KIF18A is a mitotic kinesin that plays a role in maintaining bipolar spindle integrity during mitosis. KIF18A knockdown selectively inhibits growth and induces apoptosis for cancer cell lines with chromosomal instability (CI). AMG 650 is a selective inhibitor of KIF18A that phenocopies the effects observed for KIF18A knockdown. Osteosarcoma is characterized by a chaotic genome with chromothripsis and a large number of chromosomal structural variants, and TP53 is inactivated in the vast majority of cases. Anaplastic Wilms' tumor is associated with TP53 mutation as some Ewing sarcoma cases, and alveolar rhabdomyosarcoma often exhibits tetraploidy. In this study the pre-clinical efficacy of AMG 650 was tested using PDX models for these cancers.

STUDY METHODS

AMG 650 was tested in 7 osteosarcoma, 2 Wilms' tumor, 3 Ewing tumor, 15 rhabdomyosarcoma, and 8 Ewing sarcoma PDX models. A conventional testing design was used for osteosarcoma models with ten AMG 650-treated and ten vehicle control animals for each model. A single mouse trial design was used for the other cancer types, with a single vehicle control and AMG 650-treated mouse per model. AMG 650 was administered orally at 100 mg/kg PO, QD for 22 days (B); vehicle control (A) and AMG 650 (100 mg/kg) PO, QD for 21 days (B).

RESULTS

To calculate event free survival for these models a relative tumor volume greater than or equal to 4 was used as the event. A statistical comparison of survival days was computed using two approaches: Gehan-Wilcoxon and exact rank tests. The Gehan-Wilcoxon test gives more weight to deaths at earlier time points and is most sensitive to early differences between survival. The null hypothesis of no differences between the curves is rejected at the p-value threshold of 0.05.

Log cell kill (LCK) per dose (Clark, 1997) was estimated from: 

\[ \text{LCK/dose} = \frac{T_c}{\text{V}/T_c} \] 

where \( T_c \) = tumor doubling time and \( n \) = number of treatments. The equation simplifies to \( \text{LCK/dose} = 0.301 \times n \times \text{T}/(V\times T_c) \).

For 6 evaluable osteosarcoma models, no objective responses were observed, and a single model showed > 2-fold increase in median time to event. Among 15 rhabdomyosarcoma models, one achieved a complete response with tumor regrowth beginning approximately 3 weeks after treatment completion.

No objective responses were observed for the 2 Wilms tumor models and 3 rhabdoid tumor models tested.

REFERENCES


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