Evaluation of 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG, KOS-1022) against Childhood Cancer Preclinical Testing Program (PPTP)

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Abstract

17-DMAG is a water-soluble analog of 17-allylamino-17-demethoxygeldanamycin (17-AAG), an agent currently in pediatric phase 1 trials. The geldanamycin natural-alkaloid, a drug that is involved in the folding, conformational maintenance, and assembly of proteins. In the presence of 17-DMAG, geldanamycin binds to the C-terminal domain of Hsp90, a molecular chaperone of the heat shock protein (Hsp) family, inducing Hsp90 conformational alterations, folding, and disassembly of several signaling kinases (e.g., AKT and Raf), and chimeric signaling proteins (NPM-ALK and Bcr-Abl) are affected by Hsp90 inhibition. The PPTP was established by NCI to identify novel agents that have significant activity against preclinical models of childhood cancers. Prior testing was based on prior experience showing that agents similar to their respective clinical counterparts were selected in those PPTP panels. To test if this was the case, a panel of preclinical models was established to identify drugs known to be active against their respective clinical diseases and against Childhood Cancer Models by the Pediatric Preclinical Testing Program (PPTP). The PPTP is based upon prior experience showing that signaling kinases (e.g., AKT and Raf), and chimeric signaling proteins (NPM-ALK and Bcr-Abl) are affected by Hsp90 inhibition.

Methods

Preclinical models were provided by the Developmental Therapeutics Program, NCI. 17-DMAG was dissolved in saline and administered IP weekly x 6 weeks at a dose of 1 mg/kg. Cyclophosphamide was dosed in saline and administered IP weekly x 6 weeks at a dose of 1 mg/kg. Cyclophosphamide was dissolved in saline and administered IP weekly x 6 weeks at a dose of 1 mg/kg. Cyclophosphamide.

Stage 1 screening involves testing of an agent across the pediatric Medulloblastoma, Ependymoma, rhabdomyosarcoma, neuroblastoma, osteosarcoma, and acute lymphocytic leukemia (ALL) panel.

Solid tumor testing: For each xenograft line, 10 mice bearing 50 mg tumors were dosed with a single agent dose response matrix. The proportion of mice with objective response (PR) was determined. The predominant observed response was the objective response (PR).

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17-DMAG demonstrated further evaluation is warranted for this diagnosis (e.g., confirmation of activity in an expanded regresses meeting criteria for CR observed in each.

Medulloblastoma

patterns observed for the PPTP panels have generally matched the clinical spectrum of activity of these histologies that have poor prognosis (e.g., rhabdoid tumors, GBM). To similar to their respective clinical counterparts. Models have also been selected to represent tumors and

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In summary, Stage 1 testing for 17-DMAG against the PPTP in vivo lines was successful. Additional preclinical testing of 17-DMAG against preclinical models of ependymoma, rhabdomyosarcoma, neuroblastoma, osteosarcoma, and acute lymphocytic leukemia (ALL) is needed before human trials can be considered.

17-DMAG antitumor activity

• Progressive disease (with or without tumor growth delay) was the most commonly observed response. • Significant differences (p<0.05) in EFS distributions were observed in 1 of 2 rhabdoid lines, 5 of 6 rhabdomyosarcoma lines, 1 of 4 glioblastoma lines, 3 of 6 neuroblastoma lines, and 2 of 8 ALL lines. In lines where EFS distributions were significantly different, overall treatment group response rates were still PO1 or PO2, with the exception of the rhabdomyosarcoma line, RH3, which was a PR. • Objective responses (CR) were observed in the two rhabdomyosarcoma lines tested. However, these lines were slow growing and the EFS distributions were not significantly different between treated and control groups. Further testing is required to confirm activity against ependymoma.

Ependymoma and Cyclophosphamide antitumor activity

• Testing of these agents serves as a positive control for the PPTP preclinical models. • The responses observed in multiple solid tumor lines and in the ALL panel lines were generally consistent with the expected antitumor activity for vincristine and cyclophosphamide.

DISCUSSION & CONCLUSIONS

• 17-DMAG, an Hsp90 inhibitor, is of potential pediatric relevance because of the multiple Hsp90 client proteins (e.g., transmembrane tyrosine kinases, intermediary signaling kinases (e.g., AKT and Raf), and chimeric signaling proteins (NPM-ALK and Bcr-Abl) affected by Hsp90 inhibition).

• The 2 primary measures used by the PPTP for assessing in vivo antitumor activity are growth delay and comparison of EFS distributions between treated and control animals for statistical significance. The two ependymoma lines in which CRs were observed were slow growing, and the PPTP CR was not statistically significant in EFS distributions between treated & control animals. Further evaluation of these and other ependymoma lines is needed before claiming significant antitumor activity for 17-DMAG against preclinical models of ependymoma.

• Most rhabdomyosarcoma lines showed significant differences in EFS distribution (treated vs control), but only one line demonstrated an objective response (PR). The rh3623 xenograft line was among the most sensitiveline to 17-DMAG in the in vitro panel.

• The paucity of objective responses observed for 17-DMAG in the in vivo panel could reflect drug levels inadequate to inhibit Hsp90 in tumor tissues. Experiments to address this possibility are planned and will use increased tumor levels of Hsp90 in animals treated with 17-DMAG as a pharmacodynamic readout for Hsp90 inhibition.

• Comparisons of achievable 17-DMAG systemic exposures between humans (from ongoing phase 1 studies) and mice (previously published) will allow determination of whether PK differences between mice & humans need to be considered when interpreting the activity of 17-DMAG against the PPTP in a vivo panel.

• In summary, Stage 1 testing for 17-DMAG against the PPTP’s childhood cancer preclinical models suggests limited single agent activity, but identifies areas of potential activity that warrant further evaluation.

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