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A Novel KIF18A Inhibitor for Targeting Chromosomal Instability in Cancer

Abstract 6267

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Introduction

- Chromosomal instability (CIN) is caused by errors in DNA replication and is associated with aberrant chromosome structure and number during cell division.
- CIN is considered one of the hallmarks of cancer. Patients with high CIN are associated with poor prognosis across a variety of tumor types.
- The spindle assembly checkpoint (SAC) ensures proper chromosome attachment to spindle microtubules (MT) and has emerged as a vulnerability for cancer cells with CIN due to increased dependence on proper chromosome alignment.
- KIF18A is a kinesin family motor protein that promotes chromosome alignment by dampening chromosome oscillations at the metaphase plate.
- Targeting KIF18A in cancers with CIN provides an opportunity to inhibit cancer cell division and viability with a broad therapeutic window.

Figure 1: Tumor cells with CIN require KIF18A for proliferation

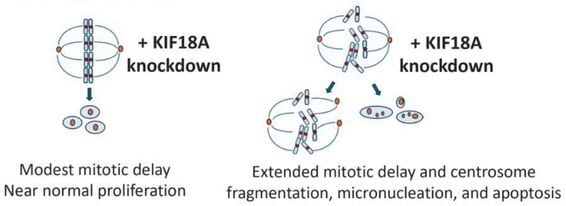

Figure 1. KIF18A is a mitotic vulnerability in chromosomally unstable cancers. CIN cells are uniquely dependent on KIF18A-mediated chromosome alignment and metaphase to anaphase transition.

Figure 2: Allosteric binding for Iambic series confirmed by a Cryo-EM structure

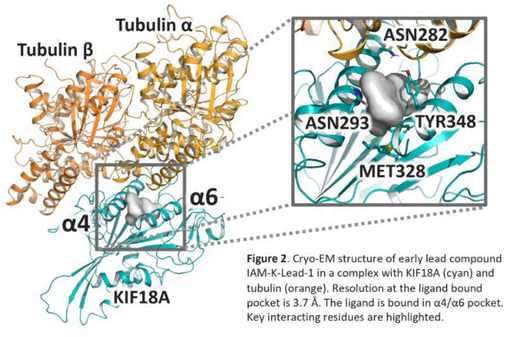

Figure 2. Cryo-EM structure of early lead compound IAM-K-Lead-1 in a complex with KIF18A (cyan) and tubulin (orange). Resolution at the ligand bound pocket is 3.7 Å. The ligand is bound in α4/α6 pocket. Key interacting residues are highlighted.

Results

Table 1: IAM-K1 is a differentiated, highly potent KIF18A inhibitor with favorable in vitro activity and ADME-PK profile

Properties	IAM-K1	Sovilnesib (AMG650)
ATPase Biochemical IC_{50} (nM)	3	4
OVCAR-3 IC_{50} (nM) – High CIN	10	23
MCF-7 IC_{50} (nM) – Low CIN	8,310	6,420
CFU-Erythroid (nM)	> 10,000	> 10,000
CFU-GM (nM)	3000	3000
HepG2 (nM)	24,190	21,190
Safety 47 Panel	clean	4 hits sub 10μM IC50
Kinesin selectivity (IC_{50}<10μM)	KIF19	KIF19
Kin. Sol. (FeSSIF; FaSSIF, μM)	> 200	> 200
MDCK Papp, 10^{-6} cm/s	2.2	0.8
Mouse $V_{d,ss}$ (L/kg)	3	1.3
LM, Eh, H/M/R/D/CM	0.23/0.75/0.17/0.19/0.55	<0.14/0.25/0.26/0.17/ND
%F, M/R/D/C (PO, 10 mg/kg)	73/90/21/60	71/ND/ND/ND
hERG (uM)/CV liability	2.2/low	>5/ND
DDI liabilities (CYPinh IC_{50}<10μM)	none	2C9, 2C19

ND = no data

Figure 3: Anti-proliferative activity of IAM-K1 correlates with mitotic arrest and apoptosis

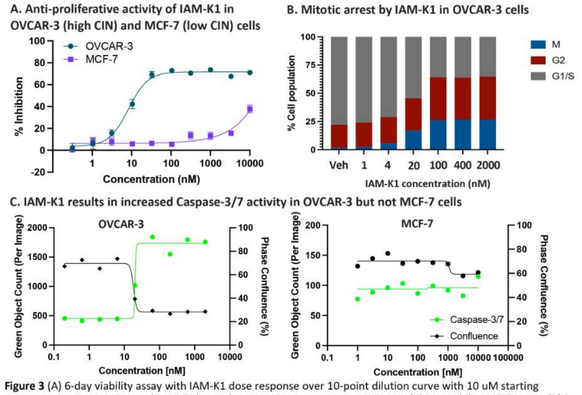

Figure 3 (A) 6-day viability assay with IAM-K1 dose response over 10-point dilution curve with 10 uM starting concentration in OVCAR-3 and MCF-7 shows that OVCAR-3 is sensitive to KIF18A inhibition while MCF-7 is not. (B) Dose dependent increase in M phase quantified by flow cytometry using phospho-histone H3 (Ser10) Alexa 488 antibody + FxCycle™ Violet stain. (C) OVCAR-3 (left panel) and MCF-7 (right panel) cells were treated with IAM-K1 dose response for 72 hours. Incucyte S3 with v.2023A software was used to quantify cell confluence and death (via Caspase-3/7 green apoptosis reagent). IAM-K1 treatment results in increased apoptosis and reduced confluence in OVCAR-3 but not MCF-7.

Figure 4: IAM-K1 results in potent anti proliferative activity in a large panel of breast and ovarian cell lines

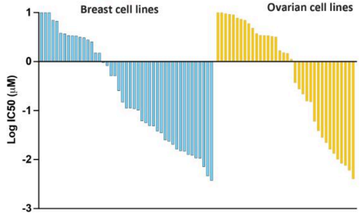

Figure 4. IAM-K1 IC_{50}s in a broad panel of cell lines, as assessed by 6-day CellTiter-Glo assay.

Figure 5: IAM-K1 demonstrates dose dependent TGI and biomarker modulation in OVCAR-3 xenograft model

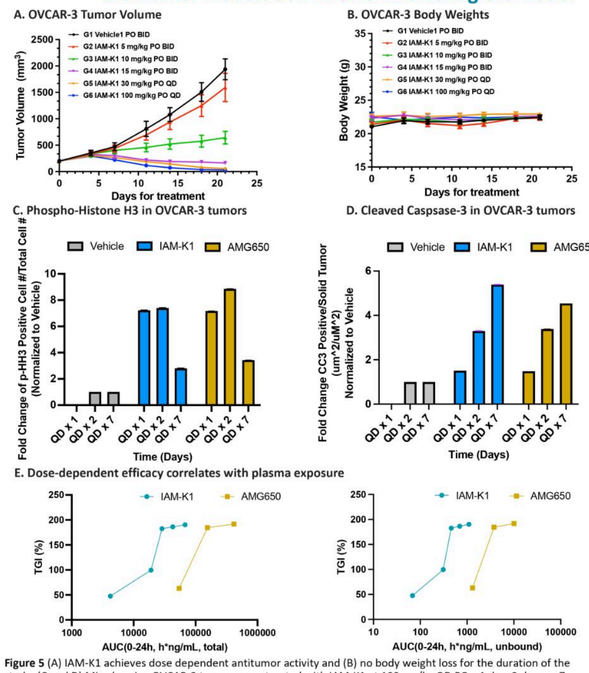

Figure 5 (A) IAM-K1 achieves dose dependent antitumor activity and (B) no body weight loss for the duration of the study. (C and D) Mice bearing OVCAR-3 tumors were treated with IAM-K1 at 100 mg/kg QD PO x 1 day, 2 days or 7 days. Tumors were harvested and stained for pHH3 or CC-3 by IHC methods and images were quantified for positive cells compared to total cells. Data shown as fold change normalized to vehicle. IAM-K1 treatment leads to mitotic arrest early in treatment phase followed by apoptosis at the later time points. (E) IAM-K1 achieves similar antitumor activity as AMG650, but at ~ 10x lower total (left panel) and unbound (right panel) drug exposures. Lower systemic exposure may result in better tolerability and toxicity profile for IAM-K1.

Figure 6: IAM-K1 exhibits a favorable therapeutic window

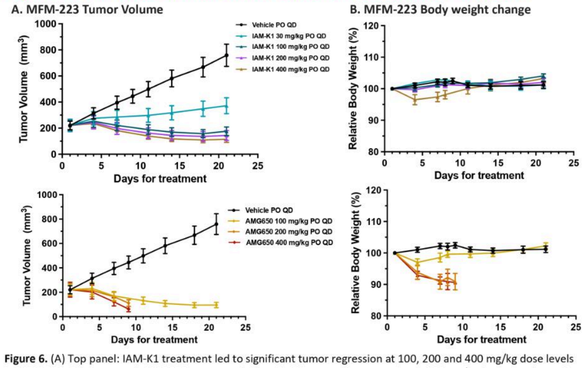

Figure 6. (A) Top panel: IAM-K1 treatment led to significant tumor regression at 100, 200 and 400 mg/kg dose levels in MFM-223. Bottom panel: AMG650 treatment led to significant tumor regression at 100 mg/kg however the study had to be stopped on day 9 at dose levels > 100 mg/kg. (B) All dose levels of IAM-K1 were well tolerated throughout the treatment duration. In contrast, AMG650 was not tolerated at doses above 100 mg/kg QD.

Figure 7: IAM-K1 achieves dose dependent TGI and similar regression with lower drug concentration than AMG650

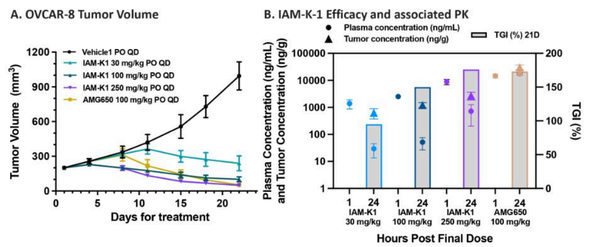

Figure 7. (A) IAM-K1 results in dose dependent antitumor activity. IAM-K1 at 100 and 250 mg/kg QD and AMG650 at 100 mg/kg QD result in similar regression in OVCAR-8 xenograft (B) Plasma and tumor PK are correlated to depth of TGI response. Similar efficacy is achieved with IAM-K1 as compared to AMG650 with ~ 10x less plasma and tumor exposure.

Figure 8: IAM-K1 achieves robust anti tumor activity in a panel of xenograft models

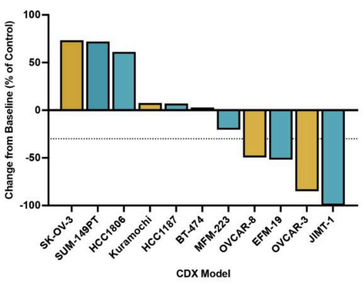

Figure 8. IAM-K1 at 100 mg/kg QD x ~ 21 days results in anti tumor activity across a panel of breast and ovarian cell line derived xenograft models. IAM-K1 achieved regressions in 3/7 (43%) of breast and 2/4 (50%) of ovarian cancer models tested.

Conclusions

- IAM-K1 is a potent, selective, and differentiated KIF18A inhibitor
- IAM-K1 results in mitotic arrest and ultimately apoptosis in a cell line with high CIN, and leads to robust anti proliferation activity in a large panel of cell lines
- IAM-K1 is well tolerated and exhibits advantageous plasma and tumor levels that correlate with tumor regression, at 5-10x lower efficacious exposures than Sovilnesib (AMG650)
- IAM-K1 demonstrates robust anti-tumor activity in a broad spectrum of xenograft models

Abbreviations: ADME-PK – absorption, distribution, metabolism, excretion and pharmacokinetics; AUC – area under the curve; BID – twice daily; CDX – cell line derived xenograft; CFU-GM- colony forming unit – granulocyte macrophage; Cryo-EM – cryogenic electron microscopy; DDI- drug-drug interaction; hERG- human ether-a-go-go-related gene; LM-liver microsomes; MDCK- Madin-Darby canine kidney cells; pHH3 – phospho-histone H3; PO – oral; QD – once daily; TGI – tumor growth inhibition.