HSP90 is an emerging therapeutic target in lung cancer with ALK rearrangement because ALK is one of client proteins dependent on HSP90 for protein stability. Considering that the resistance to target agents inevitably develops, we evaluated acquired resistance to 17-DMAG, a geldanamycin analogue HSP90 inhibitor, in H3122 lung cancer cell line with ALK rearrangement. 17-DMAG is highly active for inhibition of H3122 cell growth in vitro and tumor in xenograft model. The resistant subclone (H3122/DR) was established by chronic, repeated exposure to increasing concentrations of 17-DMAG. H3122/DR did not show cross-resistance to NVP-AUY922, a structurally unrelated synthetic HSP90 inhibitor and crizotinib, a currently available ALK inhibitor. Expression of NQO1, a two-electron-reducing flavin-containing enzyme using either NADH or NADPH as reducing cofactors which can metabolize 17-DMAG to a more active form, was decreased in H3122/DR by Western blot analysis. Accordingly, treatment of siRNA to NQO1 decreased the sensitivity of H3122 to 17-DMAG.

In summary, acquired resistance to 17-DMAG in H3122 lung cancer cells with ALK rearrangement might be caused by decreased NQO1 expression suggesting it could be a possible target for overcoming the resistance.