Molecular risk stratification is independent of EGFR mutation status in identifying early-stage NSCLC patients at risk for recurrence and likely to benefit from adjuvant chemotherapy

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Background

Adjuvant chemotherapy recommendations for early-stage non-small-cell lung cancer (NSCLC) depend on identification of patients at high risk of recurrence. Current National Comprehensive Cancer Network (NCCN) guidelines, for example, recommend using adjuvant platinum-doublet chemotherapy for stage IB-IIA patients *only* when considered by their doctors to be at "high risk," although only *possible examples* of *non-validated* clinicopathologic high-risk criteria are provided.[1]

Recently early results from the ADAURA trial demonstrated a clear disease-free survival benefit in patients with stage II and IIIA EGFR mutant tumors treated with adjuvant osimertinib.[2]

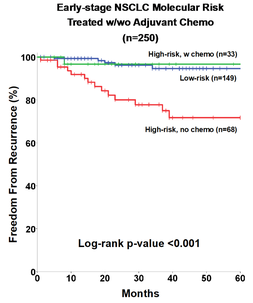
An internationally validated, 14-gene expression assay has been shown to better stratify survival based on molecular risk in non-squamous NSCLC than either conventional TNM staging or NCCN high-risk criteria.[3-6] Furthermore, we have previously shown in 100 prospectively studied early-stage patients[7] that molecular high-risk was predictive of markedly improved disease-free survival with adjuvant chemotherapy.

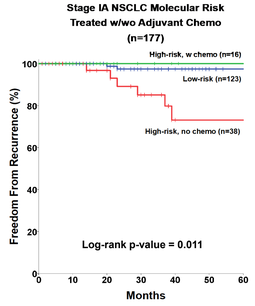
The relationship between 14-gene molecular risk stratification and EGFR mutation status has not yet been reported.

Methods

- Single institution study of 250 consecutive patients with stage I-IIA non-squamous NSCLC, following R0 resection
- Real-time tumor molecular testing by the 14-gene assay was performed in a CLIA lab to inform adjuvant chemotherapy decisions postoperatively. The test identifies patients at low-, intermediate- or high-risk of death within 5 years of surgery. For this study, intermediate- and high-risk patients were combined as one high-risk group.
- The 14-Gene Assay utilizes quantitative PCR analysis of formalin-fixed, paraffin-embedded tissues and determines the expression levels of 11 cancer-related target genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, and WNT3A) and three reference genes (ESD, TBP, YAP1). An algorithm is then used to generate a low-, intermediate- or high-risk designation.
- EGFR mutation analysis by NGS was available on 150 patients.
- Platinum-doublet adjuvant chemotherapy was recommended for molecular high-risk patients without consideration of EGFR mutation. None of the molecular low-risk patients received adjuvant chemotherapy.
- Disease Free Survival (DFS) and Freedom From Recurrence (FFR) were estimated using Kaplan-Meier analysis and compared using a log-rank test.

Results





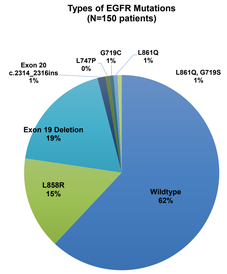


Table 3: Disease-Free Survival and Freedom From Recurrence based on molecular risk and EGFR mutation testing

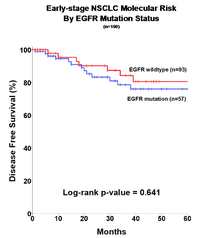
	Low-risk	High-risk no chemo	High-risk w chemo	Log-rank p-value
All Patients (N=250)				
5-year DFS rate	88.0%	65.7%	96.7%	<0.001
5-year FFR rate	94.6%	71.7%	96.7%	<0.001
Patients with Mutation Testing (N=150)				
5-year DFS rate	88.5%	54.4%	100%	<0.001
5-year FFR rate	91.1%	60.7%	100%	<0.001
EGFR Mutants (N=57)				
5-year DFS rate	91.2%	54.4%	100%	0.013
5-year FFR rate	91.2%	54.4%	100%	0.043
EGFR Wildtype (N=93)				
5-year DFS rate	85.5%	54.7%	100%	0.003
5-year FFR rate	92.0%	65.2%	100%	0.009

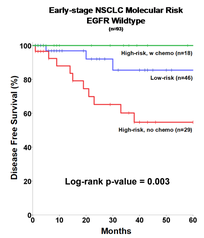
Table 1: Clinical characteristics and molecular risk stratification all Stage IA, IB, IIA

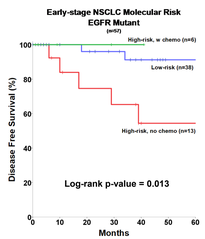
	All Patients	Molecular Low Risk	Molecular High Risk	P-value
Number of Patients	250	149 (60%)	101 (40%)	
Mean Age (years ± SE)	68.5 ± 0.6	68.8 ± 0.8	68.1 ± 1.0	0.5991
Sex				0.2301
Men	88 (35%)	48 (32%)	40 (40%)	
Women	162 (65%)	101 (68%)	61 (60%)	
Asian	46 (18%)	27 (18%)	19 (19%)	0.8875
History of smoking	162 (65%)	89 (60%)	73 (72%)	0.0416
Pathologic Stage				<0.0001
Stage IA	177 (71%)	123 (83%)	54 (53%)	
Stage IB	52 (21%)	17 (11%)	35 (35%)	
Stage IIA	21 (10%)	9 (6%)	12 (12%)	
EGFR Mutation Status*				0.0288
EGFR Wildtype	93 (62%)	45 (54%)	48 (72%)	
EGFR Mutation	57 (38%)	38 (46%)	19 (28%)	
Received adjuvant chemo	33 (13%)	0 (0%)	33 (33%)	
Median follow up (months ± SE)	29 ± 1.7	28 ± 2.0	33 ± 2.8	0.2028

Table 2: Clinical characteristics and EGFR mutation for 150 patients

	All Patients (n=150)	EGFR wildtype (n=93)	EGFR mutants (n=57)	P-value
Number of Patients	150	93 (62%)	57 (38%)	
Mean Age (years ± SE)	67.8 ± 0.8	68.9 ± 1.1	66.3 ± 1.3	0.0958
Sex				0.4839
Men	45 (30%)	26 (28%)	19 (33%)	
Women	105 (70%)	67 (72%)	38 (67%)	
Asian	29 (19%)	7 (8%)	22 (39%)	<0.0001
History of smoking	95 (63%)	71 (76%)	24 (42%)	<0.0001
Pathologic Stage				0.6307
Stage IA	101 (67%)	62 (67%)	39 (68%)	
Stage IB	34 (23%)	20 (22%)	14 (25%)	
Stage IIA	15 (10%)	11 (12%)	4 (7%)	
Molecular Risk				0.0392
Low-risk	84 (56%)	46 (49%)	38 (67%)	
High-risk	66 (44%)	47 (51%)	19 (33%)	
Median follow up (months ± SE)	30 ± 2.1	27 ± 2.7	36 ± 3.3	0.3120
5-year DFS rate	77.8%	75.9%	80.6%	0.641







Conclusions

- In this 250-patient prospective cohort, Molecular High Risk in early-stage non-squamous NSCLC patients (defined as receiving either a 14-Gene high- or intermediate-risk score) was predictive of improved freedom from recurrence and disease-free survival with adjuvant chemotherapy, *even in stage IA*.
- EGFR mutation status did not predict clinical outcomes and therefore is not expected to be an effective tool for identifying stage I-IIA patients in need of adjuvant intervention.
- The 14-Gene Assay is independent of EGFR mutation status, and effectively segregates high- and low-risk patients among those with both EGFR wildtype and mutant tumors.
- 65% of patient with an EGFR mutation were molecular low-risk and unlikely to recur; these patients would likely be overtreated with expensive, morbid, long-term TKI therapy
- Combining molecular risk stratification with EGFR mutation status to make treatment decisions may better inform adjuvant therapy recommendations, improve survival and limit treatment-related morbidity

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