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# POSTER ABSTRACTS

## 802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

### Development and Efficacy of a Novel Bromodomain and Extraterminal Domain Degrader K-256 in MYC/BCL2-Related Lymphoma

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**Background:** Although intensive chemotherapy is widely used to treat MYC/BCL2-related lymphoma, the efficacy of this treatment modality remains limited and a novel treatment method targeting MYC and BCL2 is therefore desired. While the addition of the BH3 mimetic, venetoclax, to standard immunochemotherapy has shown efficacy in treating diffuse large B-cell lymphoma (DLBCL) with BCL2 expression, bromodomain and extraterminal domain (BET) inhibitors, which suppress MYC transcription, have shown limited efficacy in treating MYC-driven lymphomas. Recently, BET degraders have been developed that irreversibly degrade BET proteins and durably suppress MYC; these degraders show promising therapeutic potential.
**Method:** To improve the prognosis of MYC/BCL2-related lymphoma, we developed a novel BET degrader, K-256, and explored its efficacy both *in vitro* and *in vivo* using preclinical models. First, we evaluated the binding activity of K-256 to 32 bromodomains using BROMOscan. Then, we compared the therapeutic effect of K-256 with existing BET inhibitors, including JQ1, OTX-015, and ABBV-075, as well as BET degraders, including dBET6 and ARB-771 in the MYC/BCL2-related lymphoma cell lines SU-DHL4 and SU-DHL6. The therapeutic effects of BET-targeting drugs combined with venetoclax were also evaluated. Finally, we verified the efficacy of K-256 using five MYC/BCL2-related, patient-derived xenograft (PDX) mouse models.
**Results:** K-256 bound selectively to BRD2, BRD3, BRD4, and BRDT, and the Kd value for BRD4, which is most important for MYC transcription, was the lowest (bromodomain 1, 0.027 nM and bromodomain 2, 0.044 nM). We then confirmed that K-256 degraded BRD4 at lower concentrations compared to dBET6 and ARB-771 in SU-DHL4 and SU-DHL6. The $GI_{50}$ of K-256 in SU-DHL4 and SU-DHL6 was 12.8 nM and 7.50 nM, respectively, and K-256 induced cell death at lower concentrations than existing drugs (vs. JQ1, OTX-015, and ABBV-075, $p < 0.0001$; vs. dBET6 and ARV-771, $p < 0.01$). Immunoblotting analysis showed that K-256, even at a tenth of the concentration, suppressed MYC expression more effectively than existing BET inhibitors and was comparable to existing BET degraders. Moreover, combining K-256 with venetoclax exhibited synergistic effects, both inhibiting cell proliferation and inducing apoptosis in SU-DHL4 and SU-DHL6 cell lines (combination index (CI) of 0.23 and 0.41 for inhibiting cell proliferation, and 0.43 and 0.64 for inducing apoptosis, respectively). In experiments using five MYC/BCL2 PDX cells, K-256 inhibited cell proliferation ($GI_{50}$ ranging from 24 to 213 nM) and induced apoptosis ($IC_{50}$ ranging from 24 to 229 nM) at lower concentrations than existing BET inhibitors and degraders. As expected, the combination of K-256 with venetoclax also demonstrated synergistic effects in PDX cells, similar to those observed in cell lines (CI of 0.515 to 0.762 for inhibiting cell proliferation; 0.085 to 0.995 for inducing apoptosis). Finally, we confirmed that K-256 showed a stronger therapeutic effect than OTX-015 and ARV-771 in *in vivo* PDX models.
**Conclusions :** The novel BET degrader, K-256, bound to BET proteins at lower concentrations than existing BET inhibitors and degraders, strongly suppressing MYC expression, primarily via BRD4 degradation. Additionally, K-256 demonstrated superior therapeutic effects in MYC/BCL2-related PDX models both *in vitro* and *in vivo*, suggesting that this novel drug could be a promising therapeutic agent for MYC/BCL2-related lymphoma. Its translation to future clinical applications warrants further consideration.

**Disclosures Furukawa:** *Chugai:* Honoraria. **Shimada:** *Incite, Daiichi Sankyo, AbbVie, Chugai, Meiji Seika Pharma, Bristol-Myers Squibb, Novartis:* Consultancy; *Bristol-Myers Squibb, Otsuka, Kyowa Kirin:* Research Funding; *AstraZeneca, Eisai, Takeda, Janssen, Bristol-Myers Squibb, Chugai, Kyowa Kirin, Nippon Shinyaku, Daiichi Sankyo, Meiji Seika Pharma, Ono, AbbVie, Novartis, Gilead, CSL Behring, Genmab:* Honoraria. **Esaki:** *Kyowa Kirin:* Current Employment. **Tanaka:** *Kyowa Kirin:*

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Figure1：Antitumor activity of K-256 monotherapy in MYC/BCL2-related PDX model

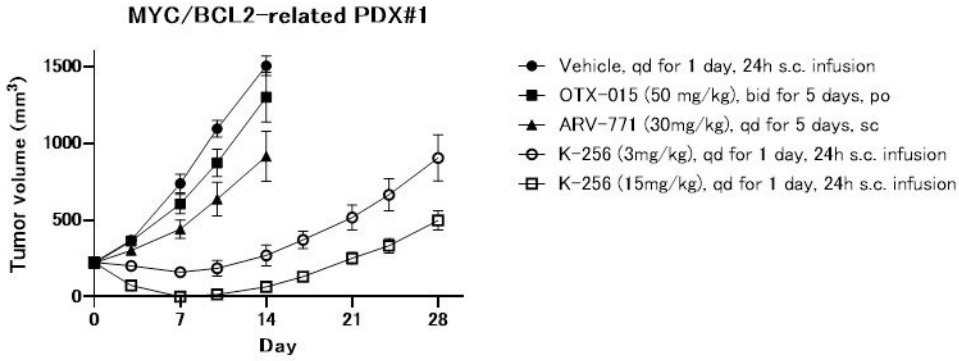


Figure2：Antitumor activity of combination of K-256 with venetoclax in MYC/BCL2-related PDX model

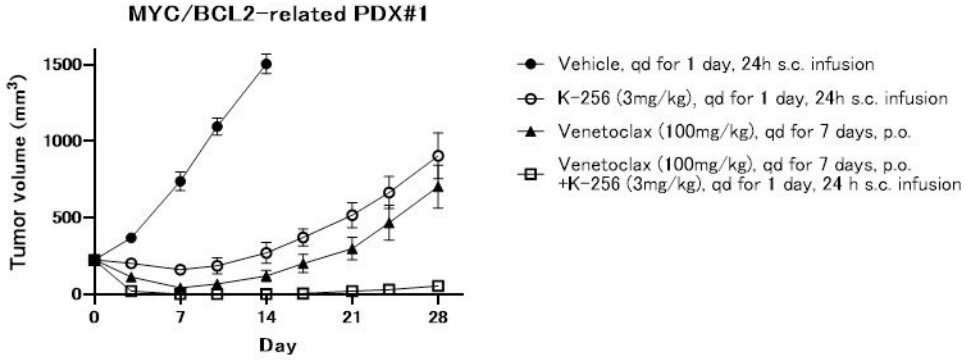


**Figure 1**

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