IKS03, a CD19-targeted antibody drug conjugate with enhanced efficacy and tolerability for treatment of B-cell lymphomas

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Abstract #1755

Background

Lymphoma is the most common hematological malignancy. Non-Hodgkin lymphomas (NHL) are a heterogeneous group of hematologic malignancies derived from cells of the immune system. Diffuse large B-cell lymphoma (DLBCL) is a common subtype of NHL and although many patients respond to frontline chemoimmunotherapy, treatment options are limited, and clinical outcomes are suboptimal for patients with relapsed or refractory DLBCL[1].

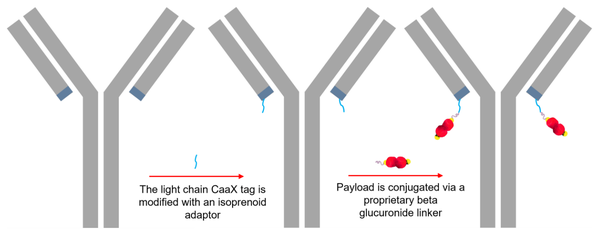
Specific B-cell differentiation antigens have facilitated the development of novel targeted therapeutics based on monoclonal antibodies, bi-specific antibodies, antibody-radionuclide conjugates, antibody-drug conjugates (ADC) and chimeric antigen receptor T (CAR-T) cells. These new approaches have provided important benefits leading to recent approvals in the relapsed and refractory setting. Nevertheless, there is an unmet medical need for novel therapies especially for refractory disease, at early relapse after frontline therapy and for transplant-ineligible patients.

CD19 is a glycoprotein expressed on the surface of both normal and malignant B-cells[2]. It serves as a well-established marker for B-cell ontology due to its expression along all differentiation stages starting at the pre-B stage until it is lost during terminal differentiation into plasma cells. CD19 expression is maintained during neoplastic transformation and is therefore expressed in most cases of B-cell malignancies derived from these precursors. Normal tissue expression is limited to B-cells thus reducing any on-target toxicity concerns.

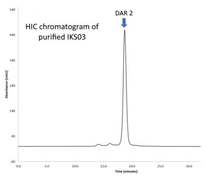
ADCs are the focus of intense interest as a means to provide selective tumor killing with increased efficacy and less toxicity than standard of care chemotherapies. The ADC, loncastuximab tesirine, has recently been approved for patients with a subset of B-cell NHL, demonstrating that CD19 can be successfully targeted by this therapeutic modality[3]. However, treatment with loncastuximab tesirine is not without significant toxicity[4].

IKS03 is an ADC comprised of an anti-CD19 antibody conjugated to a proprietary DNA-crosslinking PBD prodrug and includes a tumor-selective glucuronide-trigger technology for payload release and activation. ADC activity requires processing by beta-glucuronidase, a lysosomal enzyme often upregulated in tumor cells, while normal tissues with low levels of the enzyme are less able to process the ADC and are differentially spared.

ConjuAll: site-specific, homogeneous, and non-reversible conjugation



The manufacturing process for IKS03 involves four main steps: prenylation to add an isoprenoid adaptor molecule, conjugation of the beta glucuronide protected prodrug to the adaptor, Hydrophobic Interaction Chromatography (HIC) purification and final formulation to yield a molecule of IKS03 with a drug to antibody ratio (DAR) of 2.

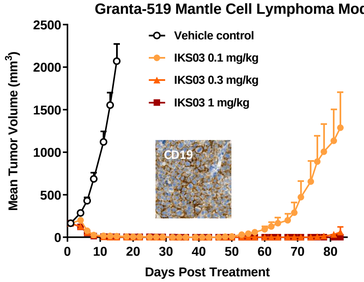


Results

IKS03 demonstrates potent *in vivo* activity in lymphoma cell line derived xenograft models

IKS03 was evaluated in female CB17-SCID mice. Tumor-bearing mice were randomized and treated when the average tumor volume reached approximately 160-180 mm^3. Formalin-fixed, paraffin-embedded samples from tumor cell line models used in mouse xenograft studies and the PDX model were assessed by standard chromogen immunohistochemistry for level of CD19 expression.

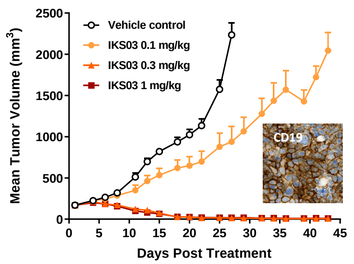
Granta-519 Mantle Cell Lymphoma Model



Mantle Cell Lymphoma (MCL) is a rare aggressive lymphoma subtype with poor duration of response and patient intolerance to current approved drugs.

IKS03 is highly active in the Granta-519 MCL model, with complete regressions observed with a single dose of 0.1 mg/kg.

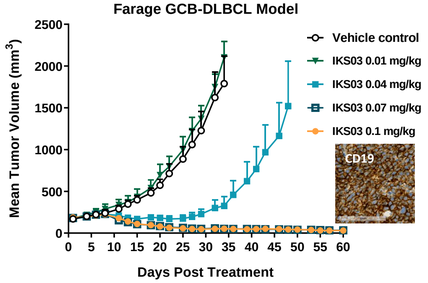
OCI-LY10 ABC-DLBCL Model



Activated B-cell (ABC) DLBCL is a distinct molecular subtype of DLBCL. ABC-DLBCL is associated with substantially worse outcomes when treated with Standard of Care.

Complete regressions were observed with a single dose of 0.3 mg/kg in the OCI-LY10 xenograft model.

Farage GCB-DLBCL Model



Although patients with Germinal Centre B-like (GCB) DLBCL tend to have better outcomes than patients with the ABC subtype, approximately 20 % will relapse following R-CHOP.

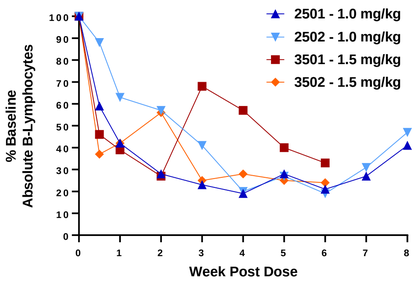
Complete regressions were observed with a single dose of 0.07 mg/kg in the Farage xenograft model.

In vivo pharmacodynamics and safety assessment

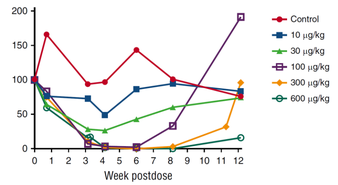
A single dose toxicity study was carried out for IKS03 in cynomolgus monkey. IKS03 was administered by intravenous bolus at 1.0 or 1.5 mg/kg followed by a 6- to 9-week observation period. Immunophenotyping was conducted by flow cytometry. Peripheral B-lymphocytes were identified as CD45+CD3-CD20+ and reported as relative percentages of the CD45+ lymphocyte gate. The absolute numbers of B-lymphocytes (cells/µL) were normalized to the Day -3 pre-dose baseline counts.

B-cell depletion in cynomolgus monkeys

IKS03 single dose



SGN-CD19B single dose



IKS03 cross reacts with monkey CD19.

IKS03 was tolerated in monkeys at the highest dose tested of 1.5 mg/kg (single dose).

In cynomolgus monkey, B-cell depletion was observed consistent with the proposed CD19-targeting mechanism of action.

No neutropenia or lymphocytopenia was noted.

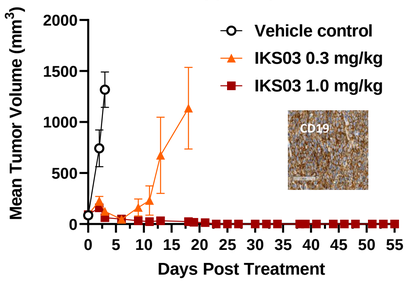
Reduced B-cell depletion was noted for IKS03 as compared to data from comparator agents[5], even at doses much greater (1.5 mg/kg) than that needed for complete responses in B-cell lymphoma mouse models (0.07 mg/kg). This more limited depletion of normal B-cells supports the hypothesis of reduced linker-prodrug activation of IKS03 in normal tissues.

Results

IKS03 is active in an aggressive lymphoma patient derived xenograft model

A low passage tumor was implanted into female NOG mice. Tumor-bearing mice were randomized and treated when the average tumor volume reached approximately 100-200 mm^3.

Non-GCB Type,Triple-hit DLBCL Model



The PDX model is a non-GCB subtype that was characterized as 'triple hit'. High-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements (known as double or triple hit) are aggressive and associated with poor prognosis.

A single dose of IKS03 at 0.3 mg/kg was active, and a single dose of 1 mg/kg induced complete regression in 10/10 mice in the group.

Conclusions

- IKS03 is a CD19-targeted ADC with a novel glucuronide trigger PBD-prodrug design for intracellular payload release and activation.
- *In vivo*, IKS03 is highly effective at causing tumor regressions in DLBCL models at single doses of 0.07 to 0.3 mg/kg, while being tolerated at 1.5 mg/kg single dose in cynomolgus monkeys.
- Limited depletion of normal B-cells in cynomolgus monkey supports the hypothesis of reduced linker-prodrug activation of IKS03 in normal tissues
- Preclinical data demonstrates that IKS03's advanced ADC design results in an increased therapeutic margin compared to traditional ADCs with DNA-crosslinking payloads, with increased efficacy and decreased toxicity.

References

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