ALK-PATHFINDER: interim results of liquid biopsy (LB) monitoring in ALK-positive NSCLC with comprehensive analysis of resistance and clonal hematopoiesis (CH)

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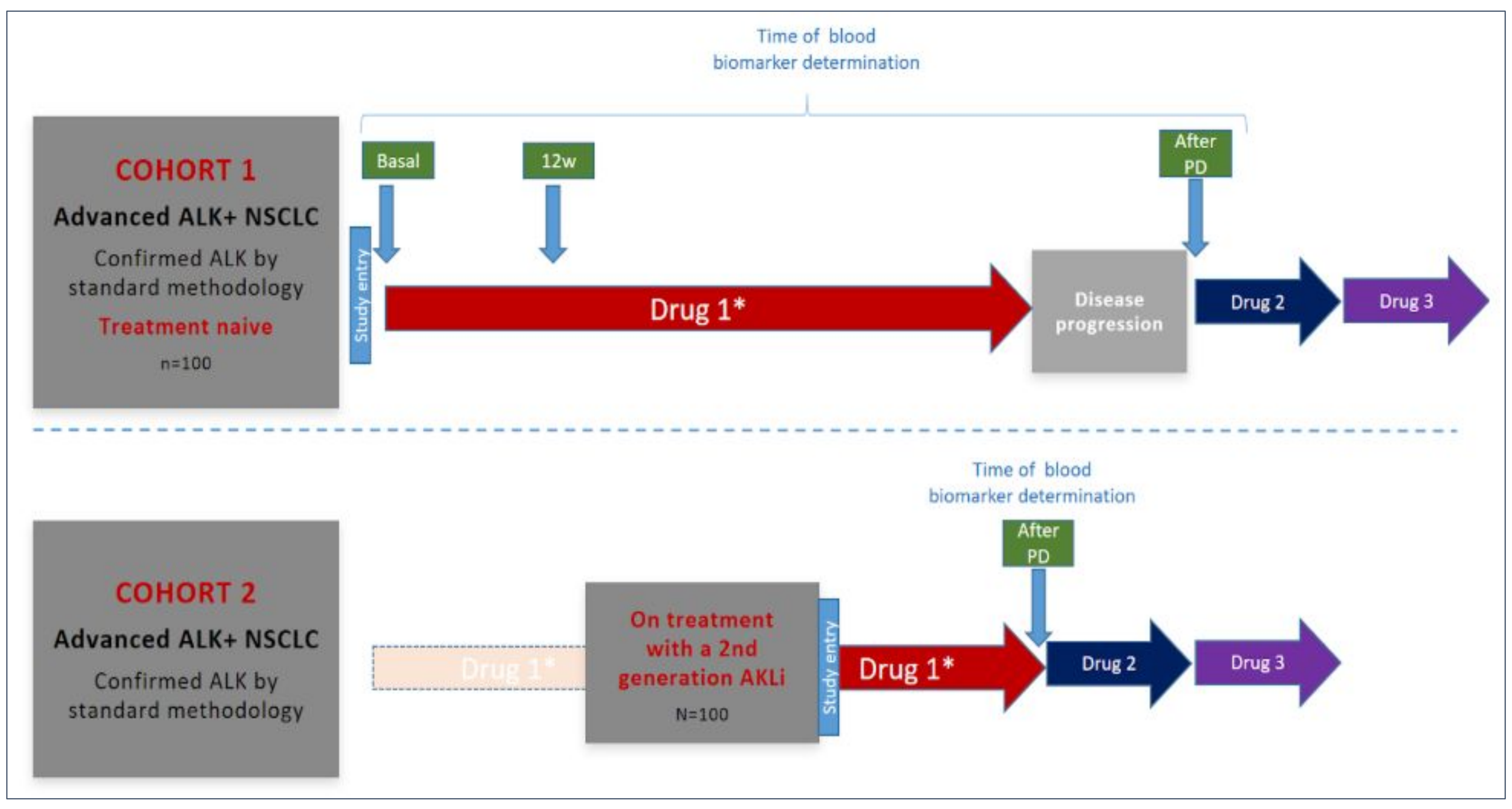
INTRODUCTION

Second-generation ALK TKIs, such as alectinib, provide durable benefit in ALK-positive NSCLC, but resistance eventually develops. LB enables non-invasive monitoring of tumor evolution, although CH can confound interpretation. We present interim results from ALK-PATHFINDER, integrating clinical outcomes with ctDNA profiling and systematic CH evaluation.

Figure 1. Trial design



METHODS

Patients with advanced ALK+ NSCLC were prospectively enrolled into two cohorts: treatment-naïve patients starting alectinib (Cohort 1, with plasma collected at baseline, week 12, and progression) and patients already receiving alectinib at enrollment (Cohort 2, with plasma collected at progression) (Fig 1). ctDNA was analyzed using FoundationOne Liquid CDx. CH-associated variants were predefined as alterations in DNMT3A, TET2, ASXL1, CHEK2, JAK2, SF3B1, or ATM.

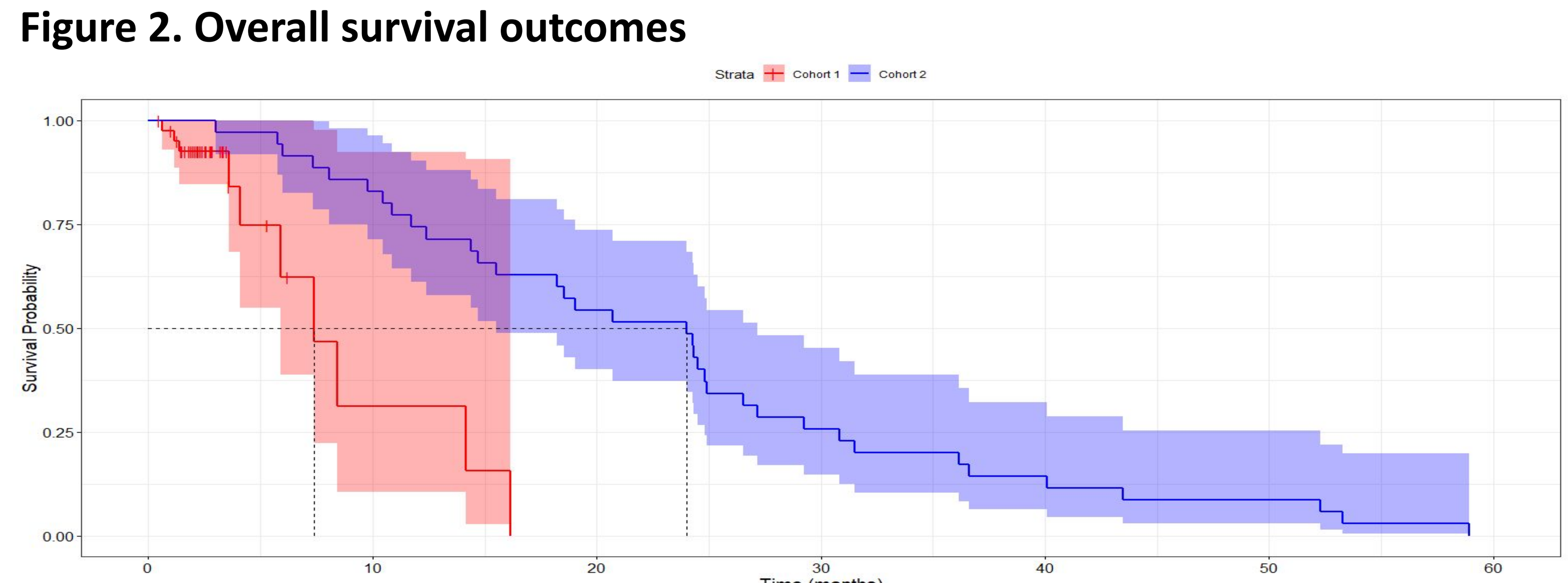
Figure 1. Patients characteristics

Characteristic	Cohort 1 (N=53)	Cohort 2 (N=98)	Total (N=151)
Age (years)			
Mean ± SD	63.04 ± 12.36	62.59 ± 13.26	62.75 ± 12.92
Sex, n (%)			
Male	23 (43.40%)	41 (41.84%)	64 (42.38%)
Female	30 (56.60%)	57 (58.16%)	87 (57.62%)
Race, n (%)			
Caucasian	48 (90.57%)	94 (95.92%)	142 (94.04%)
Asian	1 (1.89%)	1 (1.02%)	2 (1.32%)
Latin	2 (3.77%)	2 (2.04%)	4 (2.65%)
Not available	2 (3.77%)	1 (1.02%)	3 (1.99%)
Smoking history, n (%)			
Never smoked	29 (54.72%)	59 (60.20%)	88 (58.28%)
Current smoker	6 (11.32%)	6 (6.12%)	12 (7.95%)
Ex-smoker	17 (32.08%)	33 (33.67%)	50 (33.11%)
Not available	1 (1.89%)	0 (0.00%)	1 (0.66%)
Stage, n (%)			
M1	33 (62.26%)	71 (72.45%)	104 (68.87%)
CNS M1	11 (20.75%)	22 (22.45%)	33 (21.85%)
Histology			
Adenocarcinoma	50 (94.34%)	93 (94.9%)	143 (94.70%)
Method for ALK diagnostic			
IHC	13 (24.53%)	56 (57.14%)	69 (45.70%)
FISH	4 (7.55%)	11 (11.22%)	15 (9.93%)
NGS	19 (35.85%)	17 (17.35%)	36 (23.84%)
Other	4 (7.55%)	2 (2.04%)	6 (3.97%)

RESULTS

- A total of 151 patients were included (58% female; median age 63; 95% adenocarcinoma; 58% never-smokers; 22% CNS involvement). (Fig 2)
- Plasma samples were available from 53 at baseline, 53 at week 12, and 136 at progression.
- Clinical outcomes are not the primary endpoint and remain immature. In Cohort 2, retrospective time-to-progression on alectinib before plasma sampling was 24 months, with median OS 52 months. (Fig 2)
- Fusion partners were mainly ALK–EML4 at baseline (73%) and progression (60%). Rare non-EML4 partners included LPAR3, ASXL2, CD74, LINC00607, PLB1, and SDC1 at baseline, and CASP1, KLC, and POLR1A at progression. (Fig 3)
- CH-associated variants were frequent, detected in 57% of patients at baseline, 49% at week 12, and 14% at progression, dominated by DNMT3A, TET2, ASXL1, CHEK2, JAK2, SF3B1, and ATM. TP53 was seen in 39%, 15%, and 6% at the same time points, reflecting a mixed CHIP/tumor signal. (Fig 5)
- ALK kinase-domain mutations were identified only at progression in 3 patients, including G1202R/K, I1171N/S, and L1196M/Q substitutions. (Fig 3)
- Baseline co-alterations included KRAS, PIK3CA, PTEN, RET, EGFR, BRAF, NF1, KEAP1, and STK11; at progression, additional cases involved MET (including amplification), NF1, KRAS, PTEN, and EGFR. (Fig 4)

Figure 2. Overall survival outcomes



OS	Cohort 1 (N=53)	Cohort 2 (N=98)	Total (N=151)
Median (95% CI)	14.16 (9.92, 16.13)	52.27 (38.11, NA)	41.2 (20.70, NA)
1-year OS (95% CI)	63.90% (38.98, 100)	95.23% (88.99, 100)	87.33% (79.24, 96.25)

Figure 3. ALK fusion partners

Category	Baseline	Progression	
EML4–ALK	73%	60%	Predominant partner.
Non-EML4	27%	40%	LPAR3; ASXL2; CD74; PLB1; LINC00607; SDC1; CASP1; KLC; POLR1A
ALK kinase-domain mutation	0	3 cases	G1202R/K, I1171N/S, L1196M/Q.

Figure 4. Co-alterations with ALK fusions

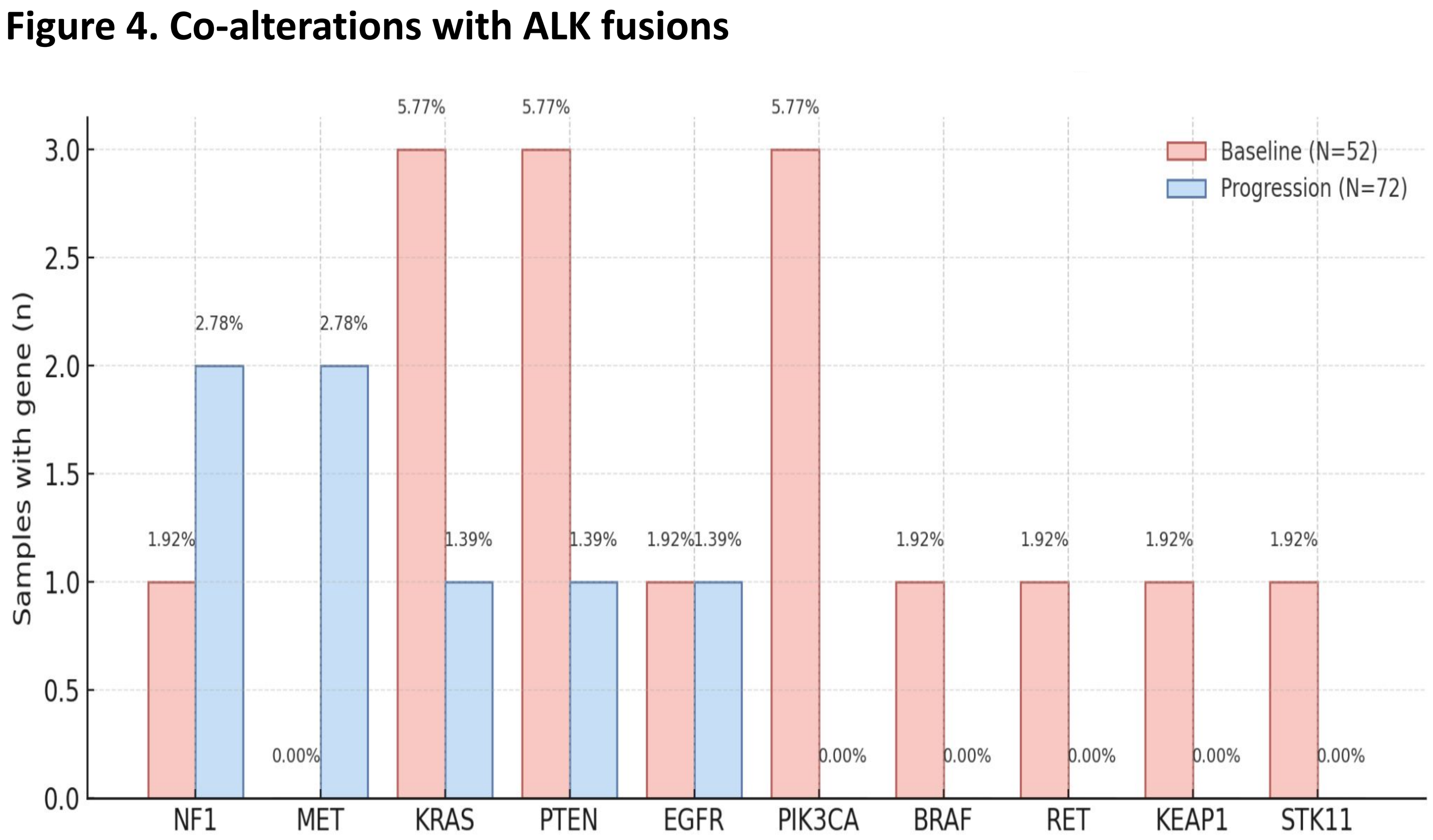
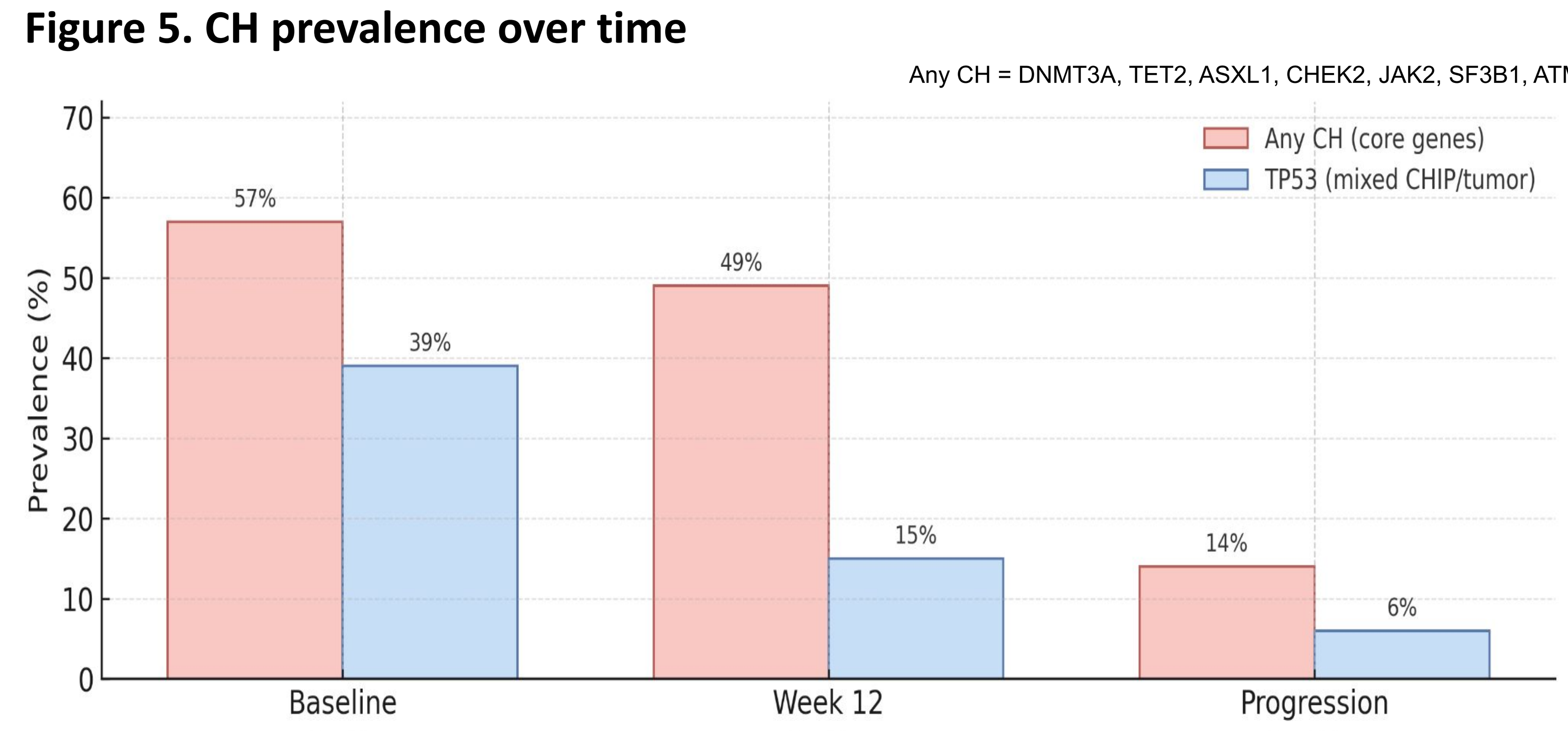


Figure 5. CH prevalence over time



CONCLUSIONS

- Longitudinal ctDNA monitoring in real-world ALK+ NSCLC is feasible.
- CH is common and mandates systematic upfront filtering to prevent misclassification.
- On-target ALK mutations are uncommon; resistance is heterogeneous, driven by TP53 and bypass events (notably MET, NF1).
- Supports CH-aware plasma profiling to refine resistance assessment and guide therapy.

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