IKS03, a Next Generation CD19-Targeted Antibody Drug Conjugate, Shows Potent Activity in Preclinical Models of Aggressive B-Cell Lymphomas

Jutta Deckert[1], Jenny Thirlway[1], Justyna Mysliwy[1] , Adam Lodge[1], Yun-Hee Park[2], Hyun-Min Ryu[2], Na Ra Han[2], Ho Young Song[2], Chul-Woong Chung[2], Robert J. Lutz[1]
[1]Iksuda Therapeutics Ltd, Newcastle-upon-Tyne, UK; [2]LegoChem Biosciences Inc. (LCB), Daejeon, Republic of Korea

Abstract #1357

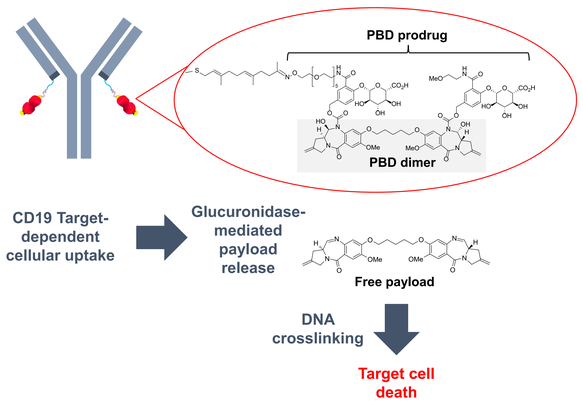
Background

Diffuse large B-cell lymphoma (DLBCL) is a common subtype of non-Hodgkin lymphoma (NHL). Although many patients respond to frontline chemoimmunotherapy, and treatment options for patients with relapsed or refractory DLBCL have improved with the success of CAR T cell therapies, clinical outcome for many patients is still suboptimal[1,2].

CD19 is widely expressed in DLBCL tumor cells, with normal tissue expression limited to B cells, making it an attractive target for targeted therapies including antibody drug conjugates (ADC).

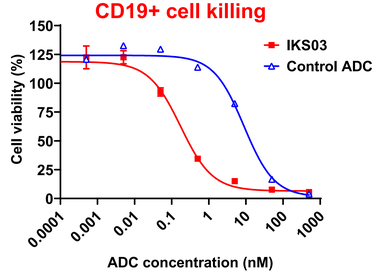
IKS03 is a CD19-targeting ADC with a PBD dimer pro-drug payload that induces DNA crosslinking and blocks DNA replication ultimately leading to cell death. IKS03 is generated by site-specific bioconjugation yielding a homogeneous conjugate with a drug to antibody ratio of 2. Linker-payload design in IKS03 utilizes LCB's proprietary glucuronide-trigger for payload release and activation. Following CD19 tumor selective binding and uptake, IKS03 requires intracellular lysosomal processing of beta-glucuronidase protecting groups to fully activate the payload which minimizes systemic release of the PBD dimer in human plasma. Prodrug design results in an increased therapeutic margin compared to traditional ADCs with DNA-crosslinking payloads, with increased efficacy and decreased toxicity.

In vitro, IKS03 results in potent and specific cell killing of CD19+ target cells with no human blood cell toxicity. This translates into significant in vivo activity in preclinical MCL and DLBCL models after single dose administration. The PBD prodrug approach confers stable ADC pharmacokinetics in plasma preclinically.



Pharmacology

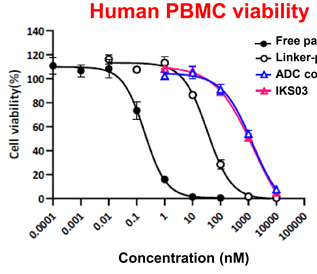
CD19+ cell killing



IKS03 induces potent, specific and dose dependent cell killing in vitro

- Sub-nanomolar EC50 values in all CD19+ lymphoma cell lines tested by CellTitreGlo assay
- Specificity confirmed with non-binding ADC

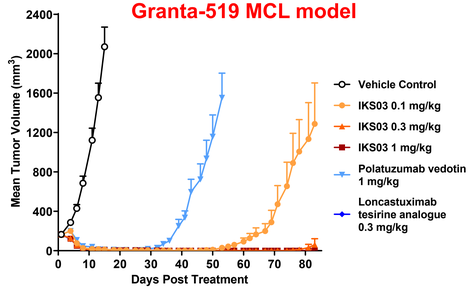
Human PBMC viability



In vitro PBMC cytotoxicity of the PBD payload is attenuated in the conjugate

- Unconjugated payload induced potent PBMC cell killing in vitro with sub-nanomolar EC50
- IKS03 EC50 was > 1 µM and similar to a non-binding ADC
- Linker-prodrug is also less cytotoxic in vitro

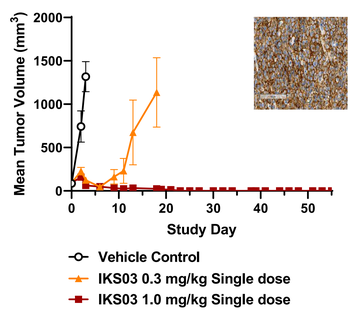
Granta-519 MCL model



IKS03 is highly efficacious in a Granta-519 Mantle Cell Lymphoma model in vivo

- Complete tumor regressions observed with a single dose of 0.1 mg/kg
- Granta-519 cells contain the CCND1 t(11;14) translocation present in MCL

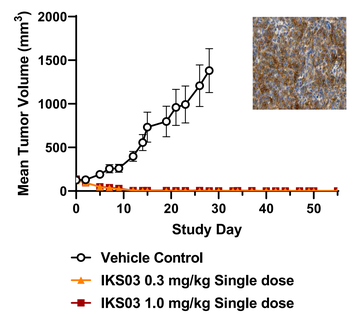
High-grade lymphoma PDX model



IKS03 is active in a high-grade 'triple-hit' lymphoma PDX model

- Tumor growth inhibition at 0.3 mg/kg and complete tumor regressions with a single dose of 1 mg/kg
- PDX derived from a treatment naïve patient with BCL2+; BCL6+; MYC+ lymphoma
- Post tumor collection, this patient was refractory to R-CHOP therapy

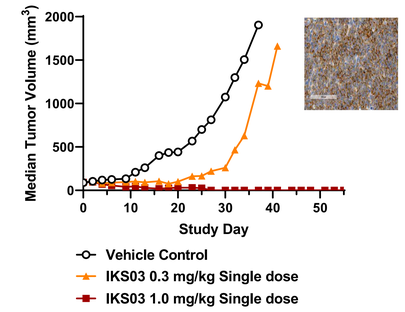
Refractory lymphoma PDX model



IKS03 is highly efficacious in a refractory lymphoma PDX model

- Complete tumor regressions with a single dose of 0.3 mg/kg
- PDX derived from a patient with no response to prior CHOP treatment
- Post tumor collection, this patient was also refractory to EPOCH chemotherapy

Pre-treated GCB lymphoma PDX model



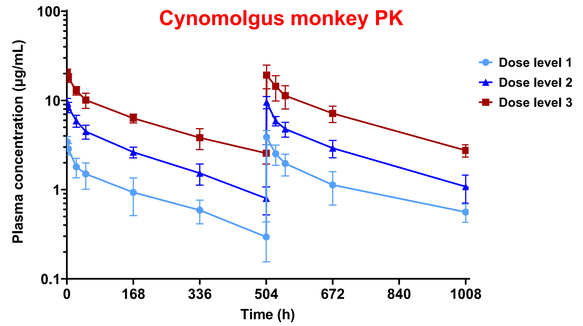
IKS03 is active in a pre-treated MYC-amplified GCB lymphoma model

- Tumor regressions at 0.3 mg/kg single dose with complete regressions at 1.0 mg/kg
- PDX derived from a patient with MYC-amplified GCB lymphoma post-rituximab relapse
- Post tumor collection, this patient responded to RCHOP + ibrutinib

METHODS: In vitro activity was evaluated by CellTitreGlo assay after 4 to 5-day incubation. Granta-519 subcutaneous xenografts were established in female CB17-SCID and low passage patient-derived xenografts (PDX) in NOG mice. Tumor-bearing mice were randomized and treated when the average tumor volume reached approximately 50 to 180 mm^3. Formalin-fixed, paraffin-embedded tumor samples from xenograft studies were assessed by semi-quantitative immunohistochemistry for CD19 expression. Total ADC and total antibody levels in plasma were determined by hybrid LC-MS/MS following repeat dose IV injection of IKS03 to cynomolgus monkeys.

Pharmacokinetics

Cynomolgus monkey PK



ADC remains stable in plasma across the 3-week dosing interval

- Pro-drug design results in favorable ADC stability and pharmacokinetics in cynomolgus monkey plasma with limited systemic payload release and activation
- Total ADC PK profile closely follows the antibody with a mean half-life of 8-10 days and slow clearance (mean 0.2 mL/h/kg)

Conclusions

- IKS03 is a CD19-targeted ADC with a novel glucuronide trigger PBD-prodrug design for intracellular payload release and activation
- Preclinical data further demonstrates that IKS03's advanced ADC design results in desirable compound properties
  - Specific target-dependent in vitro activity
  - Pro-drug design confers excellent plasma stability
  - Effective targeting of B-cell tumors while sparing normal CD19-negative cells
- IKS03 is highly effective in preclinical MCL and DLBCL xenograft models that contain some of the genetic alterations commonly found in relapsed/refractory NHL patients in need of treatment
- This warrants clinical investigation in patients with advanced B-Cell Non-Hodgkin Lymphomas (NCT05365659)

References

1. Crump *et al*, Blood 2017, 130(16): 1800-1808
2. Katz and Herishanu, Leukemia and Lymphoma 2014, 55(5): 999-1006

CONTACT: Iksuda Therapeutics Ltd, info@iksuda.com