Poster #7550

KB-0742, an oral, highly selective CDK9 inhibitor, demonstrates preclinical activity in transcription factor fusion driven adenoid cystic carcinoma patient-derived models

Michael R. McKeown[1], **Luis A. Carvajal**[1], Tressa R. Hood[1], Nicole Spardy Burr[2], Jeffrey Kaufman[2], Adam Boynton[1], Kameron R. Mori[1], Tessa DesRochers[3], Michael Wick[4], Jorge F. DiMartino[1], Charles Y. Lin[1]

[1]Kronos Bio, Cambridge, MA; [2]Adenoid Cystic Carcinoma Foundation (ACCRF), Needham, MA; [3]Kiyatec, Greenville, SC; [4]XenoSTART, San Antonio, TX.

Background & rationale

- Adenoid Cystic Carcinoma (ACC) is an aggressive rare type of cancer of the secretory glands with no approved targeted therapy and high unmet clinical need.
- Deregulated transcription driven by MYB-NFIB or MYBL1-NFIB transcription factor (TF) fusions are a hallmark of ACC pathogenesis. More aggressive disease and resistance to therapy has been associated with co-mutation in NOTCH.
- Although direct targeting of oncogenic TF fusions has remained challenging, targeting of their activity via transcriptional cofactors has emerged as an attractive and clinically actionable strategy. Cyclin-dependent kinase 9 (CDK9) is a key potentiator of TF activity via its ability to act both as an upstream regulator of TF expression and a downstream cofactor.
- KB-0742 is a potent, selective, and orally bioavailable inhibitor of CDK9 with a long plasma half-life. KB-0742 is being studied in an ongoing Phase 1/2 study (NCT04718675) in advanced solid tumors including ACC.
- KB-0742 has demonstrated on-mechanism, single agent anti-tumor activity and a manageable safety profile in heavily pre-treated patients (median 3.5 prior regimens) with transcriptionally addicted solid tumors. Here we present the preclinical rationale for targeting of oncogenic fusion TF activity in ACC (Villanlona-Calero, Miguel et al. *Molecular Cancer Therapeutcs* (2023 22 12_Supplement: Abstract #B159).

KB-0742 targets TF fusion oncogenic signaling

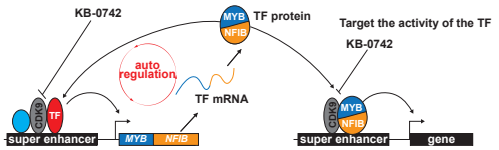

Figure 1: CDK9 is a multinodal cofactor operating both upstream and downstream of a variety of TF fusion genes in transcriptionally addicted tumors. Genomic rearrangements can generate TF fusion genes in cancer, such as MYB/NFIB or MYBL1/NFIB in ACC. CDK9 drives transcription of TF fusions genes, giving rise to TF fusion proteins that can amplify oncogenic activity.

MYB fusions are common in ACC

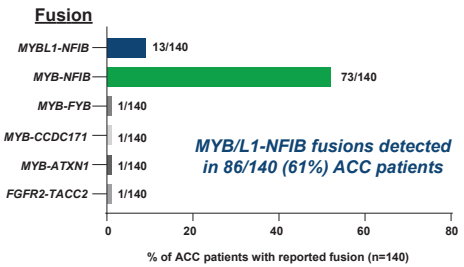

Figure 2: MYB or MYBL1 fusions detectable by RNAseq in TEMPUS dataset (n=140 patients).

KB-0742 inhibits proliferation of MYB+ ACC patient-derived spheroids

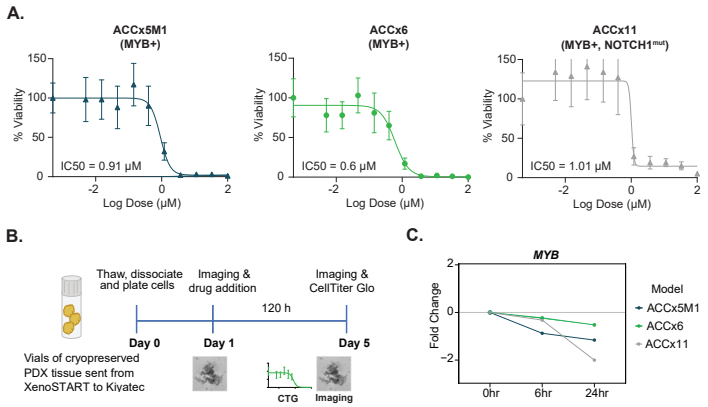

Figure 3: KB-0742 shows strong antiproliferative activity in MYB-fusion and NOTCH co-mutated patient-derived spheroid models. (A) Kiyatec's proprietary non-linear curve fitting algorithms were applied to dose response data to flag and remove outliers. Compound IC50 concentrations were calculated using a non-linear curve fitting algorithm with bottom parameter constrained to a value greater than zero. (B) Timeline of ACC PDX KIYA-PREDICT™ Single Agent Drug Screen. (C) *MYB* mRNA expression measured by RNA-seq of spheroids treated for either 6 or 24 hours with 1µM of KB-0742.

KB-0742 is active in MYB+ ACC patient-derived xenografts

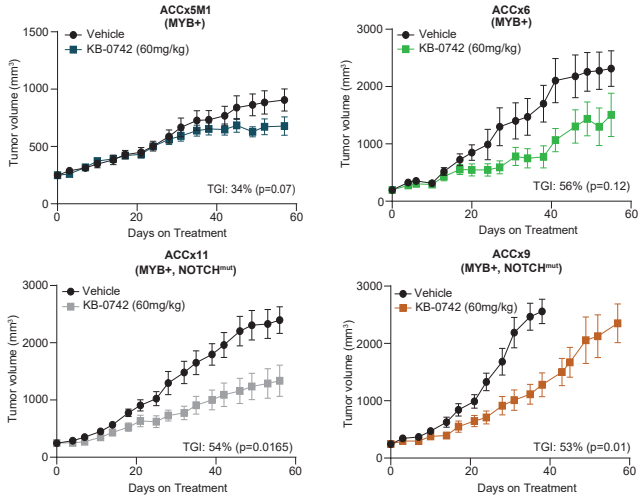

Figure 4: Animals were treated with either vehicle (saline) or 60mg/kg KB-0742 on a 3 days on/4 days off per week schedule until tumors reached 2500mm^3 or up to 60 days post start of treatment. The strongest statistically significant activity was observed in MYB+, NOTCH^{mut} models, ACCx11 (TGI 54% p=0.0165) and ACCx9 (TGI 53% p=0.01).

KB-0742 supresses MYB in MYB+ ACC patient-derived xenografts

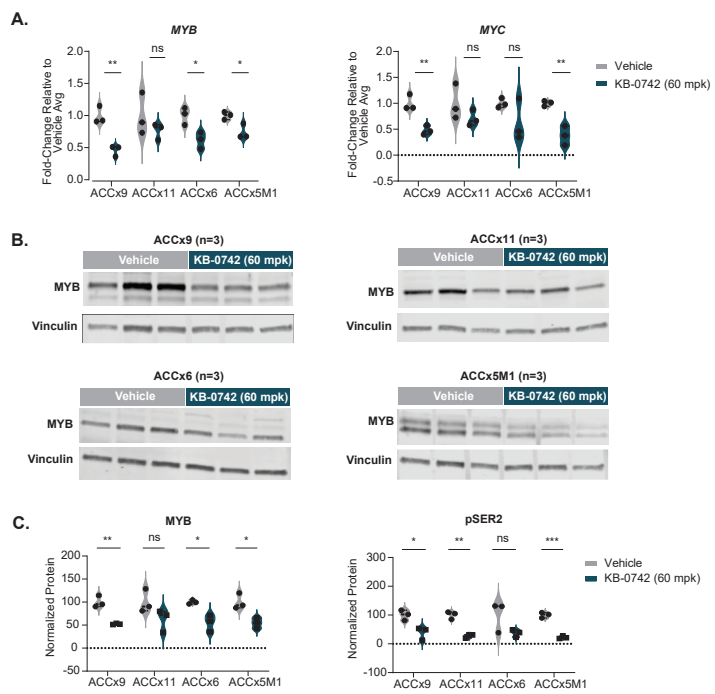

Figure 5: KB-0742 supresses MYB in MYB-driven ACC models. Animals were treated with either vehicle (normal saline) or 60mg/kg KB-0742 daily for 3-days, and then tumors were collected 2 hours after the last dose of the 1st 3-day cycle. (A) *MYB* and *MYC* mRNA expression was evaluated by RT-PCR. (B) Western blot analysis of MYB protein expression in vehicle vs KB-0742 treated animals. (C) Western blot quantification of MYB and pSER2 normalized to total Vinculin. *p ≥ 0.05, **p ≥ 0.01, ***p ≥ 0.001

Conclusions

- More than 60% of ACC patients had MYB fusions detectable by RNA-seq amongst 140 samples evaluated in the TEMPUS dataset.
- In primary MYB-fusion positive and NOTCH co-mutated patient-derived spheroid models, KB-0742 treatment induced strong antiproliferative activity and cytotoxicity.
- In XPDXs, CDK9 inhibition with KB-0742 resulted in antiproliferative activity. Importantly, KB-0742 showed strong tumor growth inhibition in MYB-fusion positive and NOTCH co-mutated tumor models.
- KB-0742 suppressed oncogenic signaling by down-regulating MYB and MYC mRNA transcripts as well as its protein expression.
- KB-0742 is being studied in an ongoing Phase 1/2 study (NCT04718675) in advanced solid tumors, including ACC. It has demonstrated on-mechanism, single agent anti-tumor activity and manageable safety profile.

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