

Abstract Number:
305

Title: ELU001, a targeted C'Dot drug conjugate (CDC) for the treatment of folate receptor alpha (FR α) overexpressing cancers

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ABSTRACT

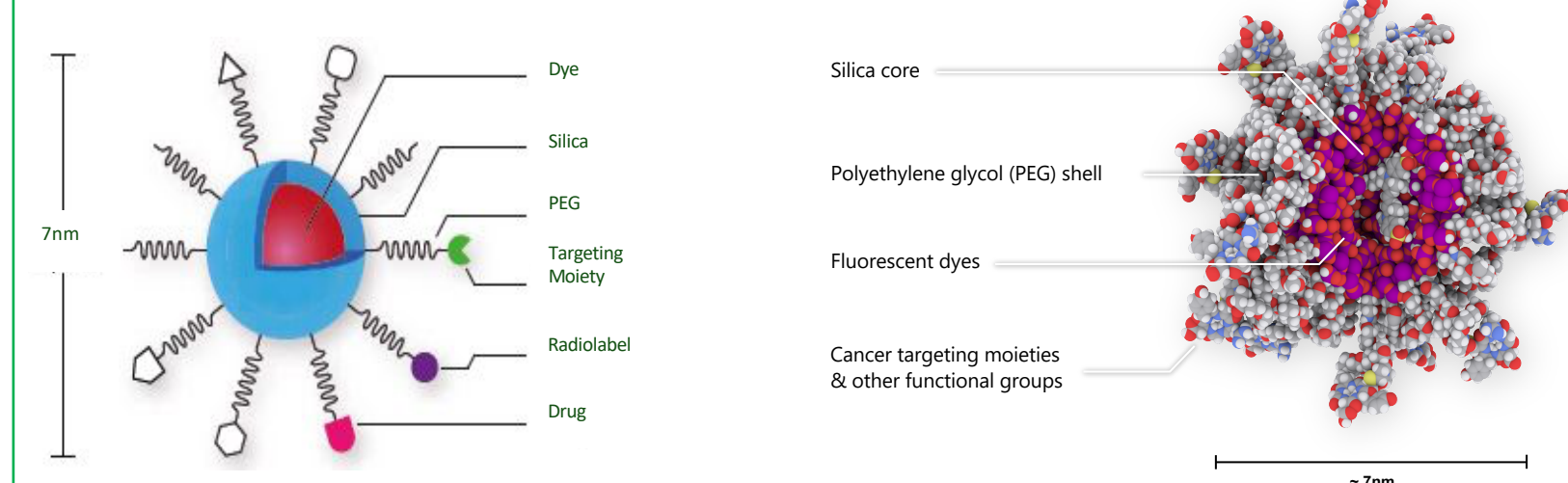
CDCs are novel ultra-small (6-7 nm) nanoparticle drug conjugates have demonstrated faster tumor targeting and deeper tumor penetration than antibody drug conjugates in animal models. CDCs are capable of targeting tumors in the brain and pancreas that are difficult to access, while exhibiting limited exposure to normal tissues due to their efficient renal elimination. CDCs are composed of a silica core, in which Cy5, a far-red dye is covalently encapsulated. The silica core is covalently coated with a layer of polyethylene glycol which is then functionalized with targeting moieties and payloads. ELU001 (EC112002) is a CDC functionalized with ~20 molecules of the topoisomerase-1 inhibitor exatecan linked via a proteolytic cleavable linker as a payload and ~15 folic acids to provide targeting to FR α overexpressing cancers. ELU001 is rapidly internalized into FR α expressing cells and is trafficked to the lysosome where exatecan is released from the CDC.

ELU001 exhibits potency in the low single digit nanomolar to sub-nanomolar range against cancer cells that express 3+ (KB, IGROV-1) and 2+ (SK-OV-3, HCC827 and OVCAR-3) levels of FR α after a 6-hr exposure in a 7-day viability study. In contrast, an anti-FR α ADC based upon mirvetuximab soravtansine exhibits lower potency (>100 nM IC₅₀) against SK-OV-3 and HCC827 cells and 40 nM IC₅₀ against OVCAR-3 cells. ELU001 exhibits potent efficacy against established s.c. KB human cervical tumor xenografts in immunodeficient mice with significantly better efficacy and safety than free exatecan payload. It is also effective in treating established SK-OV-3 tumors with lower (2+) FR α expression, a setting where the ADC is again less effective.

IND-enabling nonclinical studies are currently underway to prepare for initiation of a first-in-human clinical trial in the second half of 2021 in subjects with FR α overexpressing cancers.

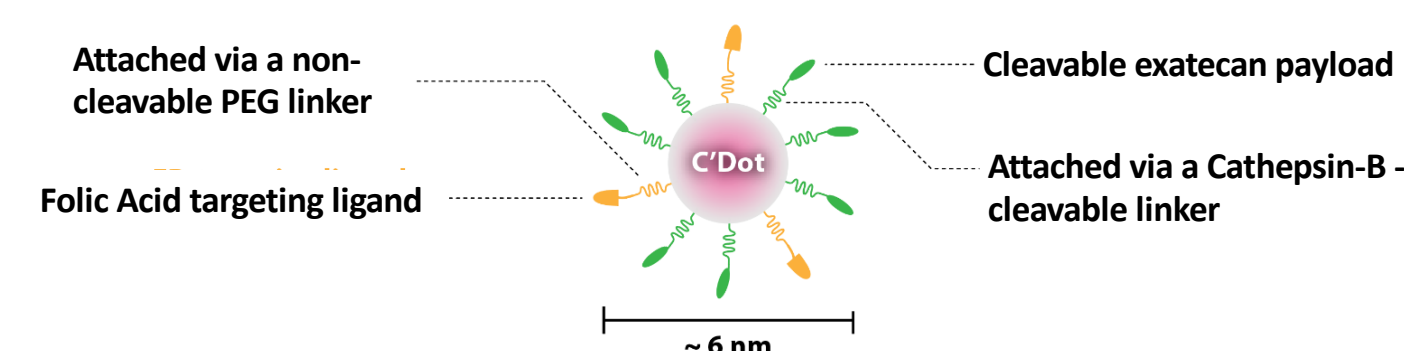
CDC Technology

C'-Dots Size and Structure



- Ultra-small, 7nm versus 50-100nm for other nanoparticles.
- Cy5 Dye core allows for direct assessment of pharmacokinetics tumor penetration in biopsies.
- Silica shell is covalently bound to short polyethylene glycol (PEG) chains, some with terminal DBCO groups for further functionalization.
- Combinations of up to 80 ligands/drugs/etc. can be coupled to a single C'Dot.
- Small size and neutral charge decreases off-target interactions and facilitates rapid and deep penetration into tumors and the ability to cross disrupted blood brain barrier

EC112002 – An anti-FR α Topoisomerase-1 Inhibitor CDC



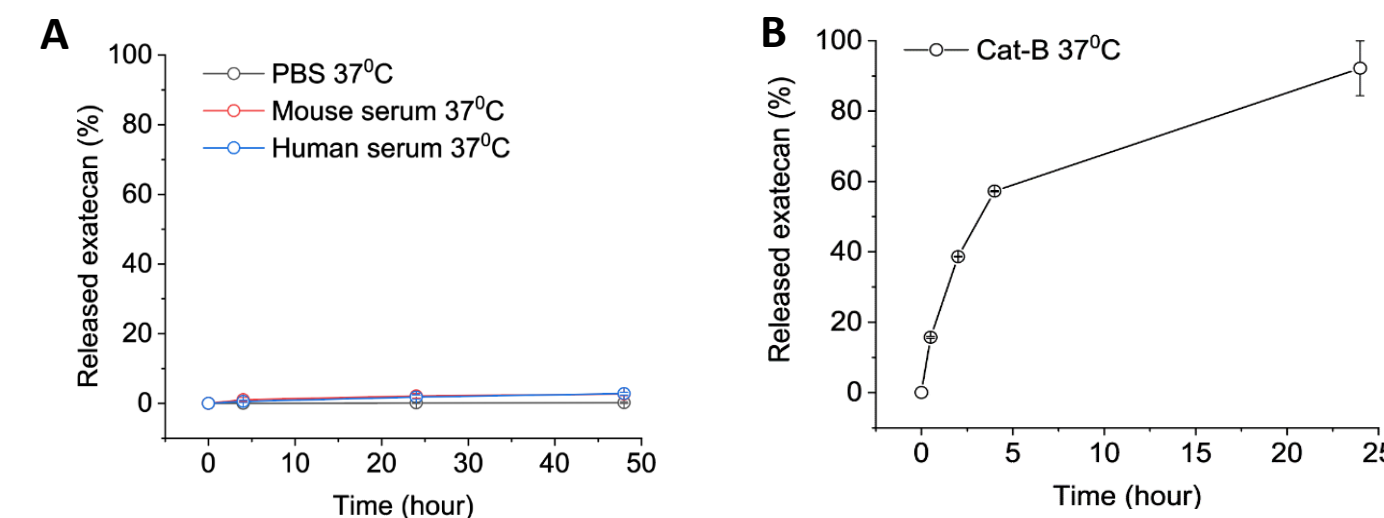
ELU001 (EC112002) is a novel C'Dot Drug Conjugate (CDC)

- Targeted via folic acid to Folate Receptor Alpha (FR α) overexpressing tumors.
- Delivering Exatecan – a potent Topoisomerase-1 inhibitor payload that blocks the action of topoisomerases which are required for the breaking and rejoining of the phosphodiester backbone of DNA strands during the cell cycle.

In vitro Payload Stability/Release

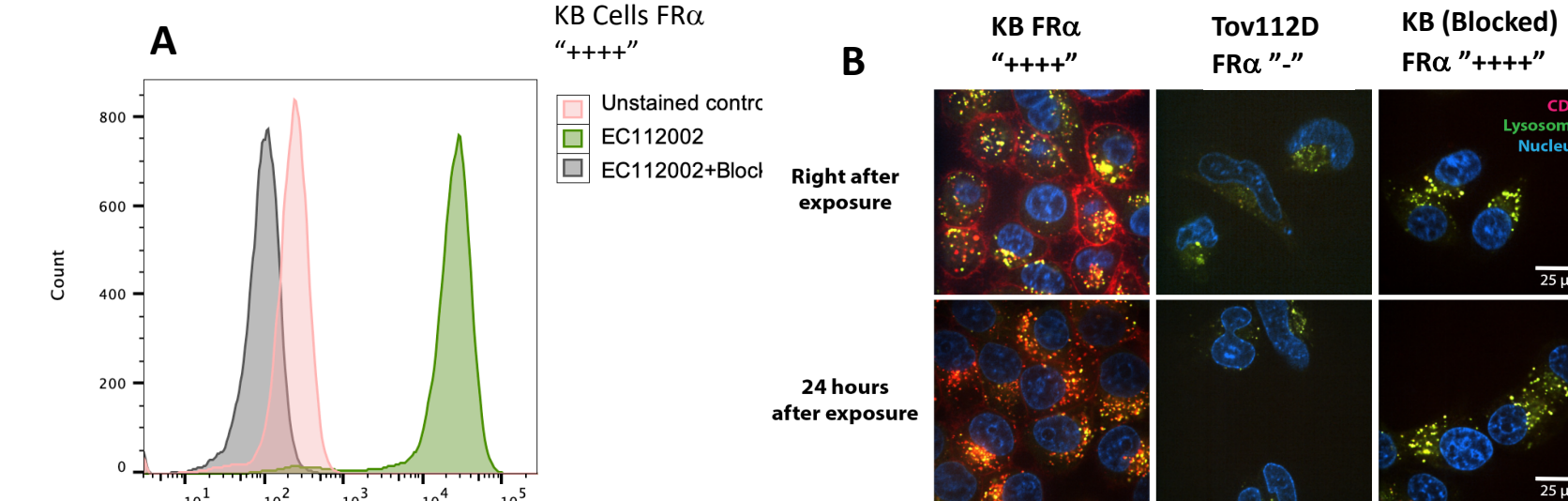
A. *In vitro* stability of ELU001 (EC112002) in PBS, human serum, and mouse serum, respectively. Sample analysis by RP-HPLC revealed limited release of exatecan payload through at least 48 hrs.

B. Efficient release of payload from EC112002 is induced by activated recombinant human cathepsin-B. Sample analysis by RP-HPLC revealed active release of exatecan.



In vitro targeting

A) Flow cytometry demonstration that ELU001 (EC112002) binds specifically to FR α -⁺ KB cells and can be blocked by a significant excess of free ligand and does not bind to FR α -⁻ KB cells
B) Confocal microscopy reveals that following binding/internalization EC112002 traffics to the lysosome (co-localization with LysoTracker dye) in un-blocked FR α -⁺ KB cells.



In vitro Tumor Spheroid Penetration

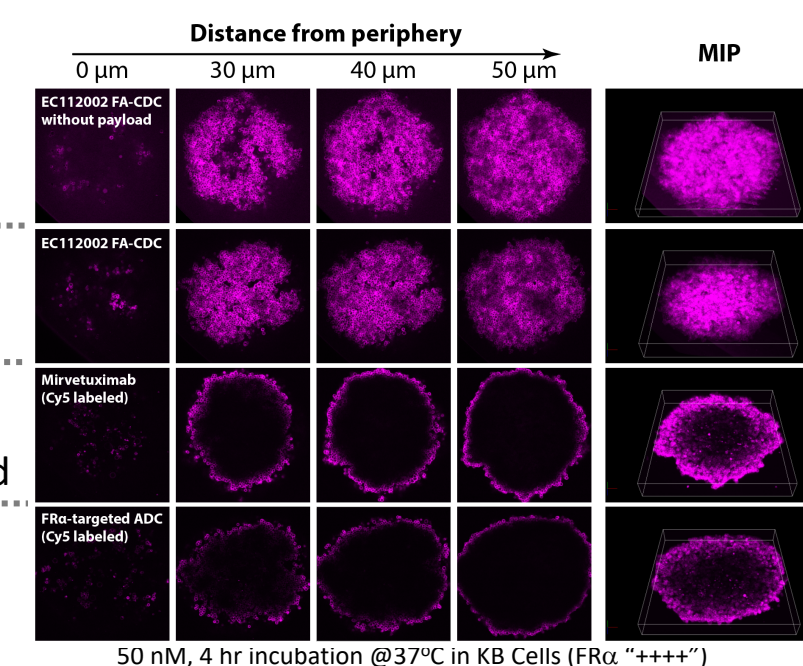
ELU001 EC112002 penetrates rapidly into FR α "+" tumor spheroid while ADC remains in periphery after 4 hr and 7-day (not shown) incubations *in vitro*

Anti-FR α C'Dot (EC112002 without payload) penetrates throughout FR α "+" tumor spheroid

EC110220 (with exatecan payload) retains ability to reach cells deep in spheroid

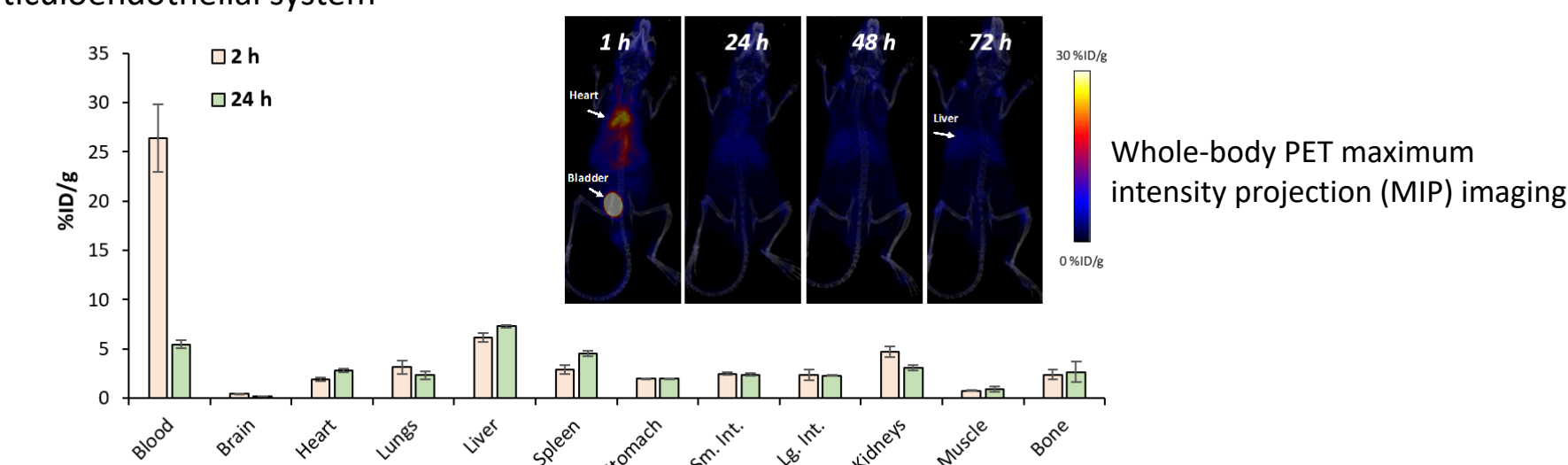
Mirvetuximab (produced by Elucida based upon Immunogen seq) remains on the periphery of the spheroid

Mirvetuximab soravtansine (with DM4 payload produced by Elucida) also fails to penetrate beyond periphery



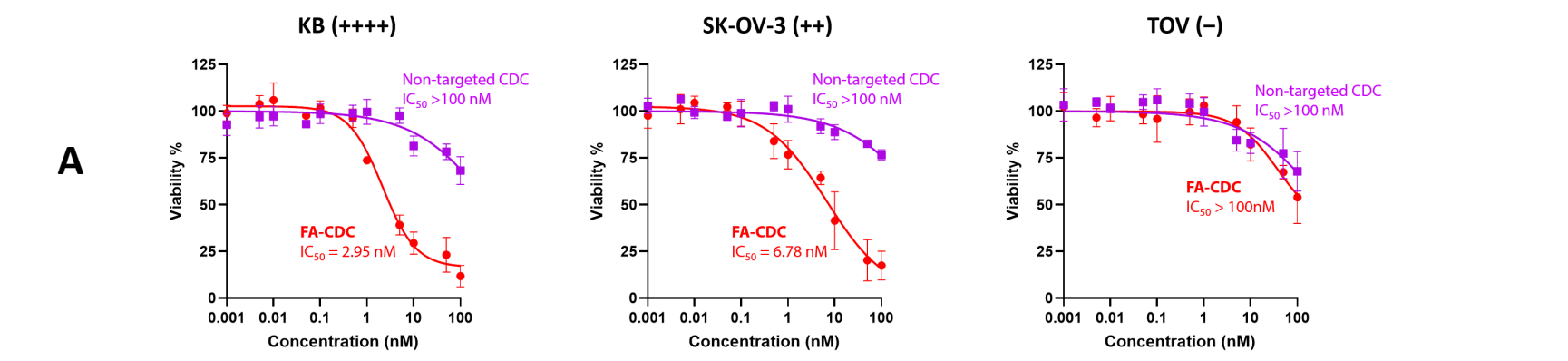
Biodistribution and PET Imaging of ⁸⁹Zr-conjugated ELU001 reveals Rapid Systemic Elimination

Imaging of ⁸⁹Zr-EC112002 (ELU001) in non-tumor bearing mice over a 72-hour period post i.v. admin. and representative normal organ biodistribution at 2- and 24-hour (n=3 mice) revealed no excessive normal tissue uptake or retention of ⁸⁹Zr-EC112002. Suggesting that EC112002 is not subject to metabolism by the reticuloendothelial system

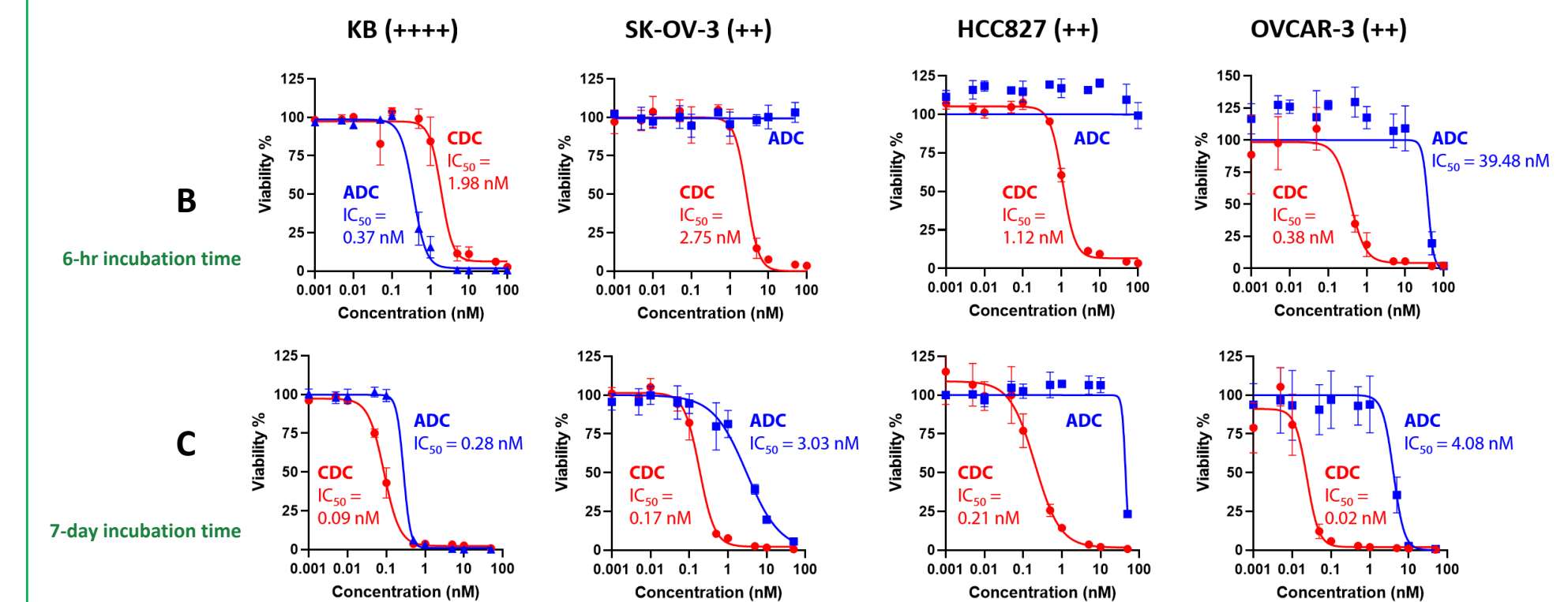


ELU001 (EC112002) Exhibits Selective and Potent *In Vitro* Cytotoxicity

EC112002 vs. non-targeted control CDC in a 6-hour exposure (72-hour total assay time) **(A)** displays specific killing of both high and moderate FR α expressing cell lines while the TOV-112D FR α negative cell line exhibited no difference

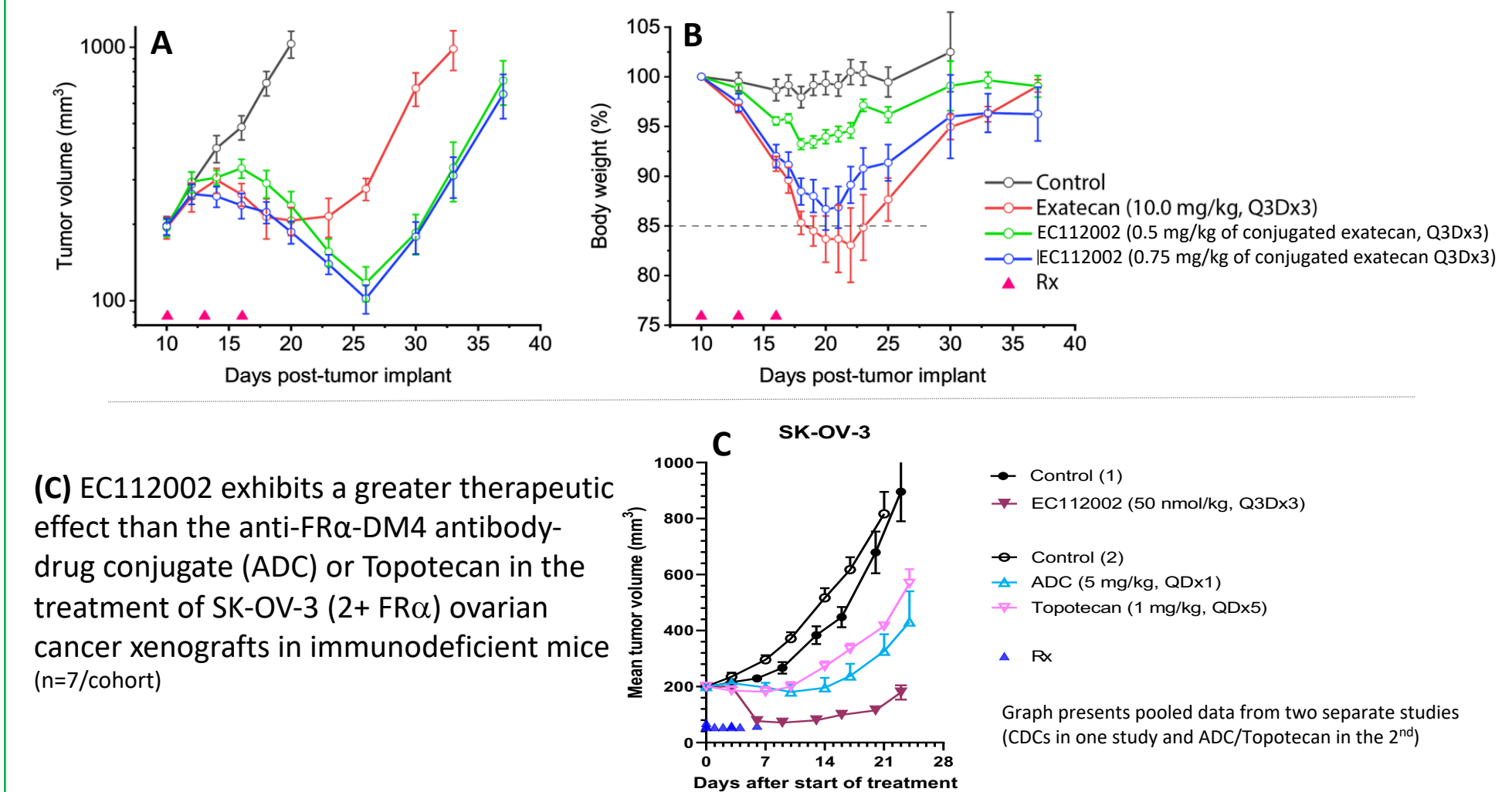


EC112002 vs. an ADC based upon mirvetuximab soravtansine with a 6-hr **(B)** or 7-day **(C)** exposure in a 7-day assay. EC112002 exhibits superior cytotoxicity after 6-hr exposure and maintains superiority in tumor cell lines cells that express lower FR α suggesting that CDCs may be effective in the setting of lower antigen expression.



ELU001 (EC112002) Exhibits Superior Efficacy to Free Payload and ADC *in vivo*

EC112002 administered at 75 or 50 nmol/kg exhibited superior efficacy in the treatment of FRα 4+ KB tumors **(A)** and better safety **(B)** than free exatecan administered at a much higher dose (10 mg/kg). (n=7/cohort)



SUMMARY

ELU001 (EC112002)

- Can deliver high concentrations of exatecan selectively to tumors.
- Exhibits potent *in vitro* cytotoxicity, out-performing an ADC against the same target in the setting of lower antigen expression.
- Exhibits efficacy and safety in preclinical studies, out-performing free drug payload and an ADC against the same target that is in advanced clinical development.
- EC112002 is being advanced towards clinical studies as ELU001 with first in human studies expected in the 2nd half of 2021