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A next generation ADC for Nectin-4 expressing tumors:

*preclinical characterization of **IPH4502**, a novel and differentiated exatecan-based ADC targeting Nectin-4*

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Disclosure Information

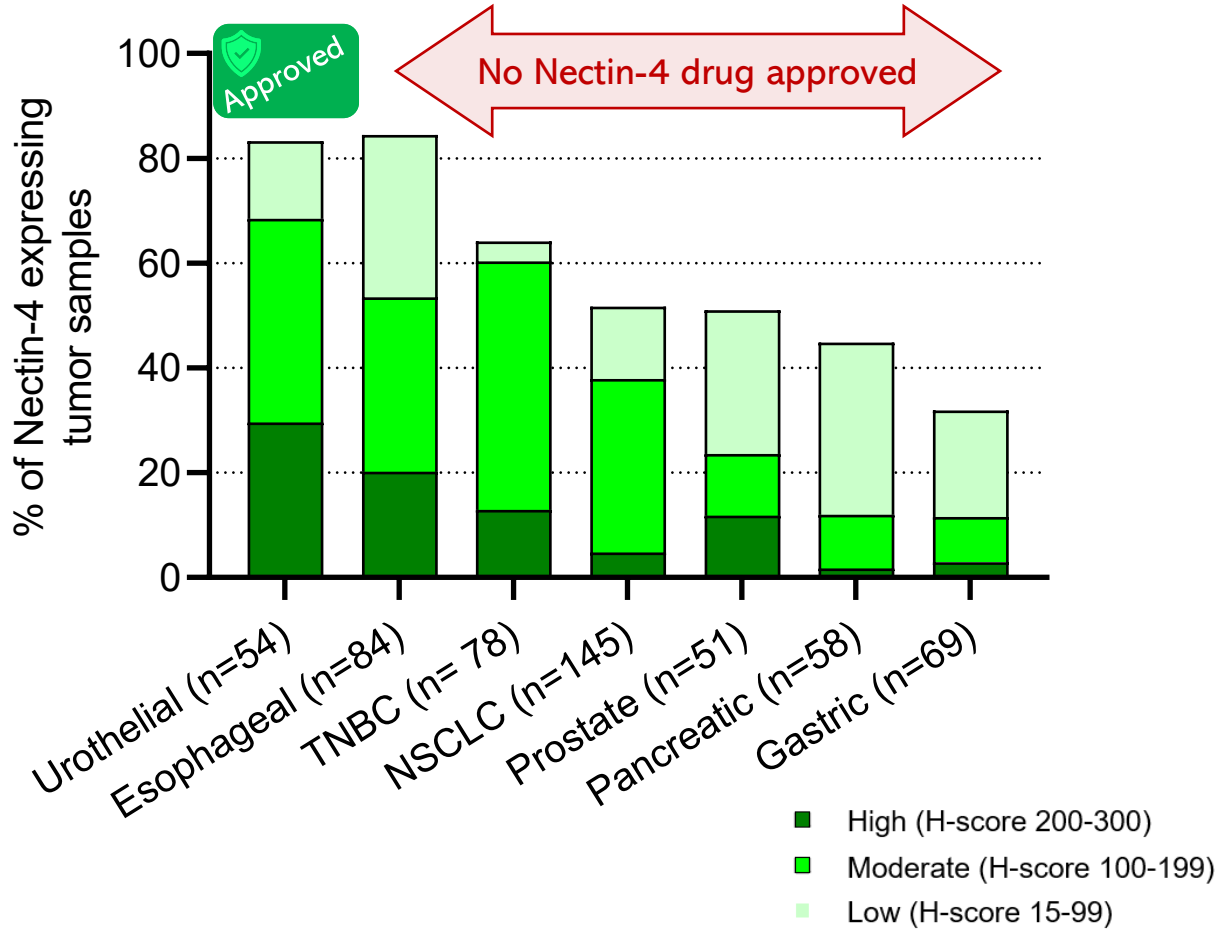
- Caroline Soulas

I have the following relevant financial relationships to disclose:

Employee of: Innate Pharma

Stockholder in: Innate Pharma

Target Nectin-4 in a broad panel of indications on top of bladder cancer



OPPORTUNITIES

- PADCEV (enfortumab vedotin, EV) is approved in bladder where expression of Nectin-4 is the highest
- Relapses are frequently observed creating a growing medical need in post-EV setting
- EV induces toxicity leading to frequent discontinuation
- Limited evidence that EV is active in other indications

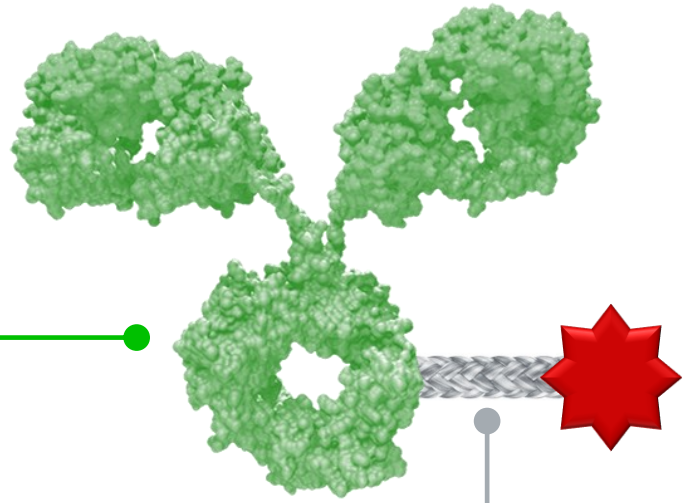
N Engl J Med 2021, Powles et al

IPH4502 is a novel and differentiated Nectin-4 DAR8 exatecan ADC

Binder

Proprietary humanized anti-Nectin-4 Antibody

- Differentiated epitope, non-overlapping with EV (no competition for binding)
- High affinity and high internalization
- Fc-competent IgG1, with the ability to mediate ADCC and CDC



Payload

Exatecan, a Topoisomerase I inhibitor

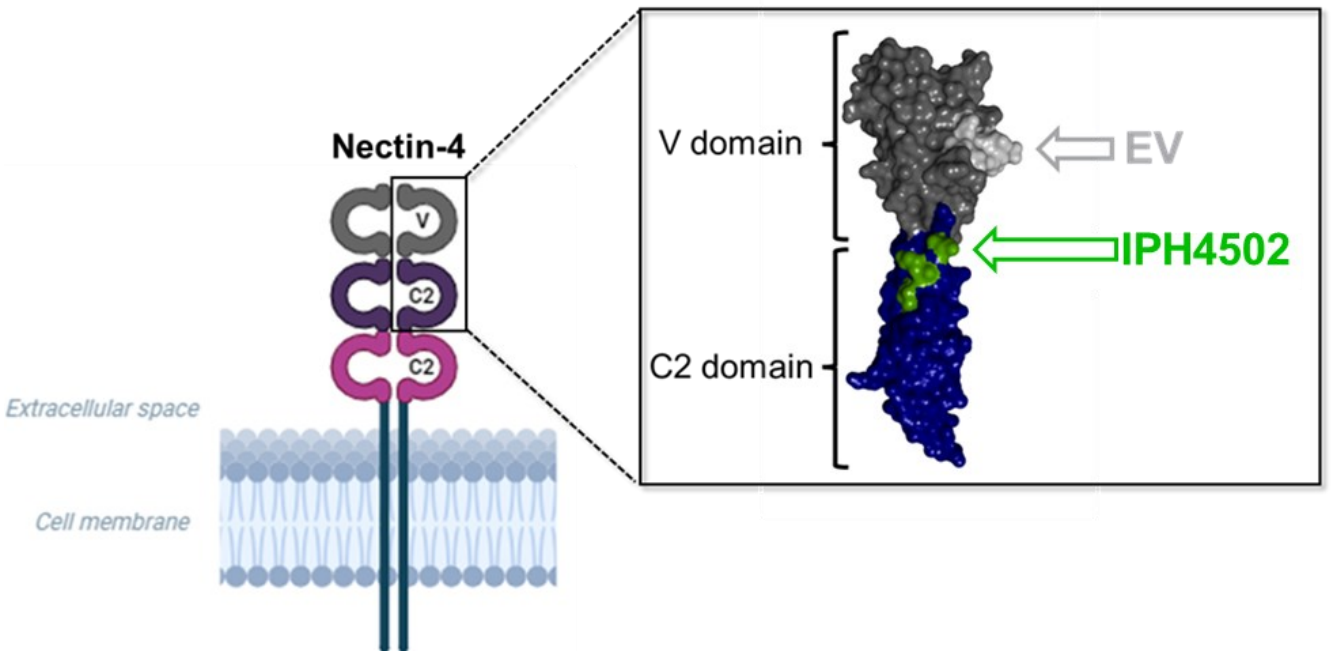
- Optimal therapeutic index expected
- Active in EV/MMAE-resistant models
- Bystander effect, higher activity than MMAE-ADCs in Nectin-4 low/ heterogenous expression

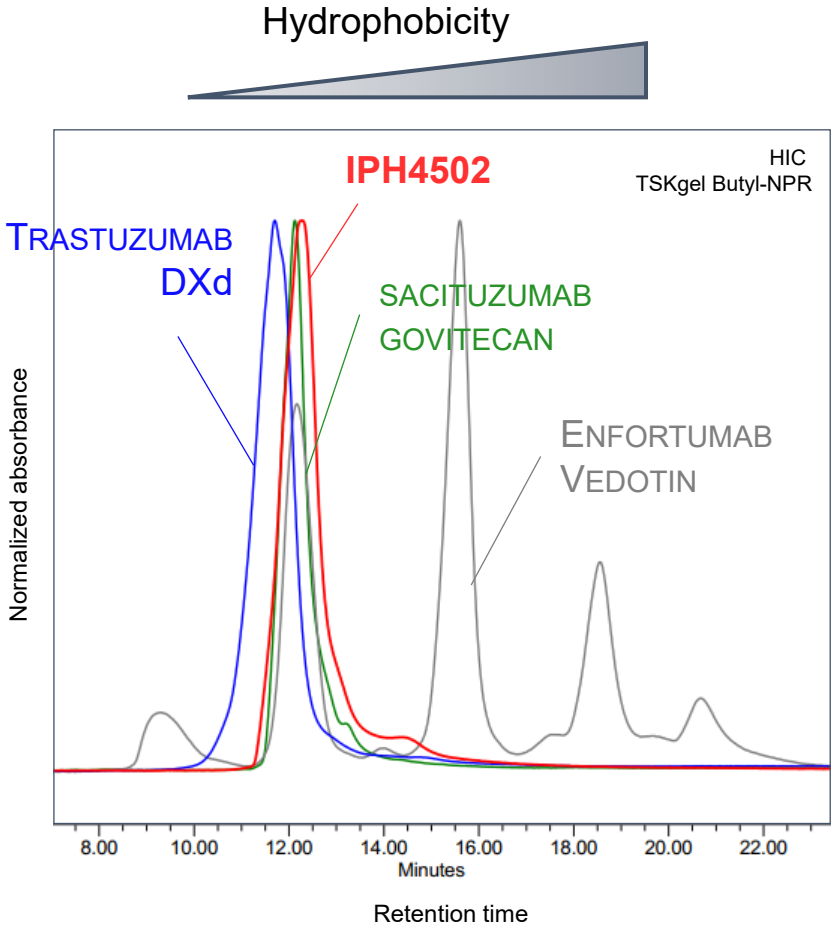
Linker

Cleavable

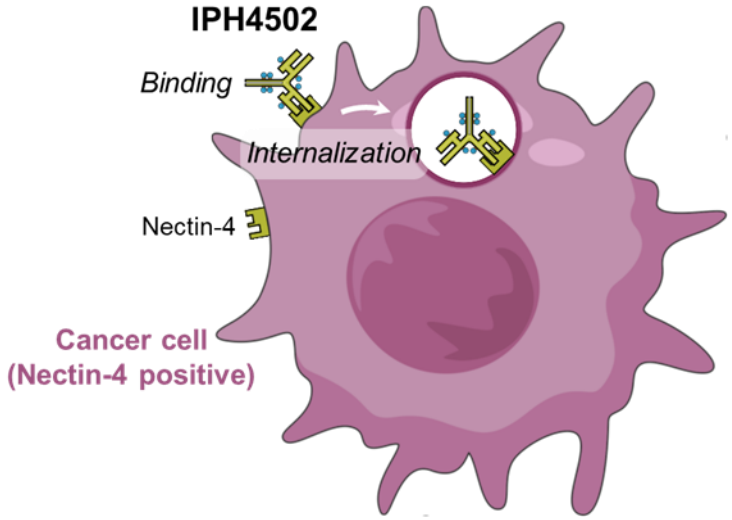
- **Hydrophylic** → improved half-life, low clearance
- **Stable** → improved safety with low release of free drug
- **Excellent conjugability** → high yield manufacturing process

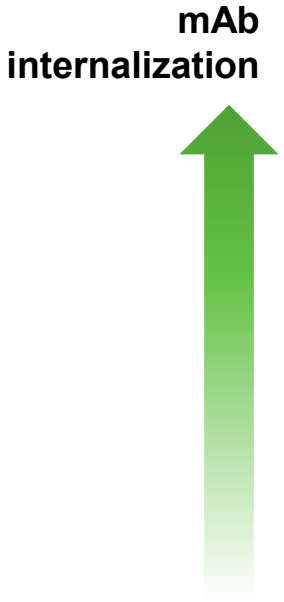
IPH4502 recognizes Nectin-4 on a different epitope and exhibits higher solubility than EV

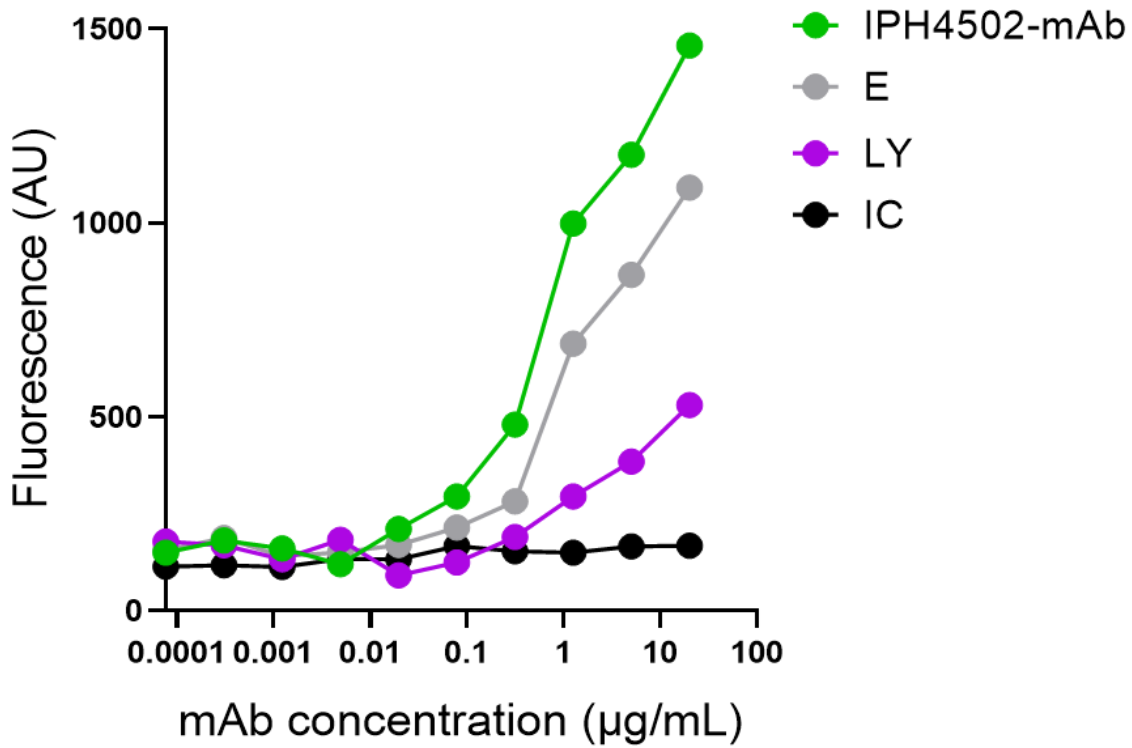




IPH4502 demonstrates more efficient internalization than other Nectin-4 ADC

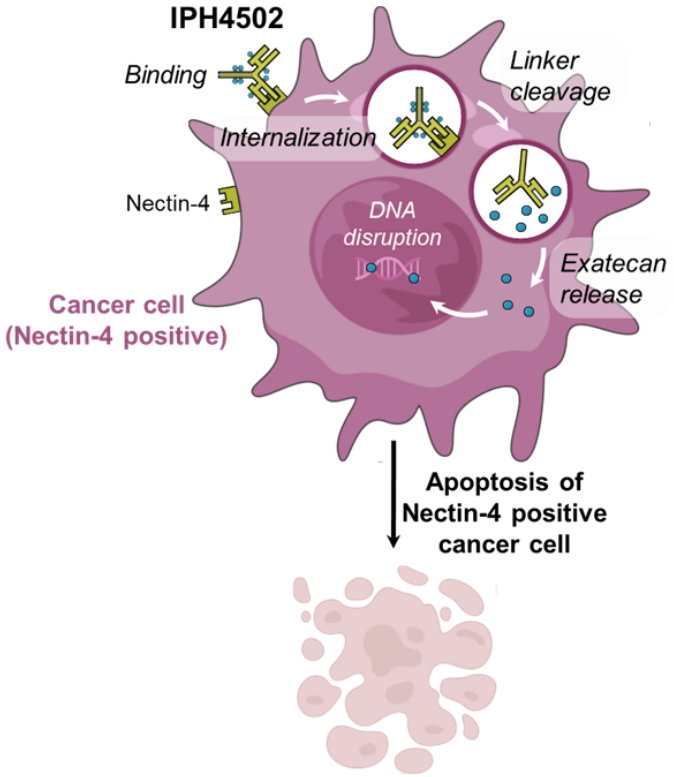




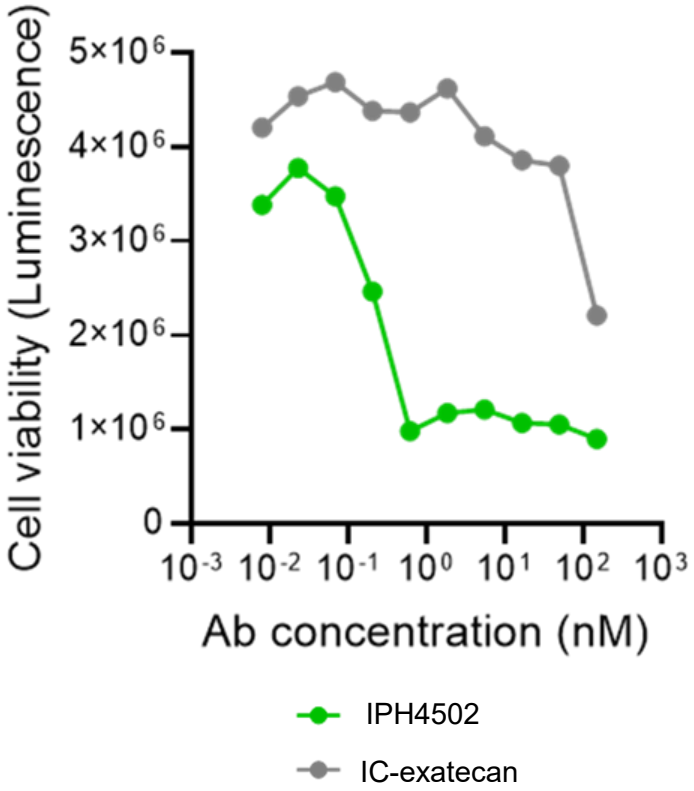


Internalization of naked antibodies coupled to pHAb amine in Nectin-4 expressing SUM190 PT cells was monitored at 24h
E = mAb having the amino acid sequence of Enfortumab; LY = humanized 15A7.5 mAb from patent EP4086284A1 (ETX-22 / LY4101174-mAb Lopez et al., 2024)
pHAb = pH sensitive dye that increases fluorescence upon internalization

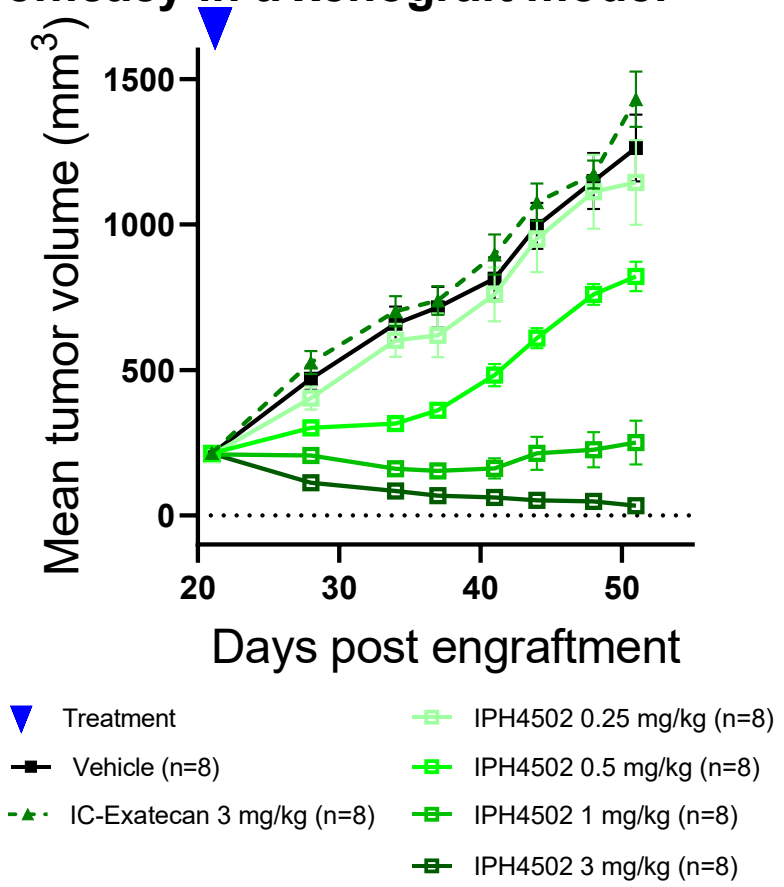
IPH4502 is a potent Nectin-4 ADC *in vitro* and *in vivo*



IPH4502 induces Nectin-4⁺ cell killing *in vitro*

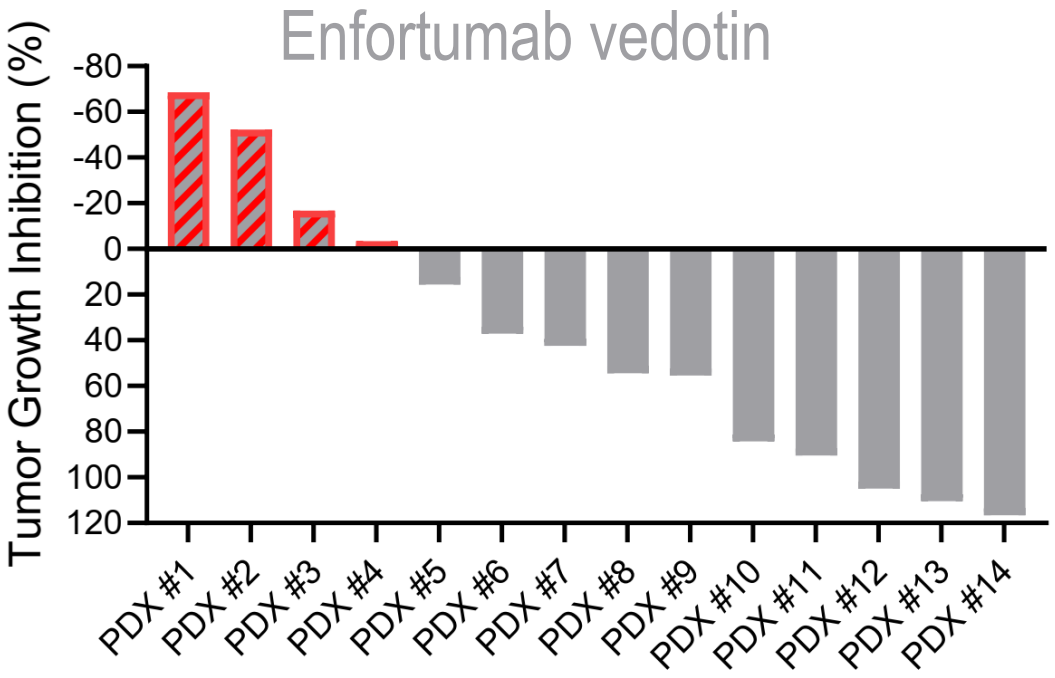


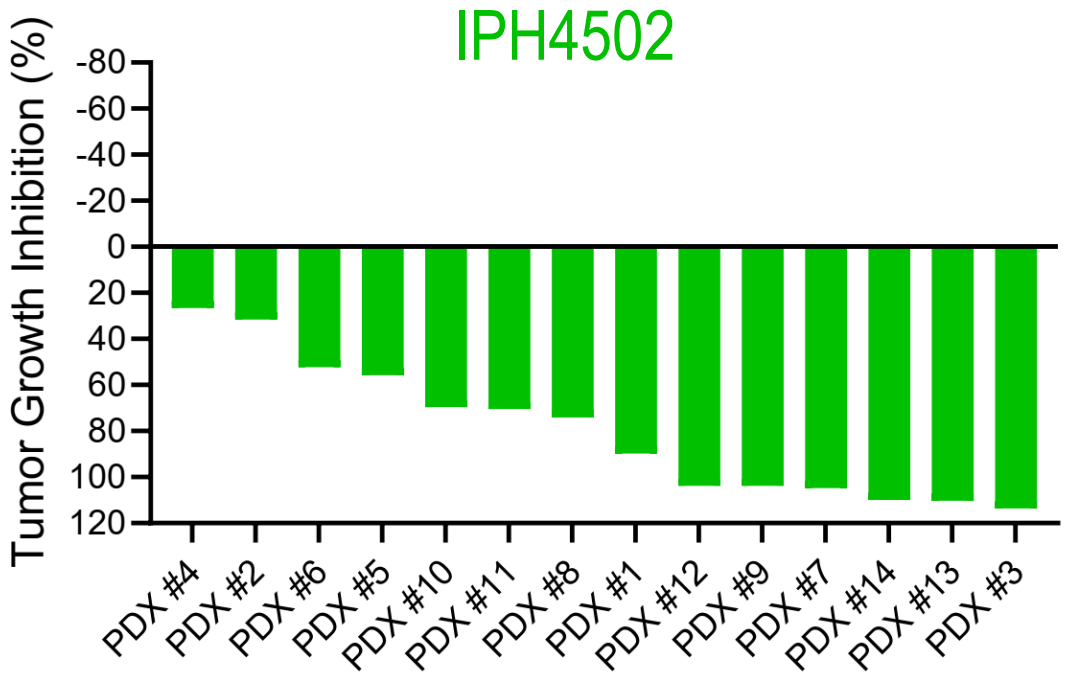
IPH4502 demonstrates robust efficacy in a xenograft model



SUM190-PT model (human breast cancer cell line)

IPH4502 shows stronger anti-tumor activity than EV in multiple PDX models from UC patients



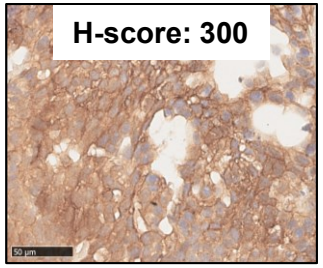


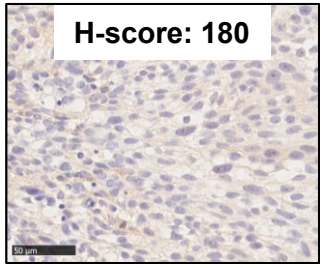
Mice were treated with the same dose (4mg/kg) for both ADCs at day 0 (randomization) and day 7

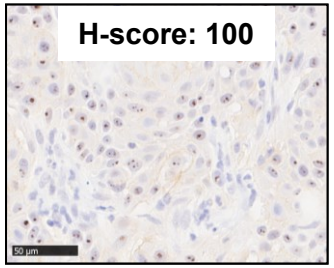
Tumor Growth Inhibition (TGI) = relative change in tumor volume compared to the initial mean tumor volume for the treated group (EV or IPH4502) and the control group (IC-Exatecan) on the last day when all mice from IC-Exa group still alive (n=3 mice per group)

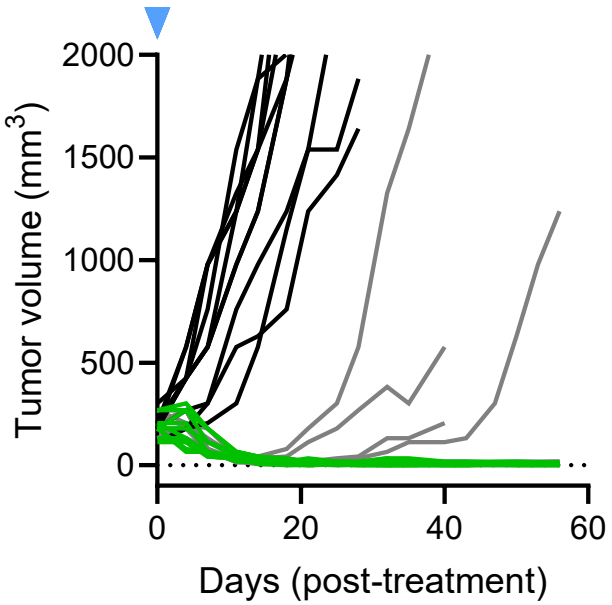
IPH4502 shows efficacy superior to EV in PDX models with low Nectin-4 expression

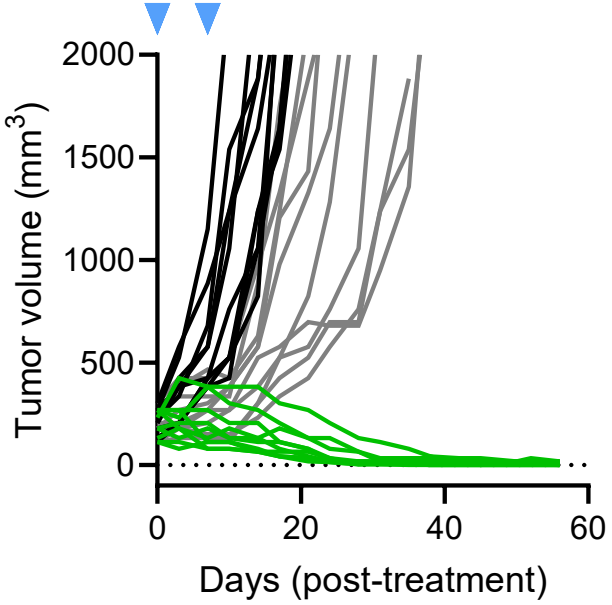
Nectin-4 expression in bladder PDX

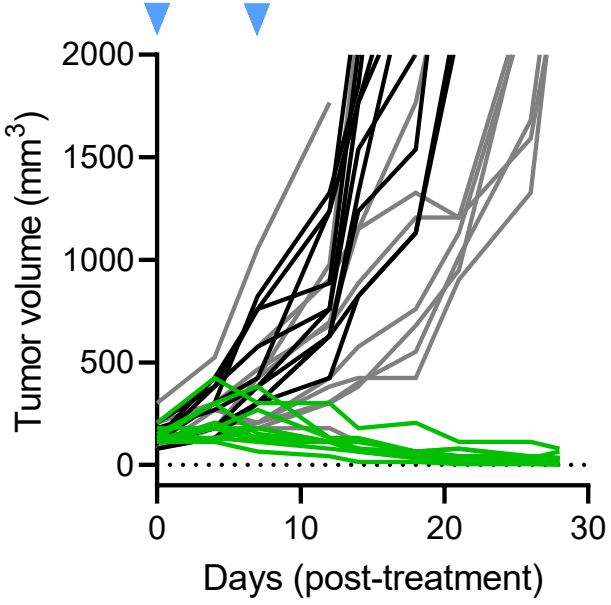


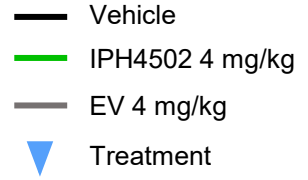






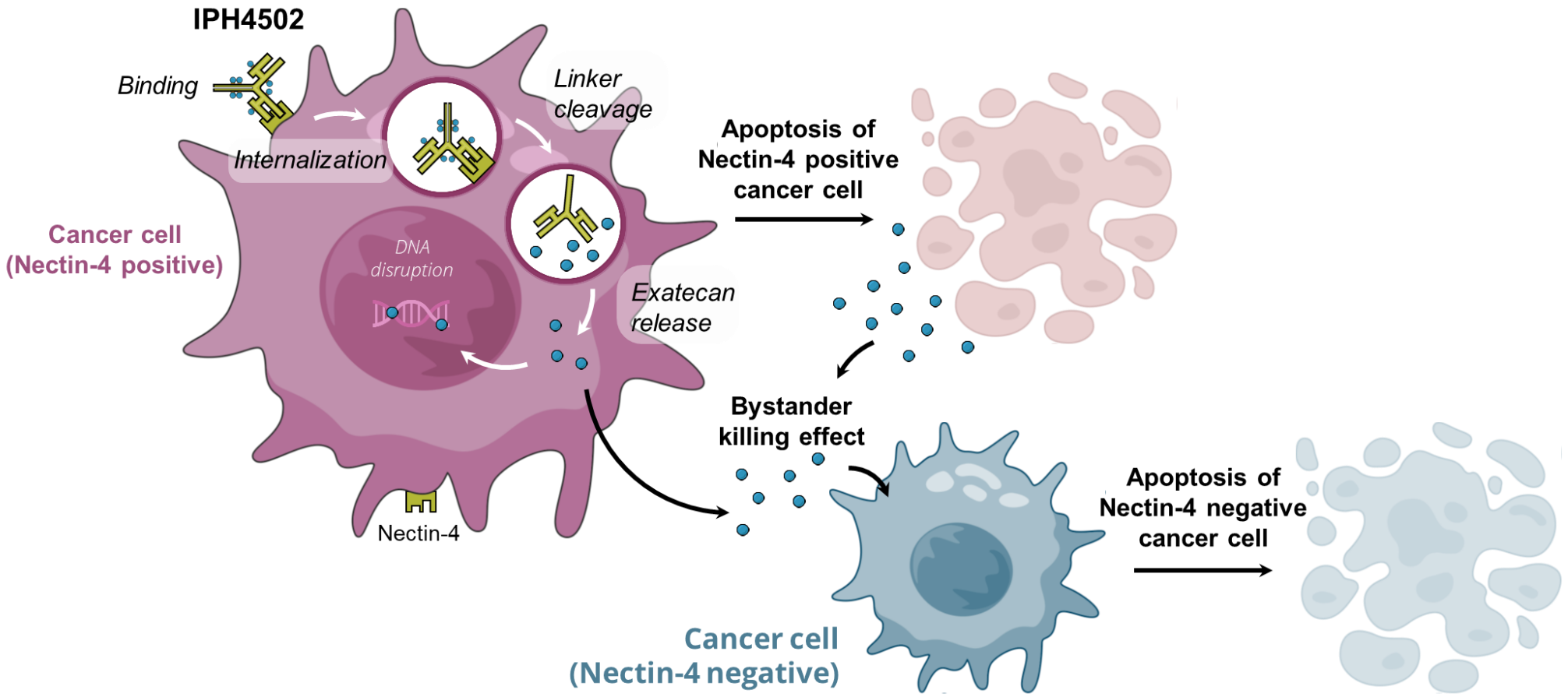




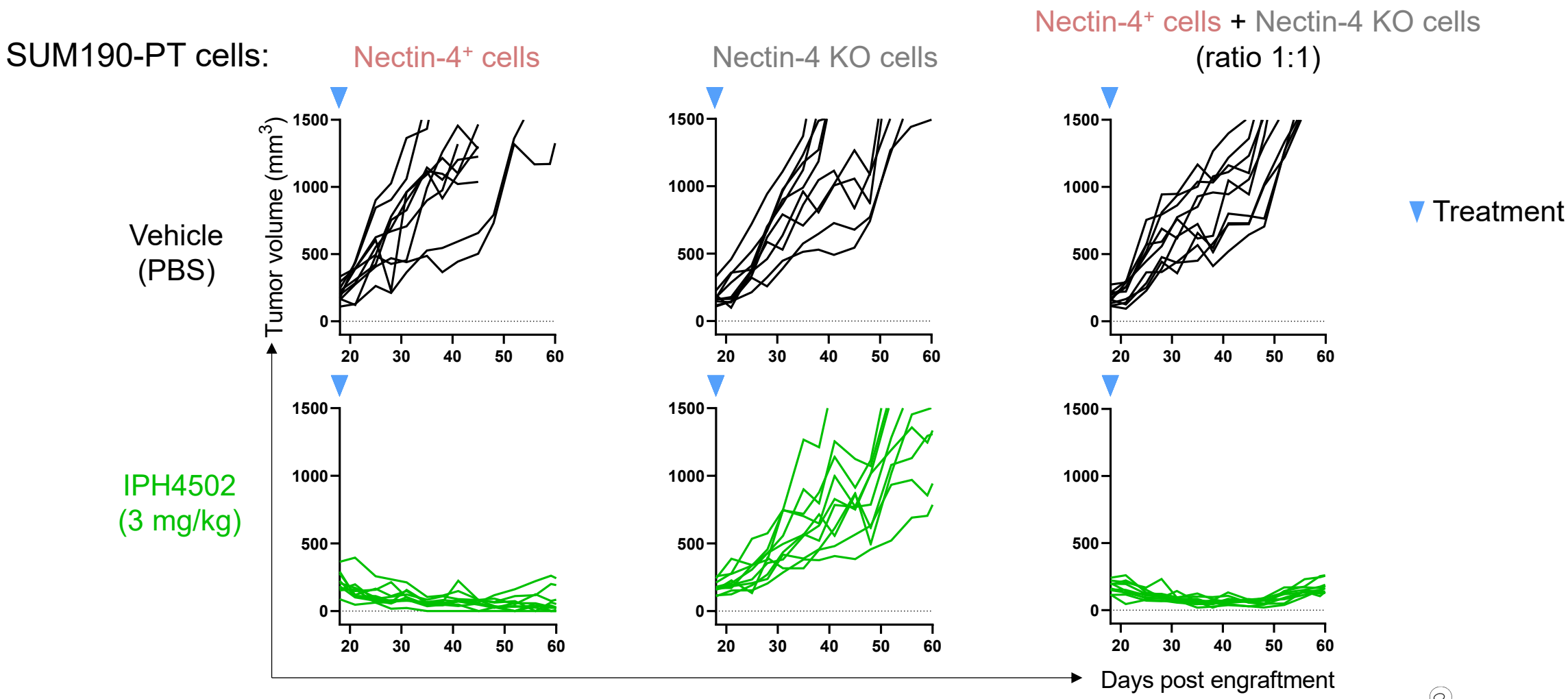


n=10 mice/group; Bladder PDX models; EV (enfortumab vedotin, PADCEV) MMAE-ADC

ADC and bystander killing effect



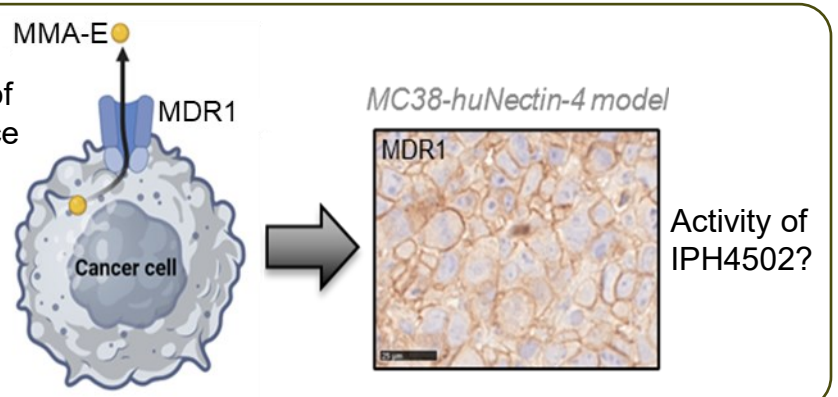
IPH4502 shows strong bystander killing effect *in vivo*



Mice were treated once with either vehicle (PBS) or IPH4502 at 3 mg/kg at day 18 (n=10 mice/group).

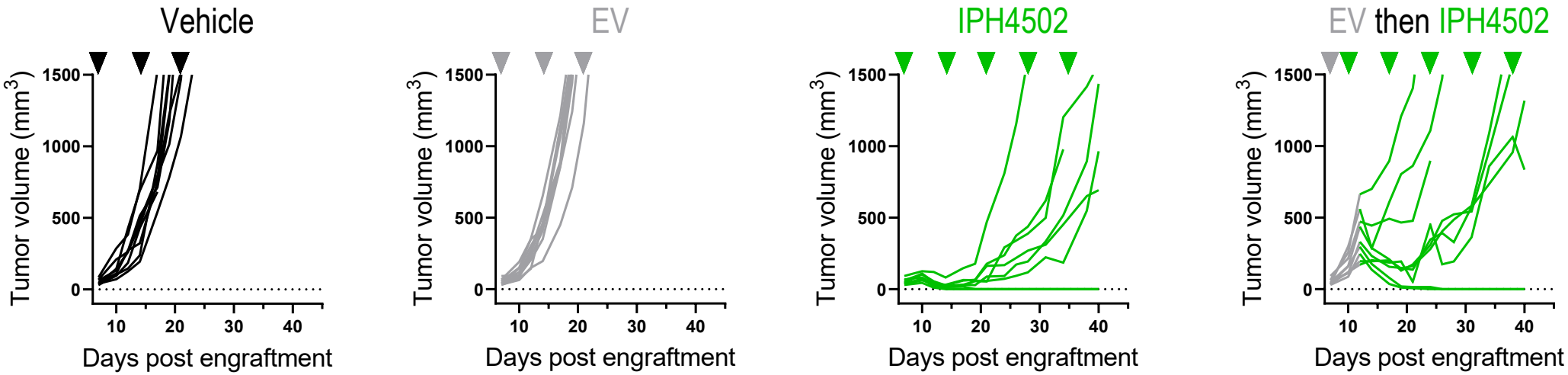
IPH4502 demonstrates efficacy in EV-primary refractory model

MMA-E is a substrate of the multi-drug resistance protein 1 (**MDR1**)



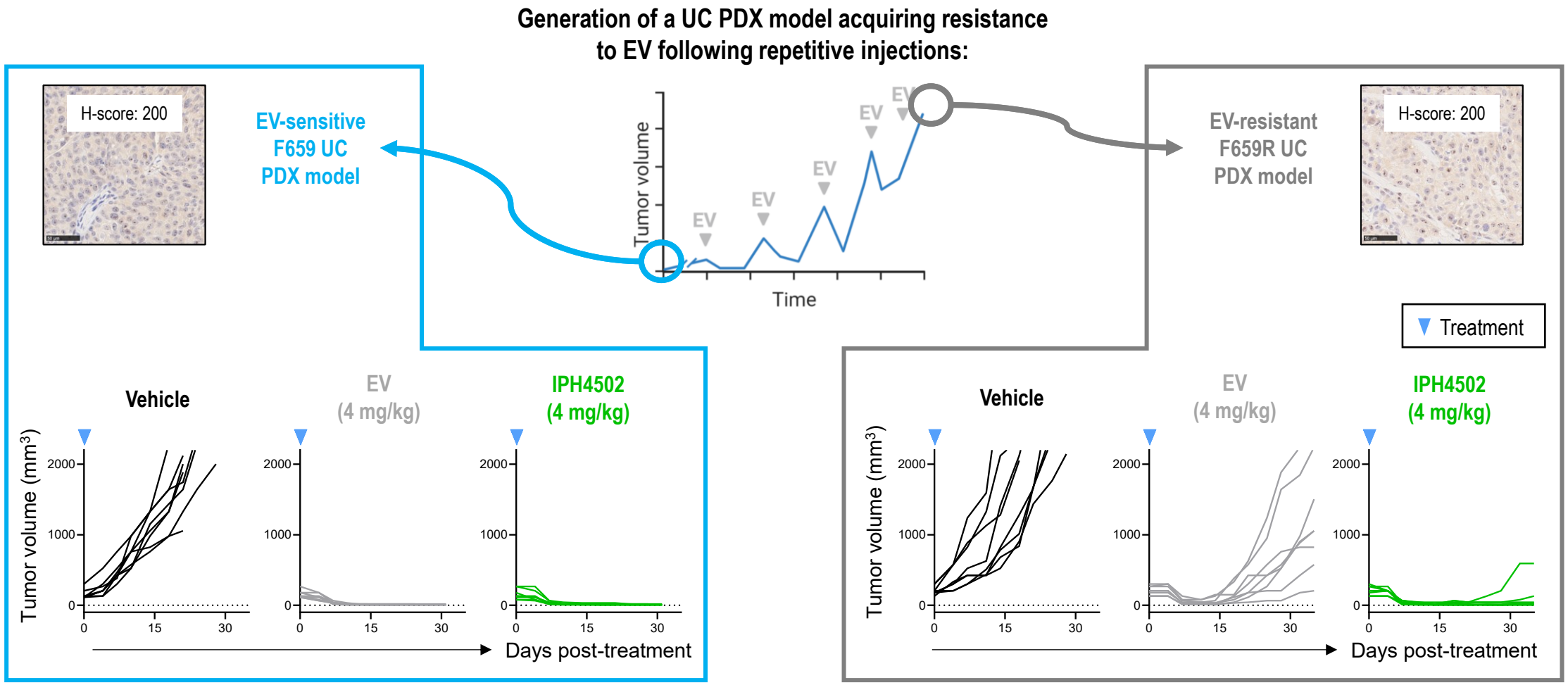
Activity of IPH4502?

▼ Treatment



9 mice/group; MC38 human Nectin-4; All treatments at 10 mg/kg; ABC Nectin-4 ~200 000
***EV** (enfortumab vedotin, PADCEV) MMAE-ADC*

IPH4502 has anti-tumor activity in a PDX-model of acquired EV-resistance

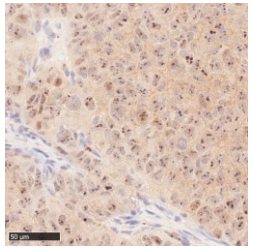


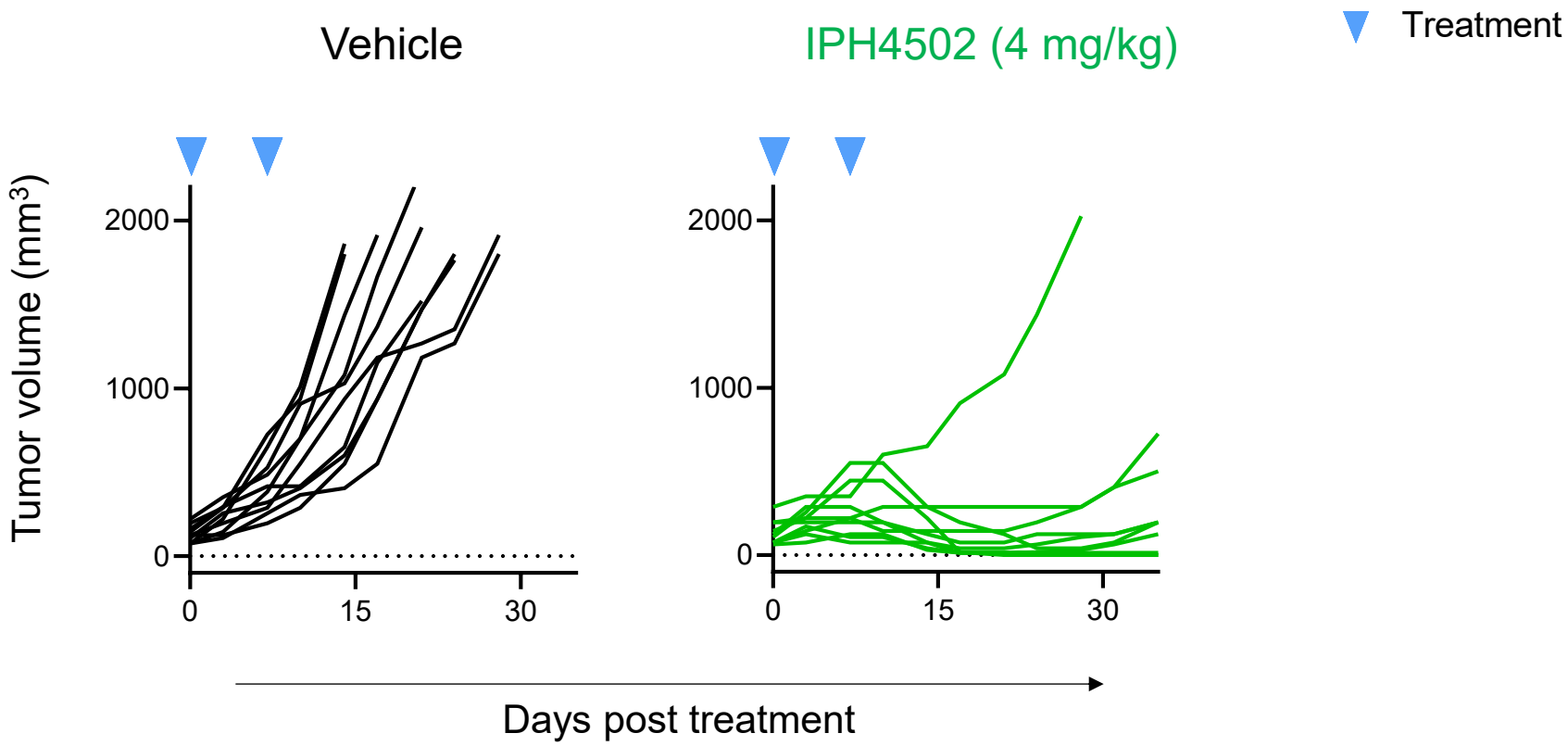
NMRI-Nude mice were subcutaneously implanted with tumor fragments. The F659R PDX model was generated through the repetitive in vivo treatment of the F659 PDX model with EV, which was repeated until the model exhibited resistance to EV. (n=8 mice/group)

IPH4502 shows anti-tumor efficacy in a PDX model from Nectin-4+ cancer indication beyond bladder

PDX model of TNBC

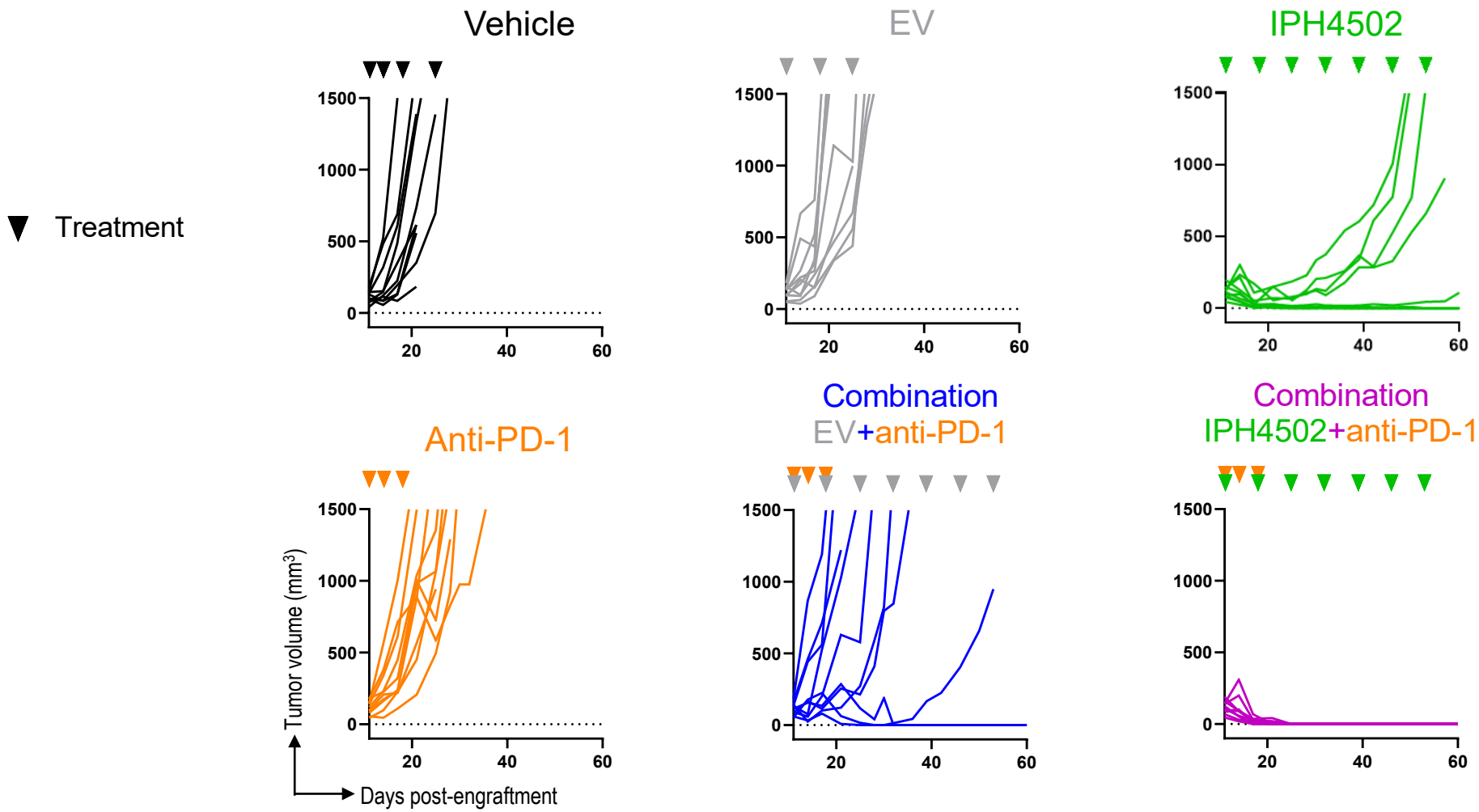
TNBC
Nectin-4
H-score: 200





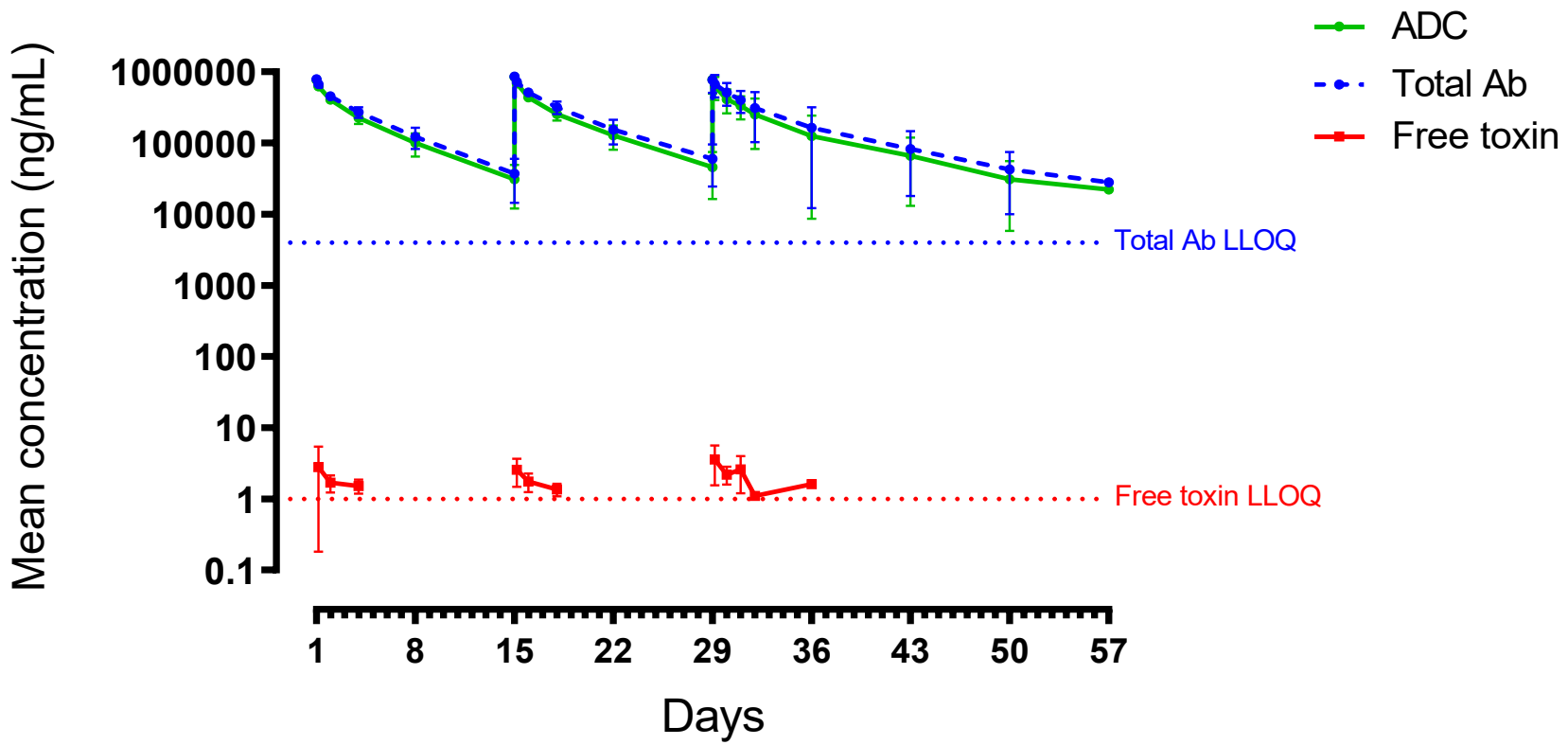
n=10 mice/group

IPH4502 shows increased anti-tumor activity in combination with anti-PD-1 in an EV-refractory model



MC38-huN4 model in C57BL/6 mice depleted of B cells, all molecules at 10 mg/kg (n=10 mice/group).

IPH4502 has high ADC exposure and minimal exatecan systemic release in NHP



GLP toxicology study: IPH4502 was administered at 30 mg/kg IV with 30 minutes infusion once every two weeks (Q2W) for a total of 3 doses
ADC, total Ab and free toxin mean concentrations (±SD) in plasma were determined using validated LC-MS/MS methods; LLOQ, lower limits of quantification
IPH4502 MW (molecular weight): 163 kDa; IPH4502-mAb (naked antibody) MW: 149 kDa; exatecan MW: 531.6 Da

IPH4502 has broad potential in Nectin-4 expressing solid tumors

- IPH4502 is a next-generation differentiated Nectin-4 exatecan ADC with high internalization and bystander effect
- Linker's hydrophilicity and stability translate into high ADC exposure and low release of free exatecan into cynomolgus monkey plasma
- IPH4502 shows superior efficacy to EV in bladder cancer models with low Nectin-4 expression, as well as in models of primary or induced resistance to EV
- IPH4502 shows efficacy in non-bladder tumor types (e.g. TNBC) and strong combination potential with PD-1 targeting agents

IPH4502 is progressing to the clinic after FDA clearance

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Thank you

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