



Association of *CBR3* rs8133052 with progression-free survival in relapsed small cell lung cancer receiving second-line or later amrubicin therapy

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INTRODUCTION

Amrubicin (AMR) is an anthracycline used for relapsed small cell lung cancer (SCLC) in Japan, but efficacy varies and predictive biomarkers are lacking. The candidate disposition pathway includes hepatic uptake via solute carrier family 22 member 16 (SLC22A16/OCT6), reduction to the more active metabolite amrubicinol (AMROH) by carbonyl reductases (CBR1/CBR3) and NAD(P)H quinone dehydrogenase 1 (NQO1), and efflux via ATP-binding cassette subfamily B member 1 (ABCB1). Single-nucleotide polymorphisms (SNPs) in anthracycline disposition genes have been linked to pharmacokinetics or clinical outcomes with doxorubicin; their relevance to AMR is unknown.

OBJECTIVE
To assess associations between eight candidate SNPs and progression-free survival (PFS) during second-line or later AMR.

METHODS

Single-center retrospective cohort: 99 patients with relapsed SCLC treated with second-line or later AMR (March 2009–March 2026).
Genotyping: TaqMan SNP Genotyping Assays using peripheral-blood deoxyribonucleic acid (DNA).
Primary endpoint: progression-free survival (PFS).
Secondary endpoints: objective response rate (ORR) and grade 4 hematologic toxicities.
Toxicity cohort: n=80 after excluding primary prophylactic granulocyte colony-stimulating factor (G-CSF).
Statistics: Kaplan–Meier/log-rank screening with Bonferroni correction across eight SNPs.
Adjusted Cox model: AMR dose, treatment line, Eastern Cooperative Oncology Group performance status (ECOG PS), first-line immune checkpoint inhibitor (ICI), age, and sex.

Eight candidate SNPs selected from prior anthracycline pharmacokinetic/outcome evidence and putative AMR disposition
ABCB1 rs1128503, rs1045642, rs2032582 **CBR3** rs8133052, rs1056892 • **CBR1** rs20572
SLC22A16/OCT6 rs174368 • **NQO1** rs1800566

CANDIDATE AMR DISPOSITION PATHWAY



COHORT AT A GLANCE N=99

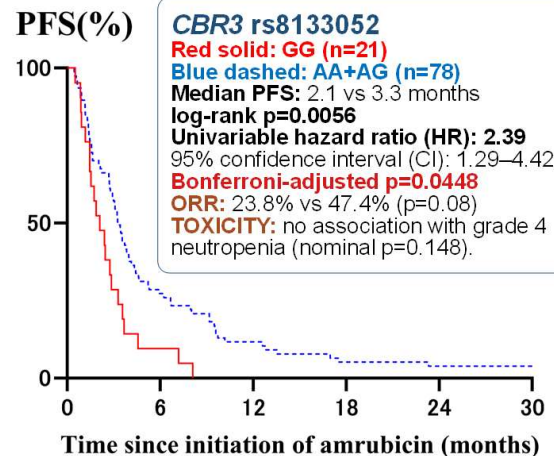
72(46-90) median age, years	79 / 20 male / female	70 / 29 ECOG PS 0–1 / 2–4
85 / 14 treatment line 2nd / ≥3rd	38 / 61 AMR dose 40 / ≤35 mg/m ²	14 / 85 first-line ICI yes / no
21 / 78 <i>CBR3</i> rs8133052 GG / AA+AG	0 pre-AMR tarlatamab	3.1 mo overall median PFS

Selected references

Takakuwa et al. Anticancer Res. 2014; Nagata et al. Clin Med Insights Oncol. 2013; Bains et al. J Pharmacol Exp Ther. 2010; Fan et al. Pharmacogenet Genomics. 2008; Okabe et al. Biochem Biophys Res Commun. 2005.
Abbreviations: AMR, amrubicin; AMROH, amrubicinol; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony-stimulating factor; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, objective response rate; PFS, progression-free survival; SCLC, small cell lung cancer; SNP, single-nucleotide polymorphism.

RESULTS — *CBR3* rs8133052

GG independently associated with shorter PFS
Adjusted HR 2.29 (95% CI 1.36–3.86); p=0.0019



Multivariable Cox model for PFS

Predictor	HR	95% CI	p value
AMR dose, 40 vs ≤35 mg/m ²	1.26	0.79–2.02	0.335
Treatment line, second vs ≥third	0.75	0.40–1.43	0.383
ECOG PS, 2–4 vs 0–1	1.86	1.17–2.96	0.0087
First-line ICI, yes vs no	1.15	0.63–2.09	0.653
Age ≥75 years	1.53	0.95–2.46	0.083
Female vs male	0.71	0.42–1.20	0.198
<i>CBR3</i> rs8133052, GG vs AA+AG	2.29	1.36–3.86	0.0019

Analysis update after abstract submission

Final verification of response assessment and follow-up, together with the prespecified correction across eight SNPs, updated efficacy estimates. The direction and interpretation of the *CBR3* association were unchanged.

EFFICACY SIGNAL
Bonferroni-adjusted log-rank p=0.0448;
multivariable Cox p=0.0019.

TOXICITY SIGNAL
Grade 4 neutropenia: nominal p=0.148
(n=80).

DISCUSSION

Biologically plausible — but not yet proven

1 Functional coding variant

rs8133052 changes amino acid 4 from cysteine to tyrosine (Cys4Tyr; C4Y). Recombinant *CBR3* C4Y shows lower catalytic activity for doxorubicin and daunorubicin; AMR itself has not been tested.

2 Distribution and tumor-site metabolism

Carbonyl reductase 3 (*CBR3*) is expressed in liver and extrahepatic tissues. Genotype-dependent reduction before tumor delivery or within tumor tissue could alter exposure to parent AMR and active AMROH.

3 Clinical phenotype

GG showed shorter PFS and a numerically lower ORR (23.8% vs 47.4%), without a significant grade 4 neutropenia signal. This pattern is compatible with—but does not prove—an efficacy-specific mechanism.

LIMITATIONS

- Retrospective, single-center study with a modest sample size.
- Candidate-gene design without external validation.
- Routine-practice response assessment without central review.
- No AMR/AMROH pharmacokinetic or tumor-tissue measurements.
- Functional inference extrapolated from other anthracyclines; AMR was not directly tested.
- No AMR-untreated comparator; the association is not yet predictive.
- Long enrollment period; first-line ICI in 14 patients; no pre-AMR tarlatamab.

CLINICAL IMPLICATION

The genotype may identify a biologically distinct subgroup receiving AMR, but should not yet guide treatment selection.

Required next steps: external replication, paired plasma AMR/AMROH pharmacokinetics, and direct functional or tumor-tissue validation.

CONCLUSION

***CBR3* rs8133052 GG was independently associated with shorter progression-free survival during second-line or later AMR.**

Replication and direct functional validation are required before clinical implementation.

ARTIFICIAL INTELLIGENCE (AI) USE DISCLOSURE

OpenAI ChatGPT (Codex) assisted with English-language refinement.
Poster Session P3 • 15 Sep 2026 • 09:30–11:00