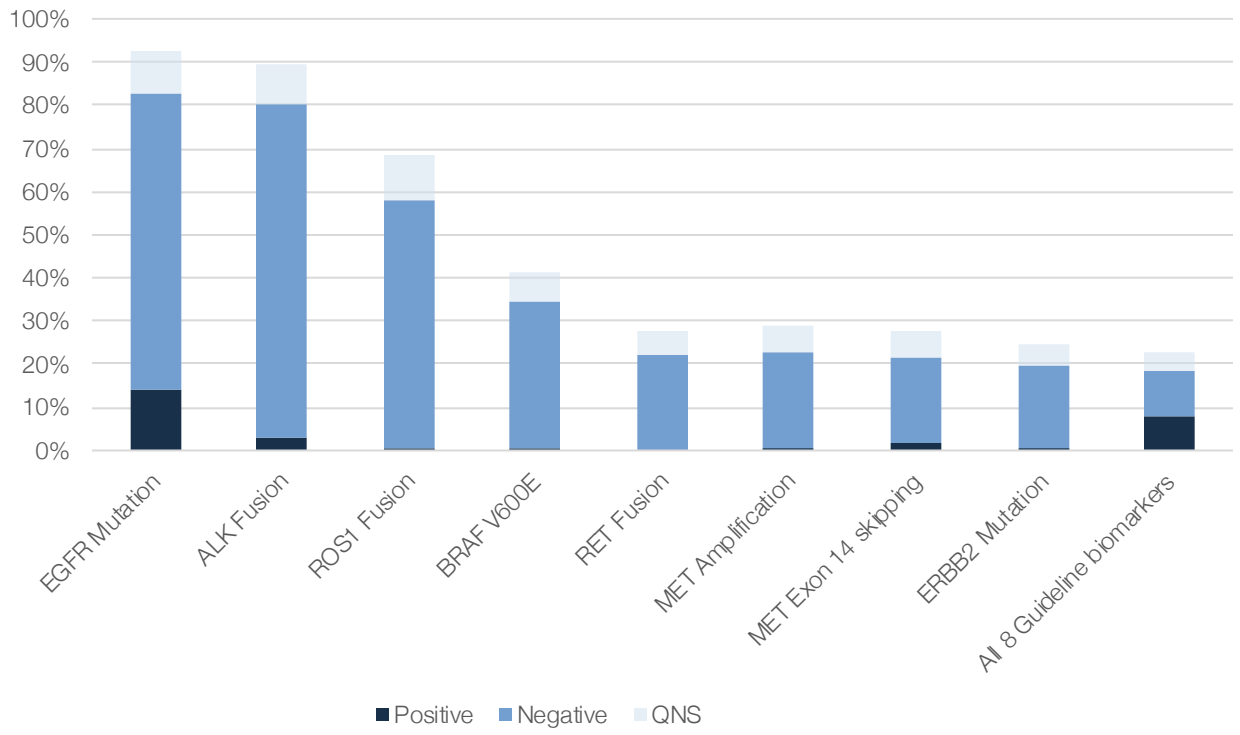
Results – Guideline Complete Genomic Testing for all 8 Biomarkers

- cfDNA testing results in significantly more patients with guideline complete genotyping ($p<0.0001$)
  - 95% (268/282) had guideline complete testing
- 18% (51/282) of patients had guideline complete tissue genotyping
  - 35/51 had comprehensive NGS
- 85% of patients underwent sequential tissue testing of some biomarkers
  - Most completed tissue testing for *EGFR* mutations (83%), *ALK* fusions (80%), and *ROS1* fusions (57%)
  - Testing for *BRAF* V600E mutation (34%), *RET* fusions (22%), *MET* amplifications (24%) and Exon 14 skipping alterations (24%), and *ERBB2* (HER2) mutations (23%) was rare

Percentage of patients with completed tissue assessment for the guideline-recommended biomarkers



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Results – cfDNA Biomarker Detection Rate

- Primary endpoint of cfDNA non-inferiority was met, with physician discretion SOC tissue genotyping identifying 60 patients (21.3%) with a guideline recommended biomarker and cfDNA identifying 77 patients (27.3%) ($p<0.0001$ for non-inferiority)

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
cfDNA	Positive	48	29	**77**
	Negative	12	193	205
	Total	**60**	222	282

- Biomarker positive patients increased from 60 using tissue alone to 89 using tissue + cfDNA
  - cfDNA found biomarkers in patients with negative (N = 7), not assessed (N = 16), or insufficient tissue results (QNS; N = 6)
- When restricted to the 64 patients with guideline complete tissue genotyping attempted (N = 13) or completed (N = 51), tissue and cfDNA each identified 22 patients with a guideline recommended biomarker (19 concordant)
- cfDNA results were returned significantly faster than tissue results (median 9 vs 15 days; $p<0.0001$)

Results – cfDNA Concordance and Positive Predictive Value

- For genes with FDA-approved targeted therapy (*EGFR*, *ALK*, *ROS1*, and *BRAF*) concordance of tissue and cfDNA results was >98.2%
- *EGFR, ALK*, and *BRAF* had 100% positive predictive value for cfDNA versus tissue (34/34)
- Modifications to the cfDNA bioinformatics pipeline, including in fusion calling and discrimination of focal copy number amplification
  - Re-analysis of samples improved *ALK* fusion sensitivity

FDA Approved Targets		Tissue +	Tissue -	Tissue Not Assessed/ QNS	Total		
EGFR Exon 19 del	cfDNA+	18	0	1	19	Sensitivity	**81.8%**
	cfDNA-	4	201	44	249	PPV	**100.0%**
	cfDNA cancelled / TND	0	11	3	14	Specificity	100.0%
	Total	22	212	48	282	NPV	98.0%
						Concordance	98.2%
EGFR L858R	cfDNA+	9	0	2	11	Sensitivity	**90.0%**
	cfDNA-	1	213	43	257	PPV	**100.0%**
	cfDNA cancelled / TND	0	11	3	14	Specificity	100.0%
	Total	10	224	48	282	NPV	99.5%
						Concordance	99.6%
ALK Fusion (ORIGINAL)	cfDNA+	5	0	1	6	Sensitivity	**62.5%**
	cfDNA-	3	207	52	262	PPV	**100.0%**
	cfDNA cancelled / TND	1	11	2	14	Specificity	100.0%
	Total	9	218	55	282	NPV	98.6%
						Concordance	98.6%
ALK Fusion (Re-analysis)	cfDNA+	6	0	1	7	Sensitivity	75.0%
	cfDNA-	2	207	52	261	PPV	**100.0%**
	cfDNA cancelled / TND	1	11	2	14	Specificity	100.0%
	Total	9	218	55	282	NPV	99.0%
						Concordance	99.1%
ROS1 Fusion	cfDNA+	0	0	0	0	Sensitivity	-
	cfDNA-	2	151	115	268	PPV	-
	cfDNA cancelled / TND	0	8	6	14	Specificity	100.0%
	Total	2	159	121	282	NPV	98.7%
						Concordance	98.7%
BRAF V600E mutation	cfDNA+	2	0	0	2	Sensitivity	**100.0%**
	cfDNA-	0	90	176	266	PPV	**100.0%**
	cfDNA cancelled / TND	0	5	9	14	Specificity	100.0%
	Total	2	95	167	282	NPV	100.0%
						Concordance	100.0%

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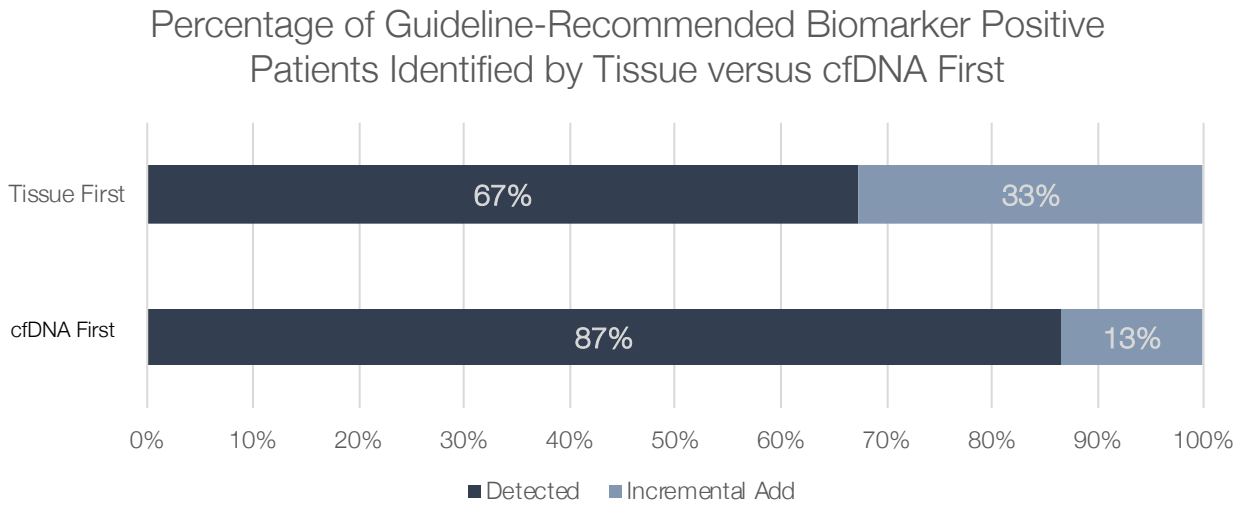
TND = tumor not detected

Results – cfDNA Testing versus Tissue Testing First

- Utilizing tissue testing first would have identified 67% of the 89 patients with a guideline-recommended biomarker
  - 33% of patients identified on reflex cfDNA testing
- If cfDNA was the first genomic testing modality, significantly more patients would be identified (87%) ($p<0.0001$)
  - 13% of patients identified on reflex tissue testing



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Conclusions

- This prospective study demonstrates that utilization of a validated, comprehensive, and sensitive cfDNA test in newly diagnosed mNSCLC patients successfully identifies guideline recommended biomarkers at a rate similar to physician discretion standard of care tissue testing
  - Concordance and PPV between tissue testing and cfDNA testing was high
  - Tissue sequential testing resulted in comprehensive genotyping in only a minority of patients (5.7%)

- cfDNA results were returned significantly faster than tissue results ($p<0.0001$)

- These results suggest that initial biomarker assessment using cfDNA rather than tissue ("blood first"), improves biomarker discovery rate, turn-around time, and increases the number of patients with newly diagnosed mNSCLC who receive guideline complete biomarker testing

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