

P1.289: Prognostic Value of Serial Ultrasensitive ctDNA Analysis in Elderly NSCLC Undergoing Metronomic Vinorelbine and Immunotherapy

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INTRODUCTION

Metronomic chemotherapy exerts antitumor effects via anti-angiogenesis, immune modulation, and direct cytotoxicity. However, evidence for its combination with immunotherapy in NSCLC remains limited. This phase II study (ChiCTR2300074586) evaluated metronomic oral vinorelbine (mOV) plus PD-1 inhibitors as first-line treatment in patients aged ≥ 70 years with locally advanced or metastatic NSCLC without driver mutations.

METHODS

- Elderly patients (≥ 70 years) with untreated locally advanced or metastatic NSCLC, without EGFR, ALK, or ROS1 alterations and with ECOG performance status 0–1, were enrolled. Patients received PD-1 inhibitors combined with mOV (30 mg, three times weekly on days 1, 3, and 5), followed by PD-1 maintenance until disease progression or unacceptable toxicity.
- Plasma samples were collected at baseline and every 2 treatment cycles for tumor-naïve ultrasensitive circulating tumor DNA (us-ctDNA) analysis using a 218-gene panel (30,000 $\times$ depth; Kanghui Biotech), targeting NSCLC-related driver mutations.

DISCUSSION AND CONCLUSION

- First-line mOV plus PD-1 inhibitors showed promising efficacy and manageable toxicity in elderly patients (≥ 70 years) with NSCLC.
- Us-ctDNA dynamics predict outcomes and aid in identifying pseudoprogression, tumor heterogeneity, and early progression.

RESULTS

In this prospective study, 54 patients with NSCLC were enrolled (median age, 79 years), with a median follow-up of 11.1 months. The median progression-free survival (mPFS) was 8.37 months, with an objective response rate (ORR) of 25.9% and a disease control rate (DCR) of 75.9%. The incidence of grade ≥ 3 immune-related adverse events (irAEs) was 9.3%. Us-ctDNA monitoring was performed in 35 patients (Table 1).

Characteristics	Number, n	Proportion, %
All Cases		
Gender		
Male	29	83%
Female	6	17%
Age		
≤ 75	13	37%
> 75	22	63%
PD-L1 expression		
$< 50\%$	24	68%
$\geq 50\%$	9	26%
NA	2	6%
TMB expression		
L	13	37%
H	9	26%
NA	13	37%

Table 1: Baseline characteristics of the us-ctDNA cohort (N = 35)

RESULTS

- At baseline, 73.5% of patients were us-ctDNA-positive, which was associated with shorter mPFS compared with ctDNA-negative patients (3 months vs. not reached; HR=5.12; P=0.016) (Figure 1) and a higher risk of lung, liver, or brain metastases. Compared with sustained-positive patients, ctDNA clearance and sustained negativity reduced progression risk (HR=0.25; 95% CI 0.06–1.02; log-rank P=0.037) (Figure 2). Baseline ctDNA positivity also correlated with lower DCR (P=0.032). All patients who failed to achieve disease control were us-ctDNA-positive.
- Importantly, us-ctDNA dynamics predicted treatment outcomes. The ctDNA dynamics (TP53 mutation VAF converted from positive to negative, while NFE2L2 mutation persisted positive), reflected inpatient response heterogeneity of patient A (one lesion showed tumor shrinkage, while another showed enlargement), and pseudoprogression of patient B (radiographic findings approaching PD after two cycles despite us-ctDNA clearance, followed by PR after six cycles)(Figure 3).

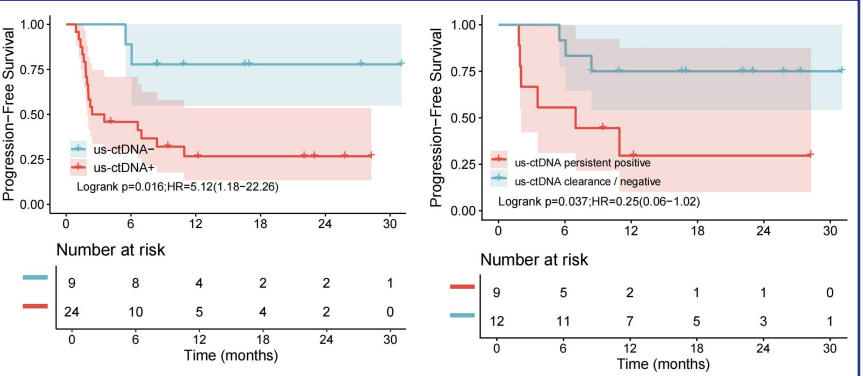


Figure 1. PFS according to baseline us-ctDNA status.
Figure 2. PFS according to serial us-ctDNA dynamics.

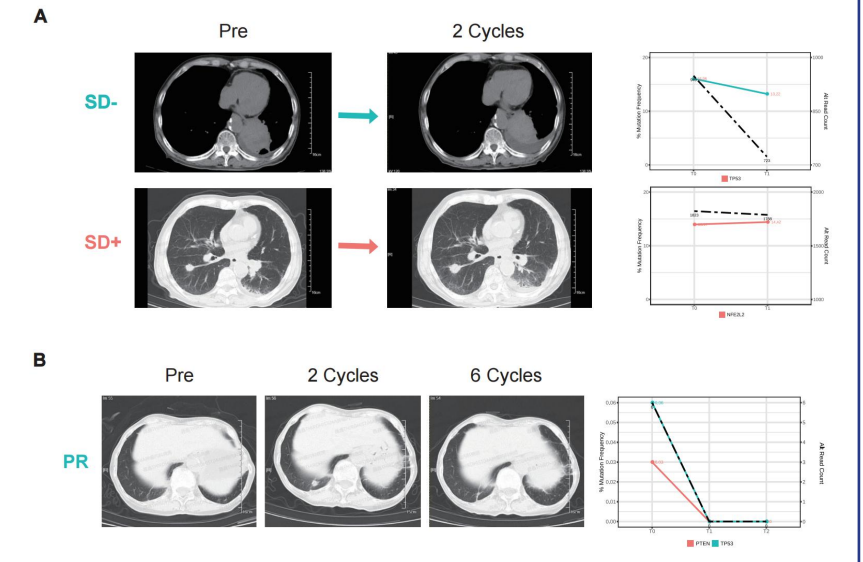


Figure 3. Representative CT images and corresponding us-ctDNA dynamics.
A. Heterogeneous lesion response in Patient A.
B. Pseudoprogression in Patient B.