# Genotypic characteristics and resistance mutations in advanced ALK+ NSCLC: The ALK-PATHFINDER study

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## BACKGROUND

ALK rearrangements occur in approximately 5% of advanced non-small cell lung cancer (NSCLC) patients.

The current standard initial therapy is a second-generation or third ALK tyrosine kinase inhibitor (TKI), which has shown great improvements in response rates, progression-free survival and global survival.

However, most patients relapse due to acquired resistance mechanisms including secondary mutations in ALK kinase domain, such as G1202R and I1171N specially for the second generation.

Indeed, ALK mutations are more frequent in patients treated with second-generation inhibitors than with first-generation (53-54% under alectinib or ceritinib, 71% under brigatinib vs. 20% under crizotinib).

In addition, the optimal sequence of ALK inhibitors has not been established yet, but the selection of the most suitable subsequent line according to ALK resistance mutations must be a key strategic approach for the therapeutic decision-making process for these patients.

## OBJECTIVES

**Primary objective**

To describe genotypic characteristics of NSCLC ALK+ patients by blood comprehensive NGS at baseline, during treatment course and at the progression disease.

## METHODS

The ALK-PATHFINDER study is a **two-cohort** and multicenter observational study in advanced ALK-positive NSCLC patients.

**Cohort 1** (N 100) will prospectively include patients that are treatment naïve.

**Cohort 2** (N 100) will include patients who are already on treatment with a second-generation ALK inhibitor after progression disease (PD).

This trial will run in **30 sites in Spain** and recruitment started in September 2021.

**Secondary objectives**

To evaluate whether blood levels of EML4-ALK at baseline, 12 weeks of treatment with TKI correlates with the evaluation of the response using imaging tests (CT, PET-CT, MRI) and according to RECIST criteria.

To determine if there are differences in both overall survival (OS) and progression-free survival (PFS) according to plasma levels of EML4-ALK translocation and the presence of resistance mutations at baseline, 12 weeks and PD.

To evaluate if differents fusion variants confer different sensitivities to TKI and compare with the OS and PFS.

To determinate whether ALK variant affect the development of molecular mechanism of resistance with TKI.

To establish a pattern of molecular progression signature.

To establish a cell derived mouse model from ALK naïve and ALK resistant patients to be able to test new treatment strategies.

## ENROLLMENT and CURRENT STATUS

- **Currently, 16 patients are eligible for cohort 1 and 79 patients for cohort 2, blood samples are being collected.**
- **The recruitment is expected to be completed by September 2023.**
- **The trial is ongoing, further updates will be provided.**

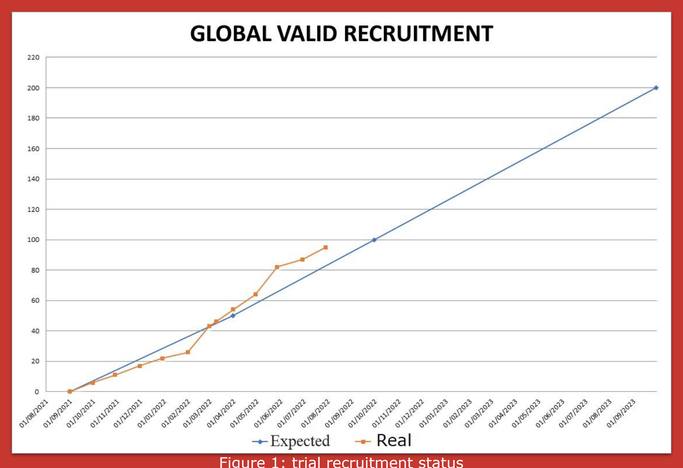

Figure 1: trial recruitment status

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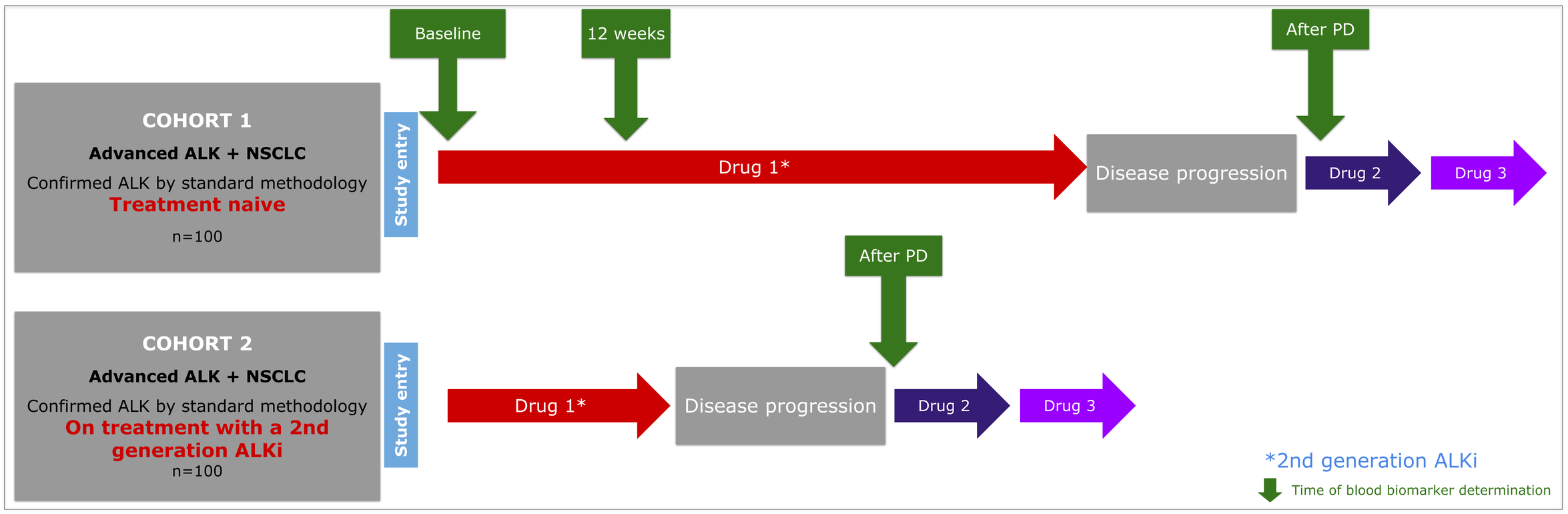


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