A CD123-targeting Antibody-Drug Conjugate (ADC), IMGN632, designed to eradicate Acute Myeloid Leukemia (AML) cells while sparing normal bone marrow

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ASH 2016

IMMUNOGEN

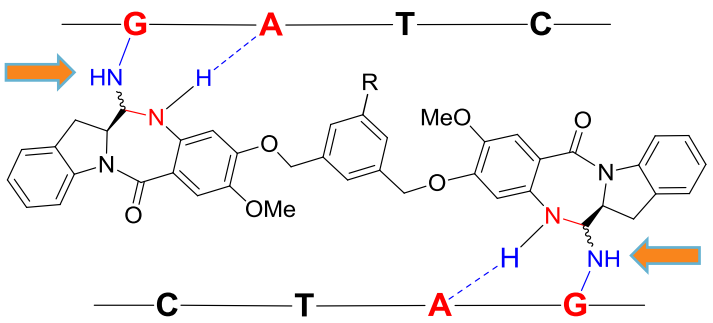
CD123 as a target for AML therapy

- CD123 is the alpha-subunit of the IL-3 receptor
- Expression in AML
  - >90% of patients express CD123 on blasts and leukemic stem cells
  - Higher levels associated with aggressive disease and poor prognosis
- Expression on normal tissues
  - Low levels on normal hematopoietic stem cells
  - Significant levels on normal myeloid progenitors
- Potential for CD123-targeted therapy to produce durable responses in AML, but also cause myelosuppression

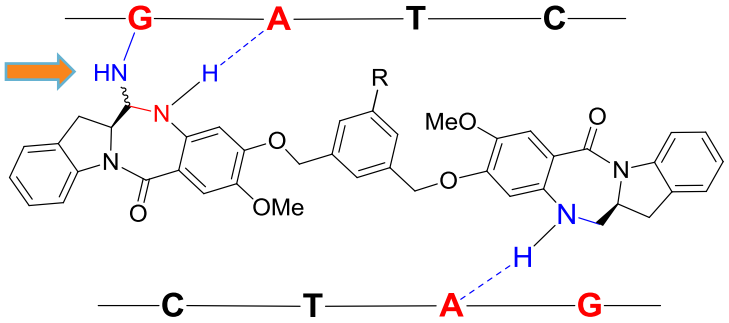
ADCs of anti-CD123 antibody with IGN payload

- Antibody
  - humanized IgG1 binding to an unique epitope on CD123
  - engineered for precise conjugation of two payload molecules
- Payload
  - novel DNA targeting Indolino-benzodiazepine dimers (termed IGNs)

Cross-linking IGN (C-ADC payload)

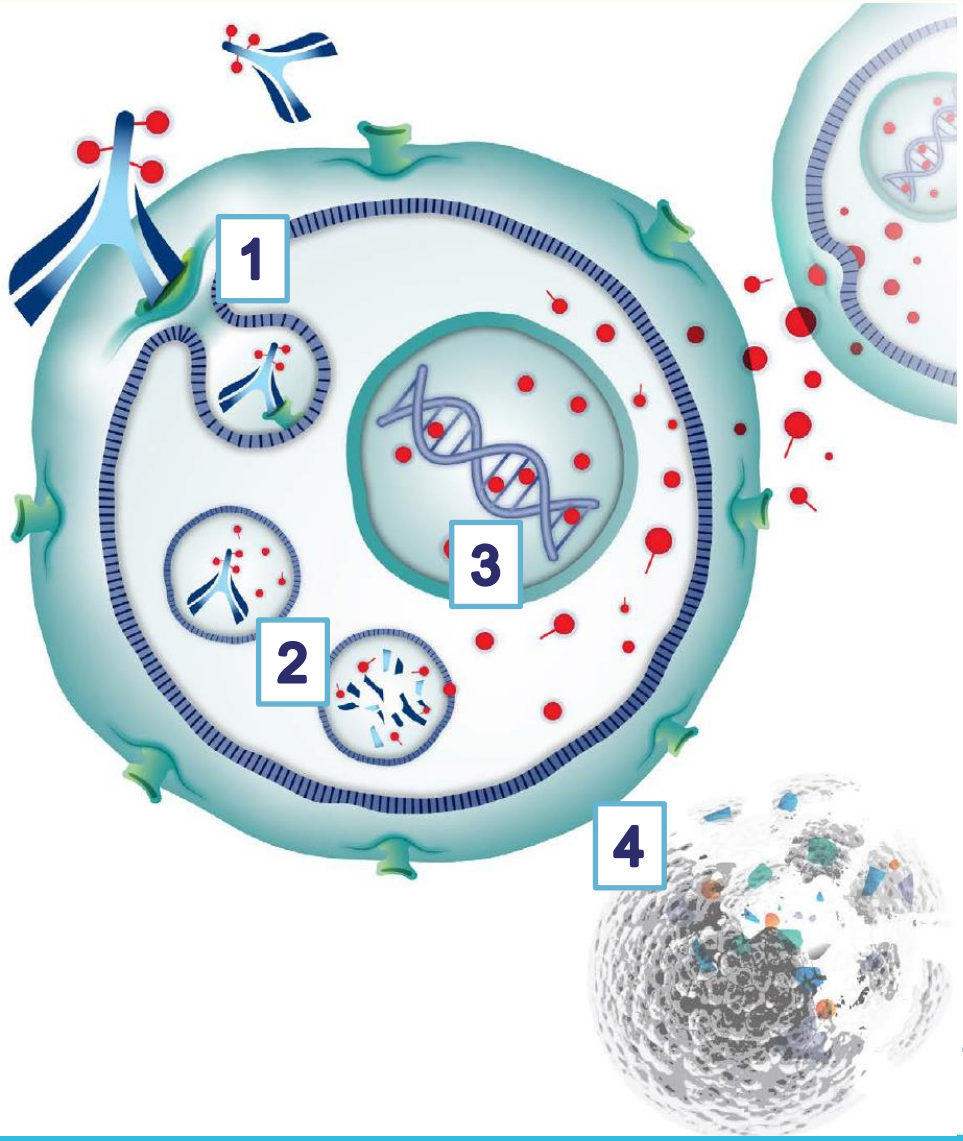


Alkylating IGN (A-ADC payload)



- Linker
  - peptide, stable in circulation

Proposed mechanism of cell killing by Antibody-IGN conjugates



1. ADC binding to CD123 triggers internalization and trafficking to lysosomes

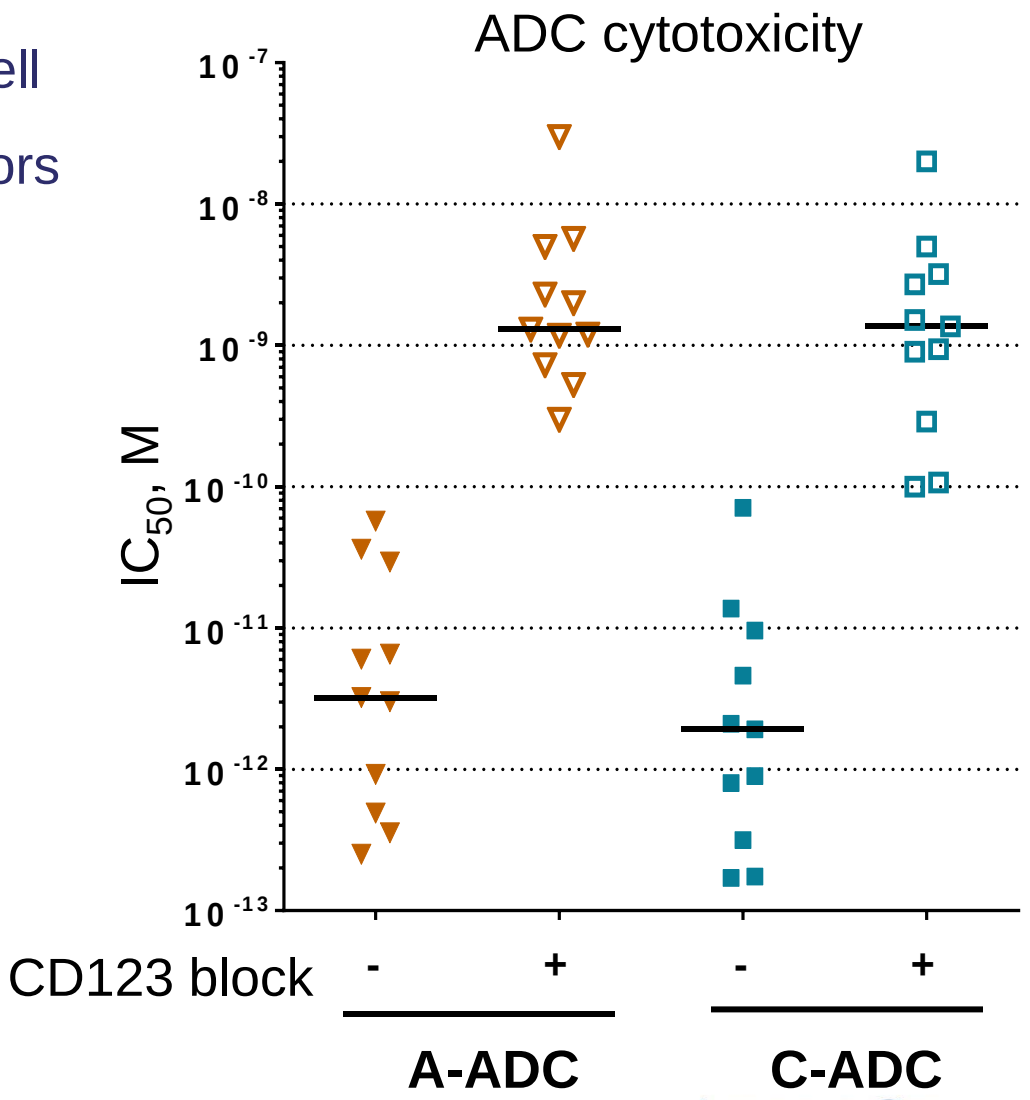
2. In lysosomes, antibody and linker are catabolized releasing cytotoxic payload

3. The payload diffuses into the nucleus and binds, alkylates or cross-links DNA, inducing cell cycle arrest and

4. apoptotic cell death

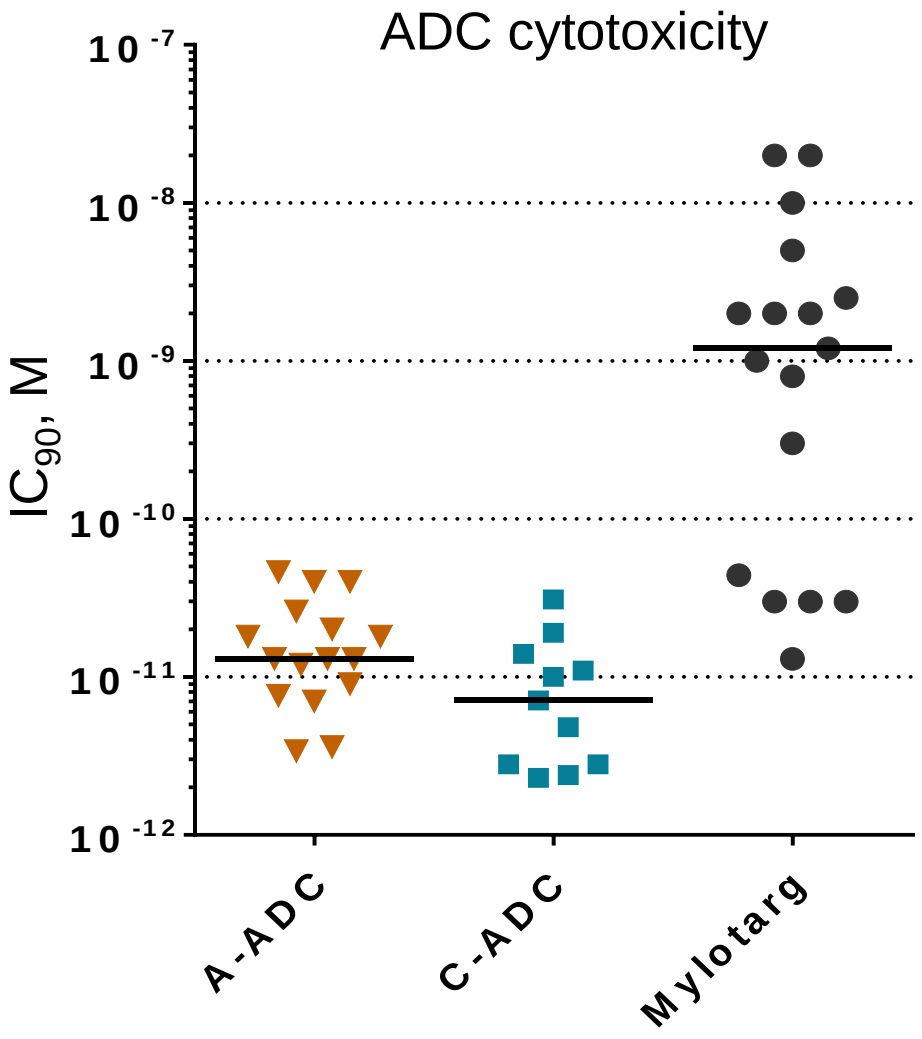
Alkylating ADC (A-ADC) and cross-linking ADC (C-ADC) are active in multiple CD123-positive AML cell lines *in vitro*

- Eleven AML CD123-positive cell lines with poor prognostic factors (FLT3-ITD, P53, EVI1, MDR1) were tested
- Both ADCs are highly active
- Blocking CD123 reduced ADC potency ~ 500-fold



Both A-ADC and C-ADC are ~ 100-fold more active than Mylotarg on primary AML samples

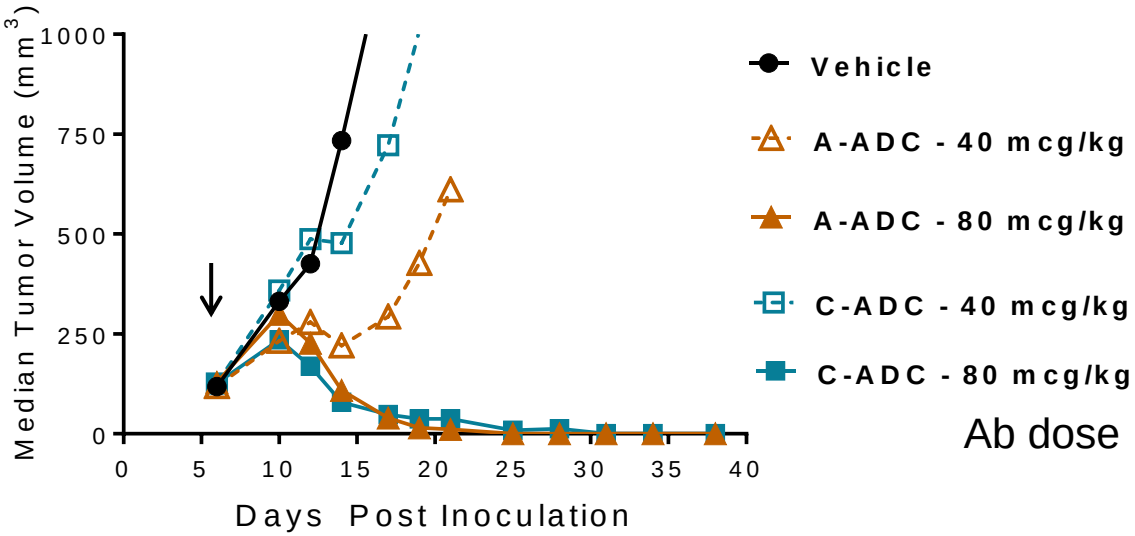
- Samples from 17 AML patients, including 4 relapsed/refractory and 10 with multi-drug resistance tested in CFU assays
- Unlike Mylotarg, A-ADC and C-ADC are highly active against all samples



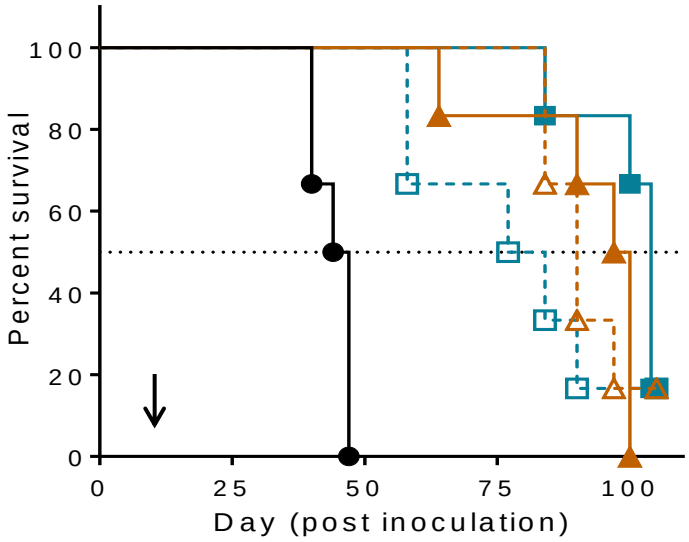
Comparable activity of A-ADC and C-ADC in AML xenograft models *in vivo*

Model resistant to SoC*
EOL-1 subcutaneous

** Cytarabine and Azacitidine*



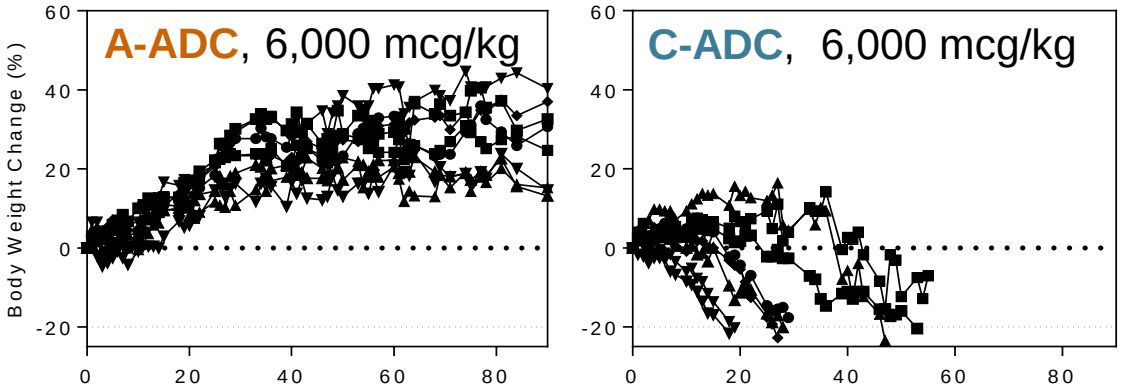
Model with FLT3-ITD
MV4-11 disseminated



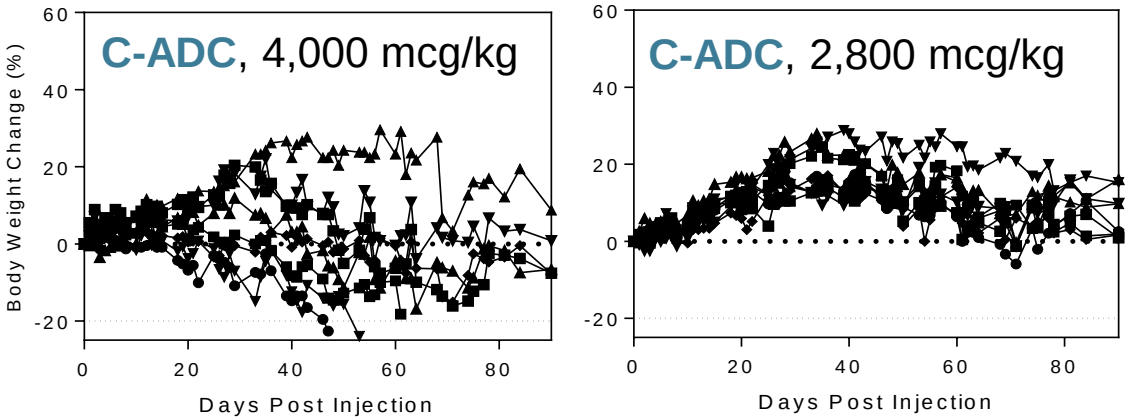
- Both ADCs at 80 mcg/kg single dose are highly active
- At 40 mcg/kg - A-ADC is at least as active as C-ADC

A-ADC is better tolerated than C-ADC in tumor free CD-1 mice

- At 6,000 mcg/kg A-ADC is well tolerated in mice, C-ADC is toxic

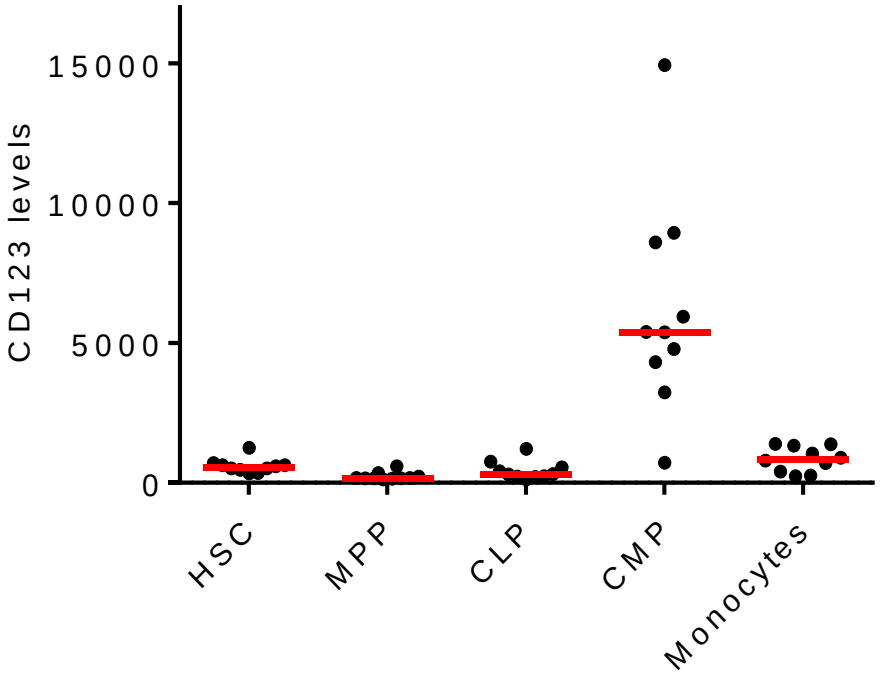


- At lower doses mice treated with C-ADC lose weight weeks after dosing

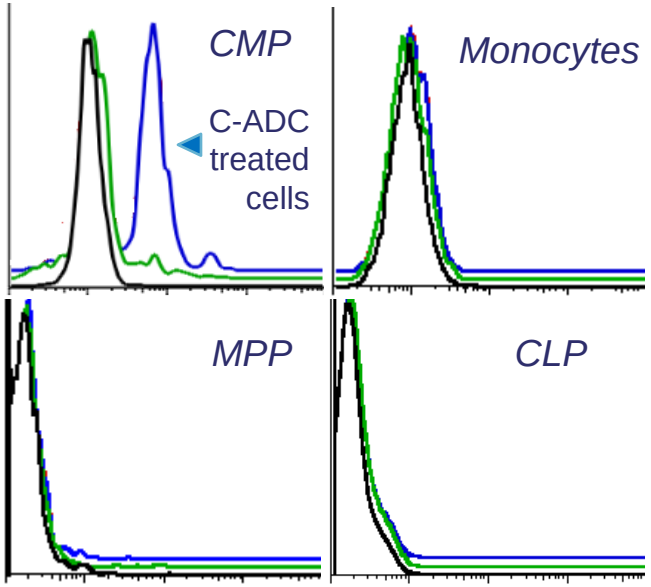


Normal human myeloid progenitors are affected by C-ADC *in vitro*

CD123 levels on normal bone marrow cells (n=10)



Apoptotic (C-caspase-3) signal



Black – no treatment

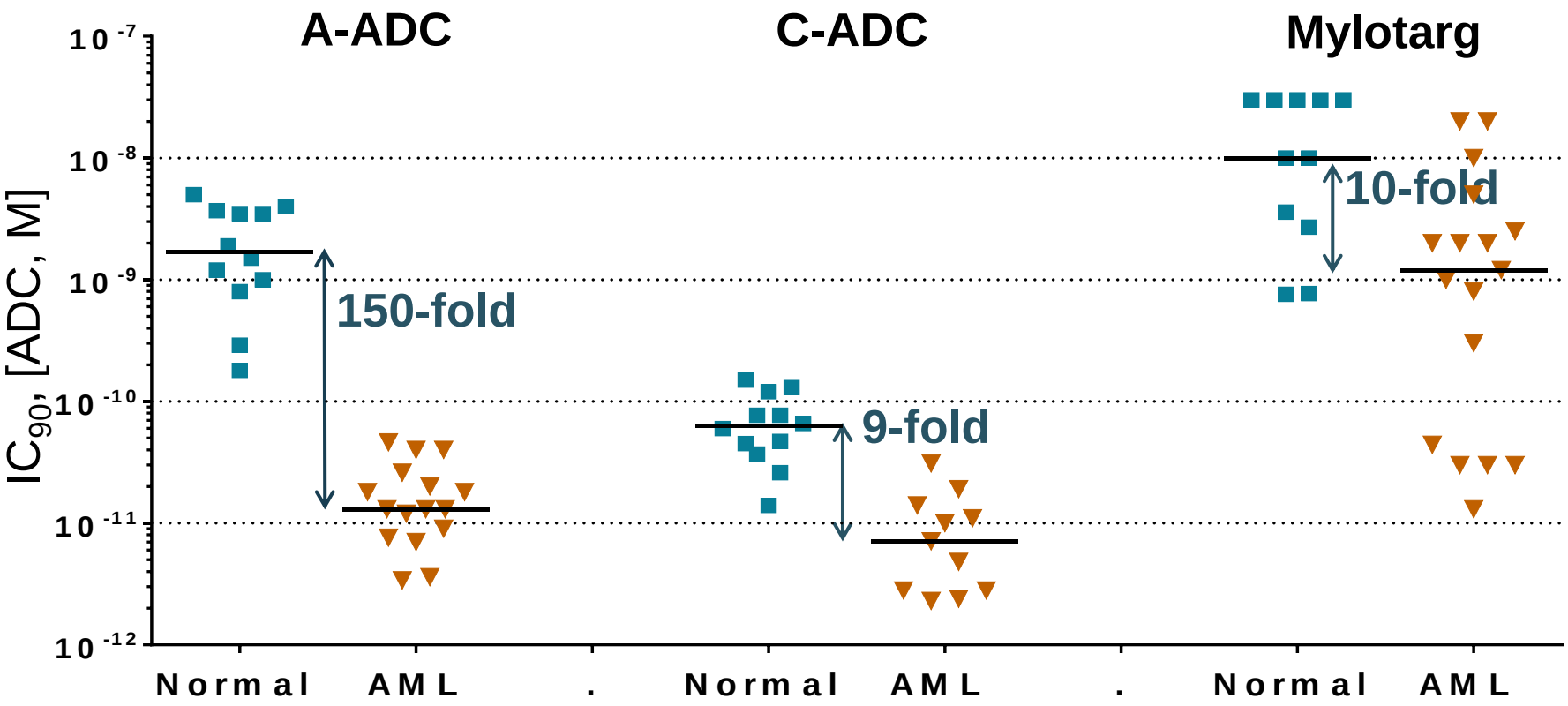
Green – cells treated with 100pM A-ADC

Blue – cells treated with 100pM C-ADC

- Neither ADC affects Multi-Potent Progenitors (MPP), Common Lymphoid Progenitors (CLP) or monocytes
- C-ADC, but not A-ADC, induces apoptosis of Common Myeloid Progenitors (CMP)

A-ADC, but not C-ADC or Mylotarg, displays pronounced preferential killing of AML over normal myeloid progenitors

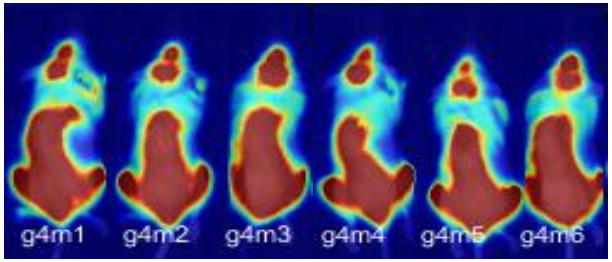
- Normal bone marrow (n=12) and AML (n=17) samples tested in GM-CFU assays
- A-ADC is ~ 50 fold less cytotoxic than C-ADC to normal myeloid progenitors



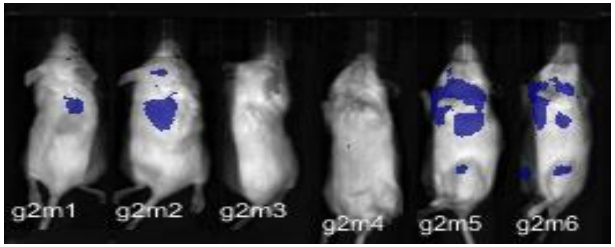
A-ADC (IMGN632) is highly active in multiple AML models with poor prognostic factors *in vivo*

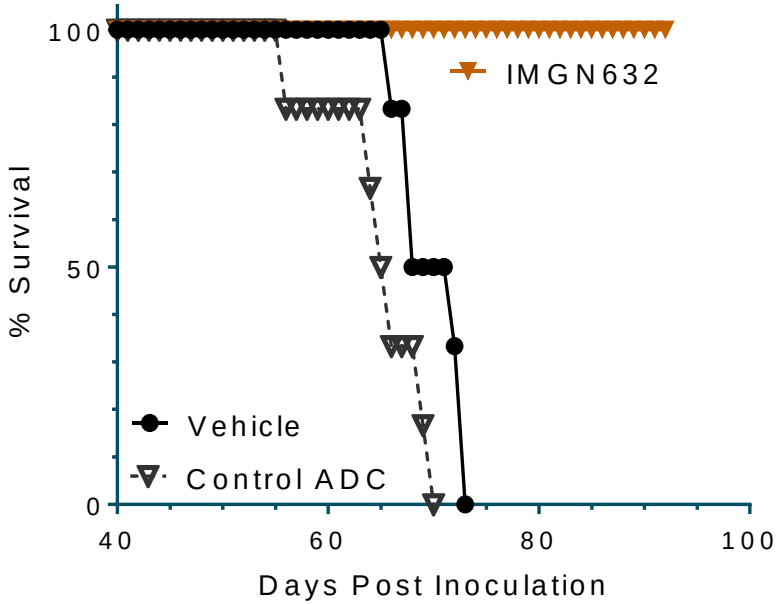
- Kasumi-3-Luciferase model (P53 and MDR) *
  - IMGN632 reduced tumor burden and extended survival in 6/6 mice

Control non-binding ADC



IMGN632





** Y.Kovtun et al., EHA 2016 poster 4122*

- IMGN632 high activity in additional *in vivo* models **

*** S. Adams et al., ASH 2016 poster 2832*

Summary

- The alkylating ADC (IMGN632) is better tolerated in mice and less cytotoxic to normal myeloid progenitors than the crosslinking ADC

- IMGN632 is highly active in:
  - AML cell lines with poor prognostic factors *in vitro*
  - multiple AML models *in vivo*
  - samples from all AML patients *in vitro*

    at concentrations that are non-toxic to bone marrow cells and

    100-fold lower than Mylotarg

- Phase 1 trial for IMGN632 in AML and other CD123-positive malignancies is planned for 2017