AIM-HIGH Trial (Adjuvant Intervention in Molecular HIGH-risk patients)

A Randomized Prospective Trial of Adjuvant Chemotherapy in Patients with Completely Resected Stage I and IIA Non-Squamous Non-Small Cell Lung Cancer Identified as High or Intermediate Risk by a 14-Gene Prognostic Assay

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Background

Very Large Unmet Need: Stage IA-IIA Non-Small-Cell Lung Cancer

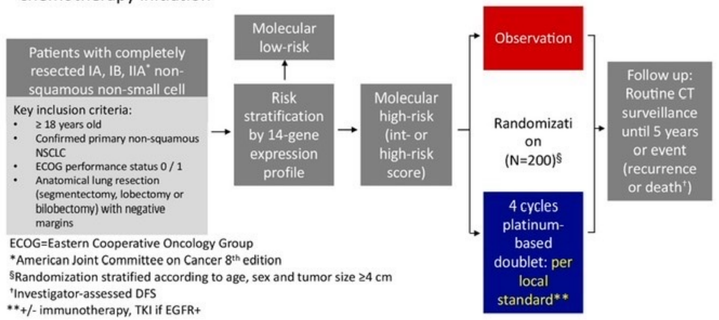
- **5-year disease-free survival (DFS) remains <65% for stage IA, lower in IB & IIA**
- **>10,000 Americans and >100,000 patients worldwide die each year despite this early diagnosis**
- **Many of them can be saved: Recurrences largely due to occult micrometastasis, known to respond to adjuvant therapy in stages IIB & III**
- **Adjuvant therapy never recommended for stage IA, often deferred in IB and IIA**
  – because truly high-risk patients must first be differentiated from patients cured by surgery alone

14-Gene Lung Cancer Assay

- Gene expression profile for non-squamous NSCLC **validated in >1,500 patients** in independent, blinded international studies
  - identified patients at high risk of early death better than conventional criteria, including NCCN guidelines (*Lancet* 2012;379:823. *JAMA* 2012;308:1629)
- **Prospectively validated for prognostic efficacy with preliminary evidence of predictive efficacy**
  - cohort of 250 patients
  - Non-randomized data showed improvement in DFS with adjuvant chemotherapy for High-Risk Patients. *(Clinical Lung Cancer* 2021;22:587)

AIM-HIGH Trial – Study Design

- **Prospective, randomized, international trial (45 centers)**
- **Conservative assumption in sample size determination**: assumed efficacy similar to seminal studies (detected benefit only in **stages IIB and III with HR ~0.65**)
- **Prespecified Interim Analysis:**
  Accounted for potential to see the much higher impact of adjuvant therapy on low-burden metastasis in **stages IA – IIA**, as reflected in preliminary, non-randomized study (DFS **HR ~0.20**)
- **Modified Intent-to-Treat (mITT):** Continued to meet eligibility criteria at the time of chemotherapy initiation



ECOG=Eastern Cooperative Oncology Group
*American Joint Committee on Cancer 8th edition
§Randomization stratified according to age, sex and tumor size ≥4 cm
†Investigator-assessed DFS
**+/- immunotherapy, TKI if EGFR+

Summary

- *First prospective, randomized, international evidence of **improved survival with use of a molecular risk discriminator in stage IA-IIA non-squamous NSCLC***
- *Interim analysis designed to detect a large discrepancy in outcomes between treated and untreated*
- *This substantial reduction in recurrence will continue to be followed*
- *Utilization of this 14-gene assay to direct the precision application of systemic adjuvant therapy in stage IA-IIA non-squamous NSCLC may substantially reduce otherwise unacceptable rates of early recurrence*

AIM-HIGH Trial Results – Prespecified Interim Analysis

Trial Profile:

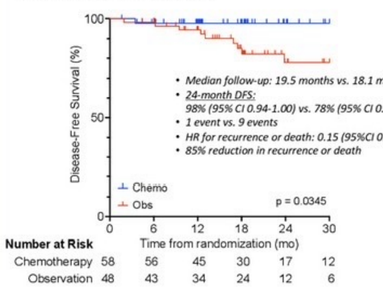
Patient Characteristics:

	Adjuvant Chemotherapy (n=89)	Control (n=111)
Age at randomization (yrs)	63 (52-74)	66 (56-76)
Sex		
Female	42 (47%)	52 (47%)
Male	47 (53%)	59 (53%)
Smoking History		
History		
Yes	80 (90%)	96 (86%)
No	9 (9%)	15 (14%)
Unknown	3 (3%)	0 (0%)
Status		
Never	9 (9%)	15 (14%)
Former	53 (60%)	69 (62%)
Current	27 (30%)	27 (24%)
Unknown	3 (3%)	0 (0%)
Pack-yr (Months)	35 (5-65)	37 (2-67)
ECOG Performance Status		
0	60 (67%)	72 (65%)
1	28 (33%)	38 (34%)
Unknown	1 (1%)	1 (1%)
Histology		
Adenocarcinoma	86 (97%)	103 (93%)
Large Cell	0 (0%)	3 (3%)
Mixed	3 (3%)	5 (5%)

	Adjuvant Chemotherapy (n=89)	Control (n=111)
Stage		
IA1	3 (3%)	10 (9%)
IA2	24 (27%)	28 (25%)
IA3	22 (25%)	23 (21%)
IB	35 (39%)	45 (41%)
IIA	5 (6%)	5 (5%)
Resection		
Approach		
Minimally Invasive	58 (65%)	77 (69%)
Open	31 (35%)	34 (31%)
Technique		
Segmentectomy	15 (17%)	33 (37%)
Lobectomy	72 (81%)	52 (45%)
Sleeve lobectomy	1 (1%)	0 (0%)
Bilobectomy	1 (1%)	0 (0%)
Adjuvant Chemotherapy		
Carboplatin / Pemetrexed	31 (35%)	
Cisplatin / Pemetrexed	26 (29%)	
Cisplatin / Vinorelbine	18 (20%)	
Carboplatin / Paclitaxel	4 (4%)	
Carboplatin / Vinorelbine	4 (4%)	
Other	6 (7%)	

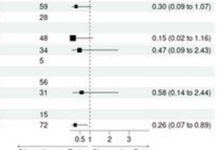
24-month Disease-Free Survival - *Stage IA*:

Chemotherapy Vs. Observation



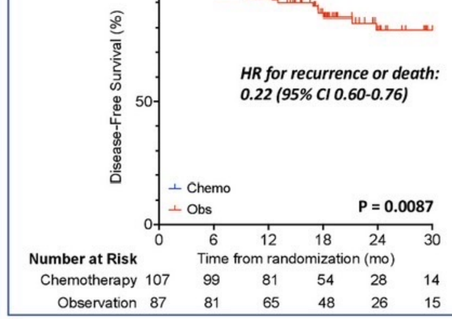
Exploratory Subgroup Analysis:

Subgroup	Observation	Chemo	HR (95% CI)
All Patients	107	87	0.22 (0.06 to 0.76)
Age			
< 65 yr	48	52	0.42 (0.08 to 2.28)
≥ 65 yr	59	35	0.14 (0.02 to 1.09)
Sex			
Male	58	47	0.10 (0.01 to 0.78)
Female	49	40	0.45 (0.09 to 2.24)
Smoking history			
Yes	92	78	0.26 (0.07 to 0.90)
No	15	8	
Pack-years			
< 35	50	42	0.19 (0.02 to 1.58)
≥ 35	59	46	0.25 (0.05 to 1.13)
ECOG status			
ECOG 0	71	59	0.30 (0.09 to 1.07)
ECOG 1	36	28	
Stage			
IA	58	48	0.15 (0.02 to 1.16)
IB	44	34	0.47 (0.09 to 2.43)
IIA	5	5	
Minimally invasive surgery			
Yes	74	56	
No	33	31	0.58 (0.14 to 2.44)
Type of resection			
Sublobar	19	15	
Lobar	88	72	0.26 (0.07 to 0.89)



- *Interim analysis not powered for multiple subgroup analyses*
- *Exploratory subgroup analysis revealed a consistent trend favoring DFS in the chemotherapy group*

24-Month Disease-Free Survival (Overall):



Chemotherapy vs. Observation

- *Median follow-up - 19.5 months vs. 19.0 months*
- *24-month DFS:*
  ***96%** (95% CI 0.92-1.00)*
  vs.
  ***79%** (95% CI 0.70-0.90)*
- *3 events vs. 16 events*
- ***78% reduction in recurrence or death***

Adverse events:

- Similar profile to those reported in previous studies of adjuvant chemotherapy
- One chemotherapy-related death (1.1%) – at or below reported rates

	Chemo (n=89)				
Adverse Event - n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	51 (57%)	33 (37%)	16 (18%)	2 (2%)	0 (0%)
Fatigue	32 (36%)	22 (24%)	8 (9%)	2 (2%)	0 (0%)
Anemia	23 (26%)	13 (14%)	7 (8%)	3 (3%)	0 (0%)
Asthenia	23 (26%)	14 (16%)	8 (9%)	1 (1%)	0 (0%)
Constipation	23 (26%)	19 (21%)	3 (3%)	1 (1%)	0 (0%)
Diarrhea	18 (20%)	13 (14%)	5 (6%)	0 (0%)	0 (0%)
Neutropenia	15 (17%)	4 (4%)	4 (4%)	6 (7%)	1 (1%)
Dyspnea	12 (14%)	8 (9%)	4 (4%)	0 (0%)	0 (0%)
Headache	10 (11%)	8 (9%)	2 (2%)	0 (0%)	0 (0%)
Decreased Appetite	10 (11%)	5 (6%)	3 (3%)	2 (2%)	0 (0%)
Vomitting	9 (10%)	4 (4%)	4 (4%)	1 (1%)	0 (0%)
Cough	9 (10%)	7 (8%)	2 (2%)	0 (0%)	0 (0%)

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