ABSTRACT

Gilteritinib is a multitarget tyrosine kinase inhibitor (TKI), approved for the treatment of FLT3-mutant acute myeloid leukemia, with a broad range of activity against several tyrosine kinases including anaplastic lymphoma kinase (ALK). This study investigated the efficacy of gilteritinib against ALK-rearranged non-small cell lung cancers (NSCLC). To this end, we assessed the effects of gilteritinib on cell proliferation, apoptosis and acquired resistance responses in several ALK-rearranged NSCLC cell lines and mouse xenograft tumor models, and compared its efficacy to alectinib, a standard ALK inhibitor. Gilteritinib was significantly more potent than alectinib as it inhibited cell proliferation at a lower dose, with complete attenuation of growth observed in several ALK-rearranged NSCLC cell lines, and no development of drug tolerance. Immunoblotting showed that gilteritinib strongly suppressed phosphorylated ALK and its downstream effectors, as well as mesenchymal-epithelial transition factor (MET) signaling. By comparison, MET signaling was enhanced in alectinib-treated cells. Furthermore, gilteritinib was found to more effectively abolish growth of ALK-rearranged NSCLC xenograft tumors, many of which completely receded. Interleukin-5 (IL-15) mRNA levels were elevated in gilteritinib-treated cells, together with a concomitant increase in the infiltration of tumors by natural killer (NK) cells, as

assessed by immunohistochemistry. This suggests that IL-15 production along with NK cell infiltration, may constitute components of the gilteritinib-mediated antitumor responses in ALK-rearranged NSCLCs. In conclusion, gilteritinib demonstrated significantly improved antitumor efficacy than alectinib against ALK-rearranged NSCLC cells, which can warrant its candidacy for use in anticancer regimens, after further examination in clinical trial settings.