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Pemetrexed is a key drug for therapy of non-small cell lung cancer (NSCLC). In a search for biomarkers for study of the efficacy of pemetrexed treatment, we examined the thymidylate synthase (TYMS) copy number in NSCLC cell lines and in clinical NSCLC samples treated with pemetrexed, combined with platinum drugs. TYMS copy numbers in lung adenocarcinoma cell lines were significantly lower than in squamous cell carcinoma ( $p=0.0105$ ), and a significant correlation was found between the TYMS copy number and the 50% inhibitory concentration value for pemetrexed in all 17 lung cancer cell lines tested ( $r=0.6814$ ,  $p=0.0026$ ). Moreover, TYMS copy number was significantly lower in clinical NSCLC samples responsive to treatment with pemetrexed combined with platinum drugs ( $p=0.0067$ ). Furthermore, the decrease in the baseline CT size measurement of pemetrexed combined with platinum drug treatment correlated significantly with TYMS copy number ( $r=0.7967$ ,  $p=0.0011$ ). To our knowledge, this is the first report of a significant association between TYMS copy number and response to pemetrexed treatment in tumor biopsy specimens. Our results suggest that TYMS copy number could be a predictive biomarker for pemetrexed based chemotherapy.