



Nectin-4 ADC Update

New York, NY

Jonathan Dickinson | CEO, Innate Pharma

February 5th, 2025

EURONEXT: IPH.PA NASDAQ: IPHA

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Agenda

1. Introduction

Jonathan Dickinson | Chief Executive Officer, Innate Pharma

2. Current Nectin-4 landscape

Yohann Lorient | Deputy Chair of the Department of Early Drug Development, Gustave Roussy, Université Paris-Saclay

3. IPH4502 Preclinical data

Yannis Morel | EVP, Chief Operating Officer, Innate Pharma

4. IPH4502 Clinical development plan

Sonia Quaratino | EVP, Chief Medical Officer, Innate Pharma



2025: Focus on 3 Strategic Growth Pillars



NK-cell engagers

- **IPH6501** (CD20) ANKET[®] Phase 1
- **IPH6101** (CD123) ANKET[®] Phase 2 trial underway | Phase 1 data presented (Sanofi) | 1L study underway | Fast Track Designation for the treatment of acute myeloid leukemia
- **IPH6401** (BCMA) ANKET[®] Phase 1 (Sanofi)



Antibody Drug Conjugates

- **IPH4502** (Nectin-4) IND cleared, Phase 1 start Jan 2025
 - Differentiated topo-1 ADC targeting varying levels of expression of nectin-4 across tumor types
- **IPH43** (MICA/B) in research



Current Late-Stage Assets

- **Lacutamab** positive Phase 2 data, FDA feedback on next steps, Partnership discussions underway
- **Monalizumab** PACIFIC-9 Phase 3 underway (AstraZeneca)

Key Takeaways

Innate has a solid strategy to deliver long term growth with proprietary and partnered assets and we have 8 key programs in clinical stages of development

- **DRIVING FORWARD OUR ANKET® CLINICAL PORTFOLIO**
 - Phase 1/2 clinical trial underway with IPH6501 in B-cell NHL, agreement with IFLI to include Follicular Lymphoma
 - IPH6101/SAR'579 progressed to Phase 2 by Sanofi, Front line combination with venetoclax study initiated
- **PURSUING DIFFERENTIATED ADCs**
 - IPH4502, anti nectin-4 Antibody Drug Conjugate Phase 1 in Jan 2025
- **LACUTAMAB**
 - Encouraging FDA feedback on regulatory pathway, Phase 3 planning underway
 - Partnership discussions underway
- **MONALIZUMAB**
 - PACIFIC-9 milestone in 2026


Cash position of €96.4m as of September 30, 2024

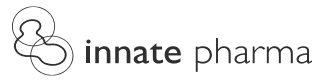
A Robust Pipeline of Innovative, Differentiated Proprietary & Partnered Assets

Pre-Clinical	Phase 1	Phase 2	Phase 3
IPH67 <i>Undisclosed, solid tumors</i>	IPH6501 (CD20-IL2v) B-NHL	IPH6101/SAR'579 (CD123) <small>sanofi</small> Blood cancers (Phase 1/2)	Monalizumab (NKG2A) <small>AstraZeneca</small> Unresectable Stg III NSCLC
IPH81 <i>Undisclosed Target</i>	IPH6401/SAR'514 (BCMA) <small>sanofi</small> Multiple Myeloma	Lacutamab (KIR3DL2) CTCL	
Others <i>Undisclosed Targets</i>	IPH4502 (Nectin-4) Solid tumors	Lacutamab (KIR3DL2) PTCL	
IPH62 <small>sanofi</small> B7-H3	IPH5301 (CD73) Solid tumors	Monalizumab (NKG2A) <small>AstraZeneca</small> Neoadjuvant NSCLC	
IPH43 MICAB		IPH5201 (CD39) <small>AstraZeneca</small> Neoadjuvant NSCLC	
Others <i>Undisclosed Targets</i>			

Monoclonal antibody (mAb)

Antibody Drug Conjugate (ADC)

Antibody-based NK cell engager Therapeutics 



Nectin-4 landscape



Pr Yohan Loriot, MD, PhD

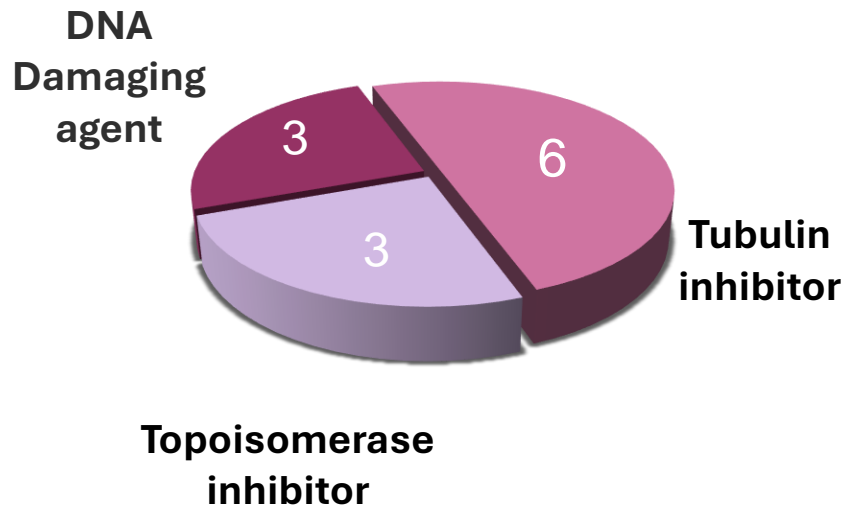
Professor of Medicine at Paris-Saclay University and
Deputy Chair of the Department of Early Drug Development at Gustave Roussy, Villejuif, France



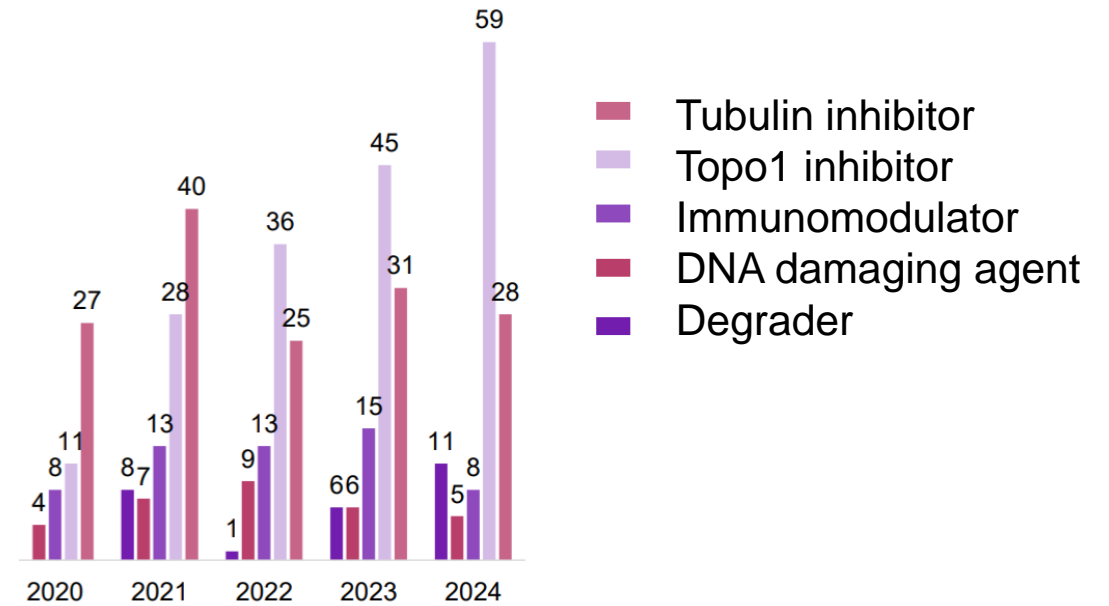
- Medical oncologist specialized in genitourinary cancers*
- Research focuses on drug development, particularly in connection with biomarker discovery, targeted therapies, and immunotherapies
- Leads phase I-III trials in urothelial and prostate cancers
- Member of the steering committees for multiple international clinical trials which have led to drug approvals (erdafitinib, enzalutamide, abiraterone, atezolizumab, sacituzumab, enfortumab)
- >300 peer-reviewed papers (NEJM, Lancet Oncology, JCO, Cancer Discovery, etc.)

Shifting ADC Landscape: Growth of Topoisomerase Inhibitors based ADCs

ADC approved by payload



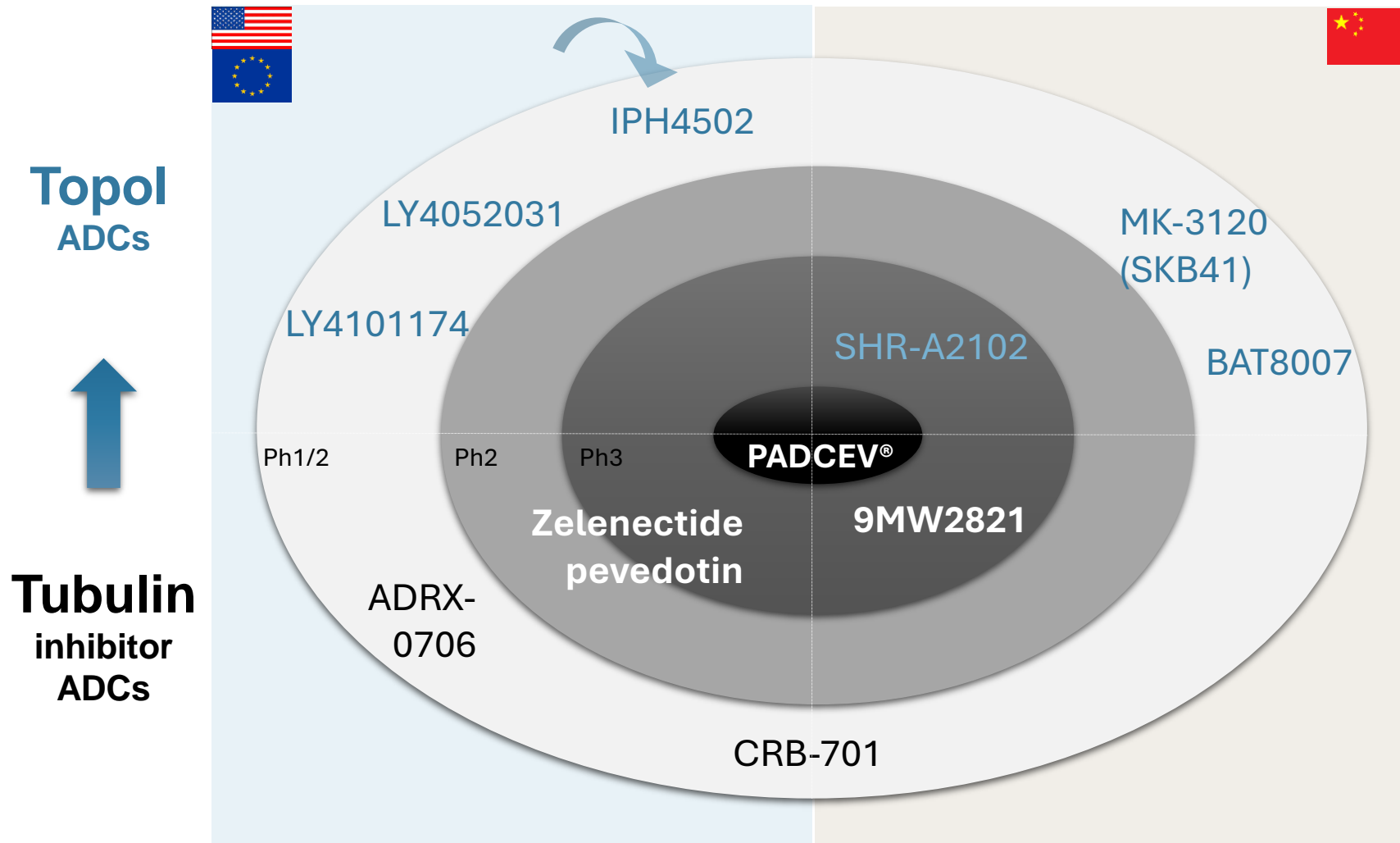
255 ADCs (Clinical)



ADC Beacon by Hanson Wade, Nov 2024

Since 2022, the number of **Topoisomerase inhibitor based ADCs** in the clinic per year is superior to Tubulin inhibitor; with a growing number Exatecan-based ADC (two candidates in Ph3 studies)

Nectin-4 ADC Landscape: MMAE-based ADC Approved; Next Generation Includes Tubulin and Topoisomerase Inhibitor-based ADCs



- EV is the only anti-Nectin-4 ADC approved (UC)
- Most advanced new aNectin-4 ADCs have tubulin inhibitors
- Next generation of **Nectin-4 ADCs Topol** are in Phase 1/2, except SHR-A202 entering Ph3 in China

Enfortumab Vedotin is approved in LA/mUC* in monotherapy (3L) and PD-1 combination (1L). Relapses create a growing medical need in post-EV setting

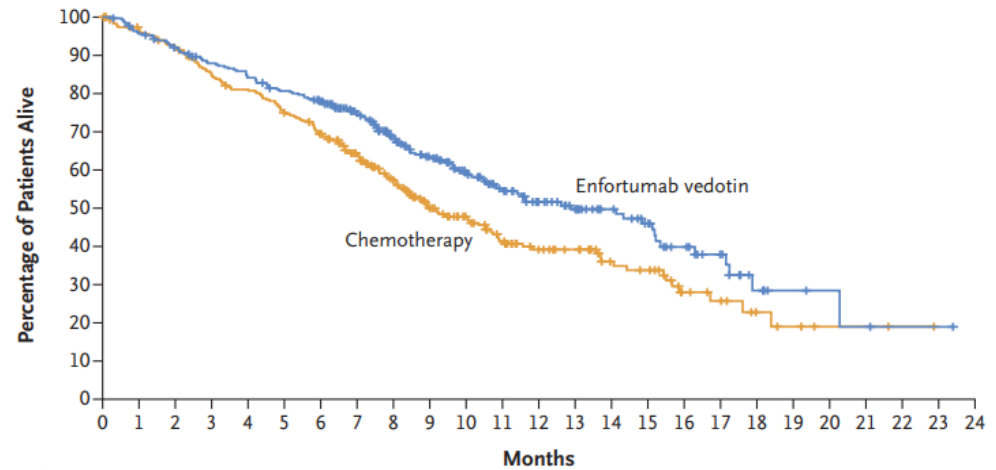
3L LA/mUC

Phase 3 EV-301

EV vs chemotherapy

1.25 mg/kg IV D1+D8+D15 of 28D cycle

ORR	40.6% vs. 17.9%
Median PFS	5.55 mo vs. 3.71 mo
Median OS	12.91 mo vs. 8.94 mo



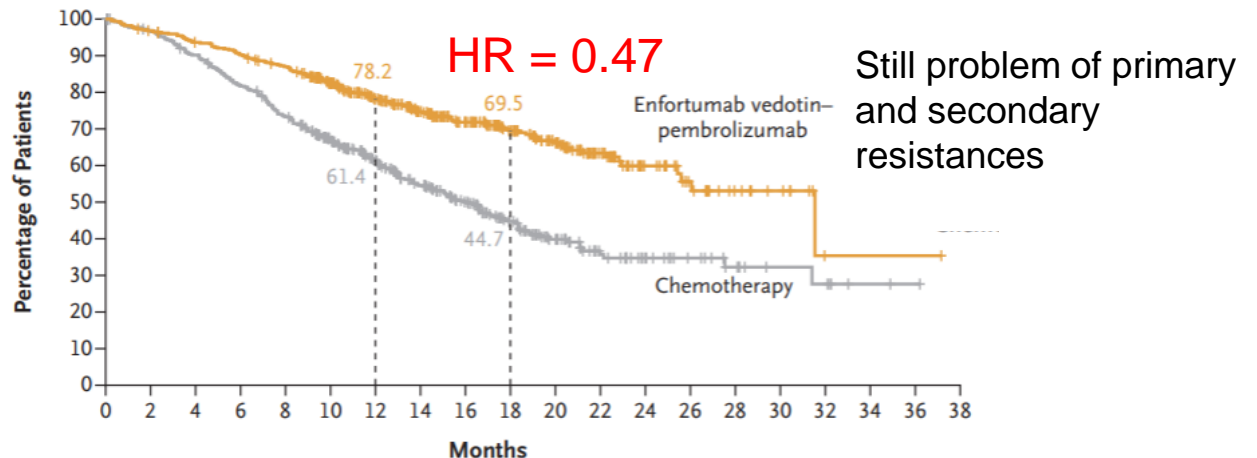
1L LA/mUC

Phase 3 EV-302/ KEYNOTE-A39

EV + pembro vs chemotherapy

1.25 mg/kg IV EV D1+D8 of 21D cycle

ORR	67.7% vs 44.4%
Median PFS	12.5 mo vs. 6.3 mo
Median OS	31.5 mo vs. 16.1 mo



*Locally advanced or metastatic urothelial cancer (LA/mUC)

Enfortumab Vedotin treatment related adverse events

TRAE		Phase 3 EV-301 3L+ la/mUC	Phase 3 EV-302/KEYNOTE-A39 1L la/mUC
Serious adverse reactions		22.6% (vs 23.4%) (incl. Urinary tract infection, Acute kidney injury, Pneumonia)	27.7% (incl. Rash, Acute kidney injury, Pneumonitis/ILD)
Peripheral Neuropathy	All grades	48.0%	63.2%
	≥ Gr3	7.4%	6.8%
Skin Reaction	All grades	47.3%	66.8%
	≥ Gr3	14.9%	15.5%
TRAE resulting in	EV Dose Interruption	51 %*	60.5 %
	EV Dose Discontinuation	15.2 %	29,5 %
Fatal adverse reactions		2.4%	0.9%

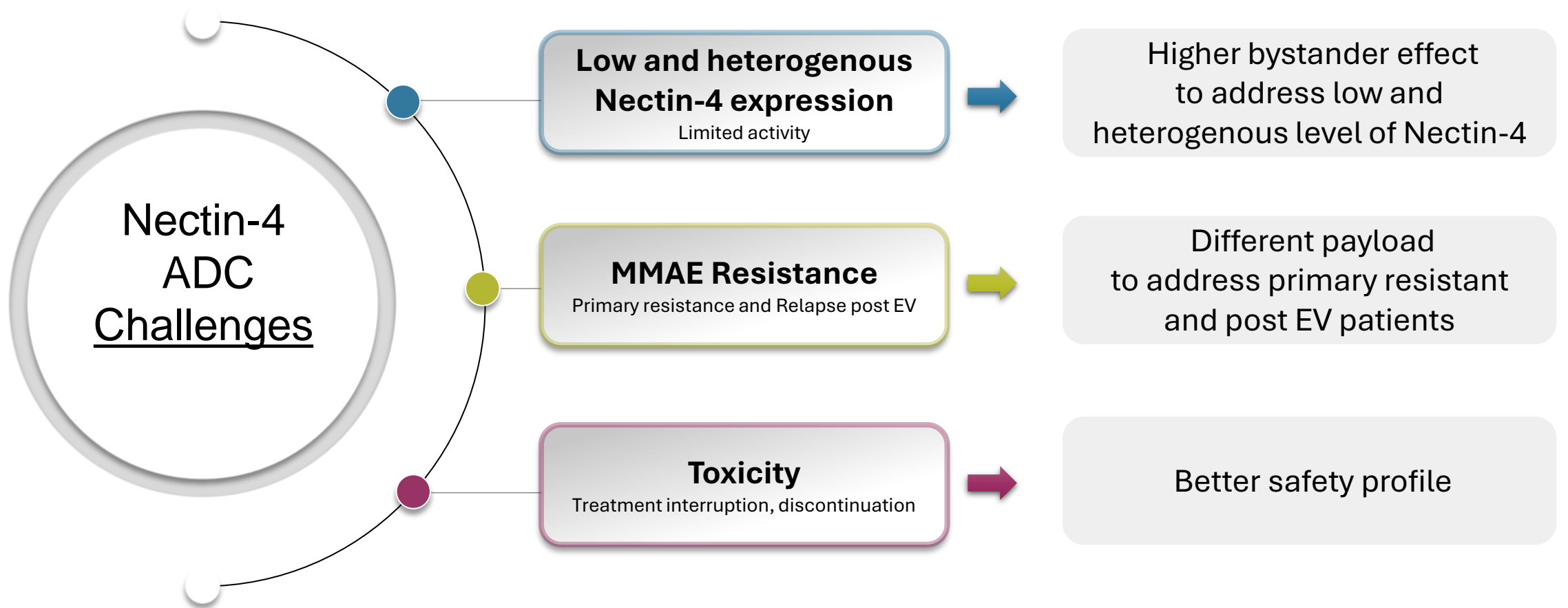
Most common TRAE leading to discontinuation **Peripheral neuropathy**

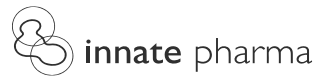
Clinical research priority: how to de-escalate therapy (risk of neuropathy) or to develop new agent without risk of neuropathy

Beyond bladder, not validated signs of activity with Nectin-4-ADCs

Nectin-4 expression	MMAE-Based Nectin-4 ADC				TopoI ADC
	Enfortumab Vedotin	BT8009 Zelenectide pevedotin	9MW2821	CRB-701	SHR-A2102
Urothelial 2L+	Phase 3 EV-301 ORR 41%	N=38 EV-naïve ORR 45% (ESMO24)	n=37, ORR 62.2% (ASCO24)	N=9, ORR 44% (ASCO24)	
Esophageal	GEA: n=42 ORR 9.5% ESCC: n=44 ORR 18.2% (ASCO24)		N=39, ORR 15.4% (ASCO24)		
TNBC	n=42, ORR 19% (ASCO24)	n=30, ORR 13% (PR Dec24)	n=20, ORR 45% (ASCO24)		
Cervical			N=53, ORR 30.2% (ASCO24) Phase 3 ongoing	N=7, ORR 43% (ASCO24)	
NSCLC	Sq: n=23, ORR 4.3% Nsq: n=43, ORR 14.0% (ASCO24)	n=34, ORR 8.8% (PR Dec24)			Sq: n=16, ORR 18.8% Nsq: n=30, ORR 36.7% (ESMO24)
HNSCC	n=46, ORR 23.9% (ASCO23)				
Ovarian		n=10, ORR 20% (R&D day Dec23)			

Next generation of Nectin-4 ADCs to overcome challenges associated with approved therapy





IPH4502 – Preclinical data

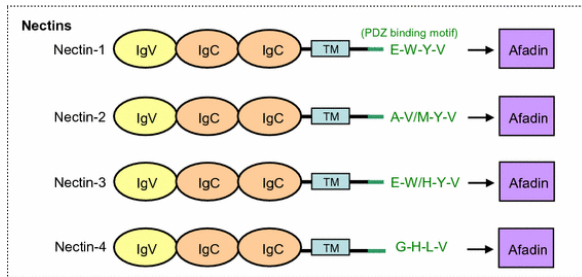


Introduction to Nectin-4

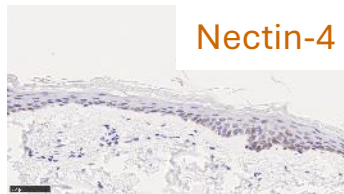
Nectin-4 is a type I transmembrane adhesion molecule with **limited expression in healthy adult tissues**

Overexpressed in multiple **cancers**, making it a relevant tumor target

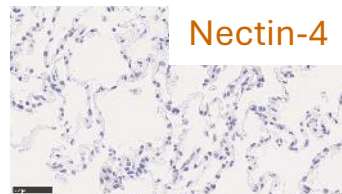
Expression associated with tumor proliferation, metastasis, and **with poor prognosis**



Healthy tissues

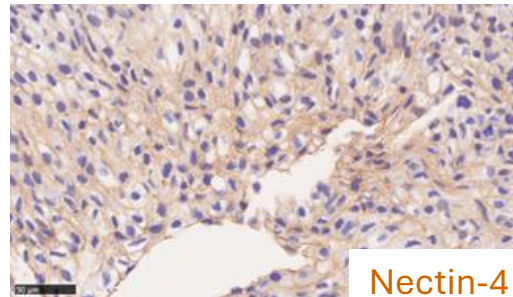


Skin



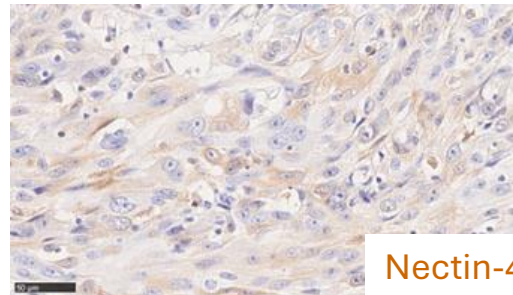
Lung

Urothelial cancer

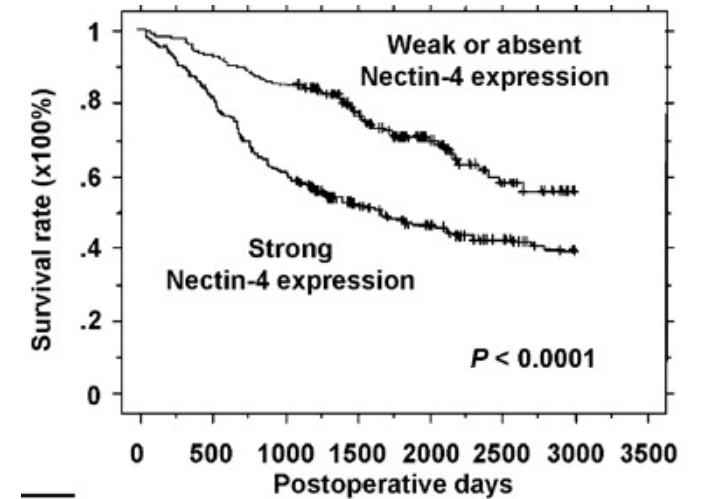


Nectin-4

NSCLC

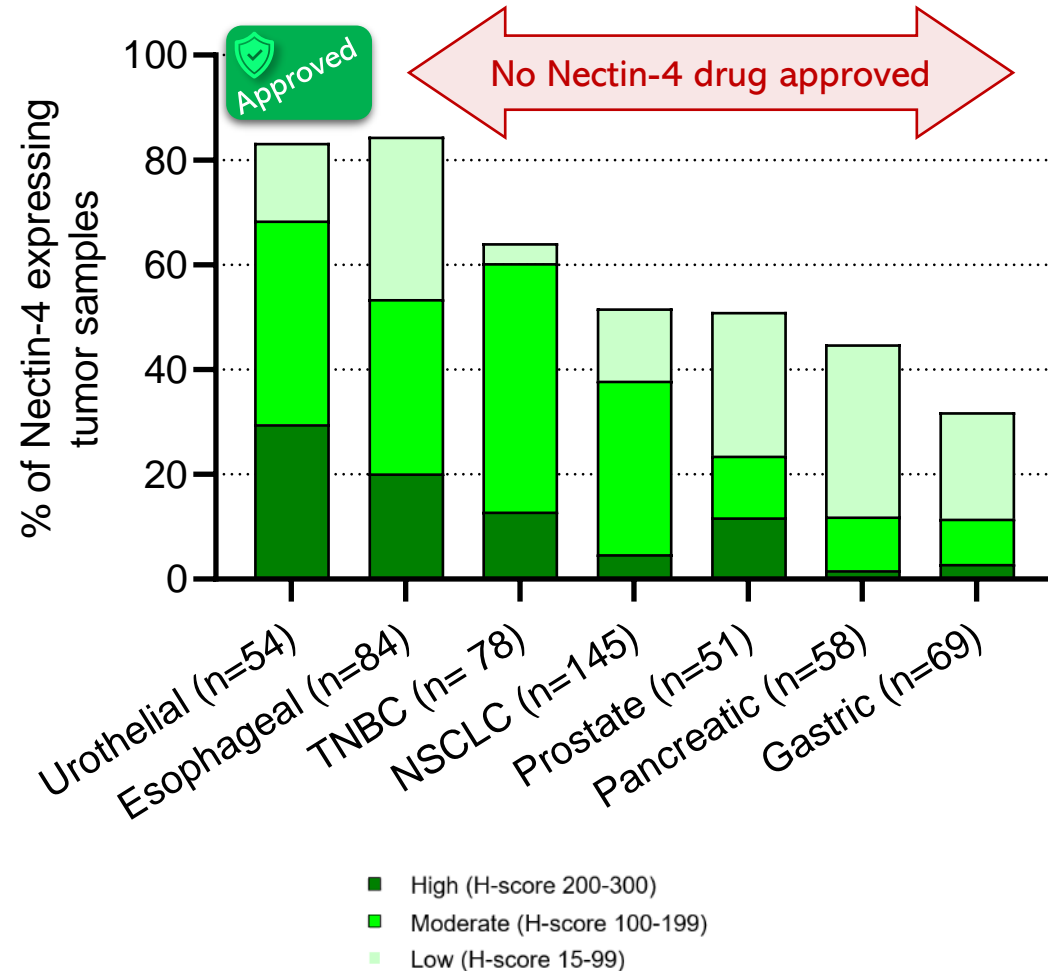


Nectin-4



Takano et al., Cancer Res, 2009

IPH4502: A differentiated Nectin-4 targeted ADC with potential to show efficacy in moderate to low Nectin-4 expressing and Padcev resistant tumors



OPPORTUNITIES

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

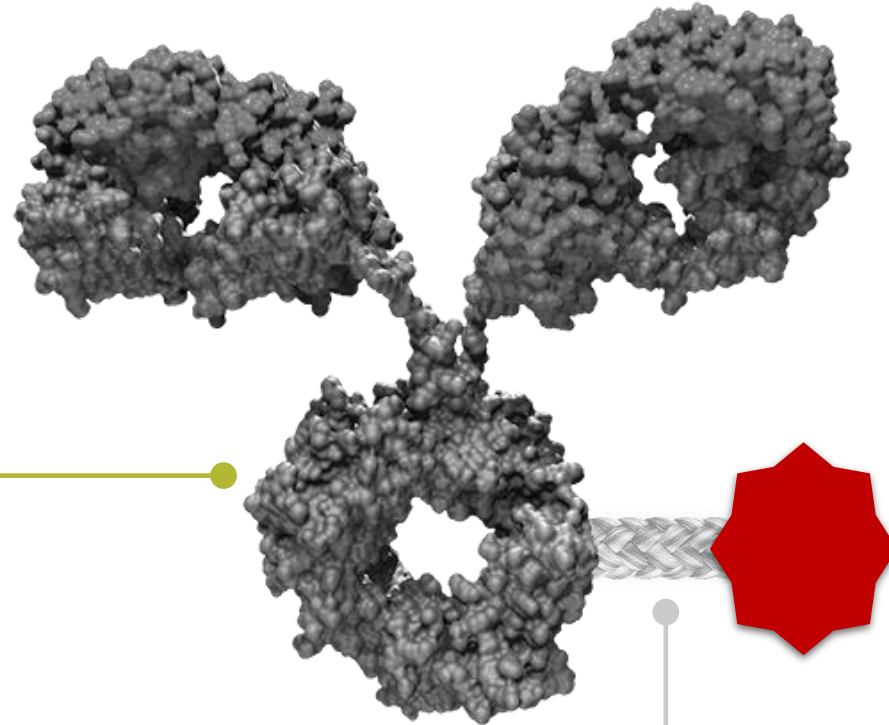
IPH4502: A novel and differentiated Nectin-4 DAR8 exatecan ADC

Phase 1 start in Jan 25

Binder

Proprietary humanized anti-Nectin-4 Antibody

- High affinity
- Non-overlapping epitope with EV*
- Fc-competent IgG1, with the ability to mediate ADCC and CDC



Payload

Exatecan, a Topoisomerase I inhibitor

- Active in EV/MMAE-resistant models
- Higher Bystander Effect than EV, leading to stronger activity in Nectin-4 low tumors
- DAR = 8
- Improved therapeutic index expected

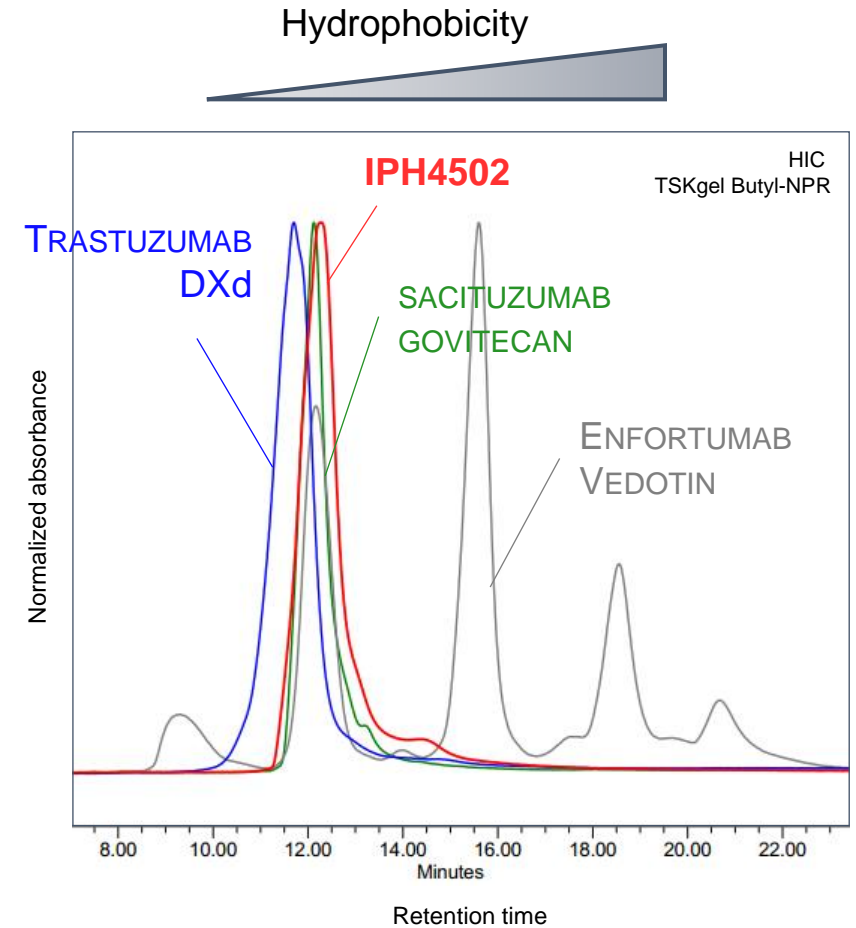
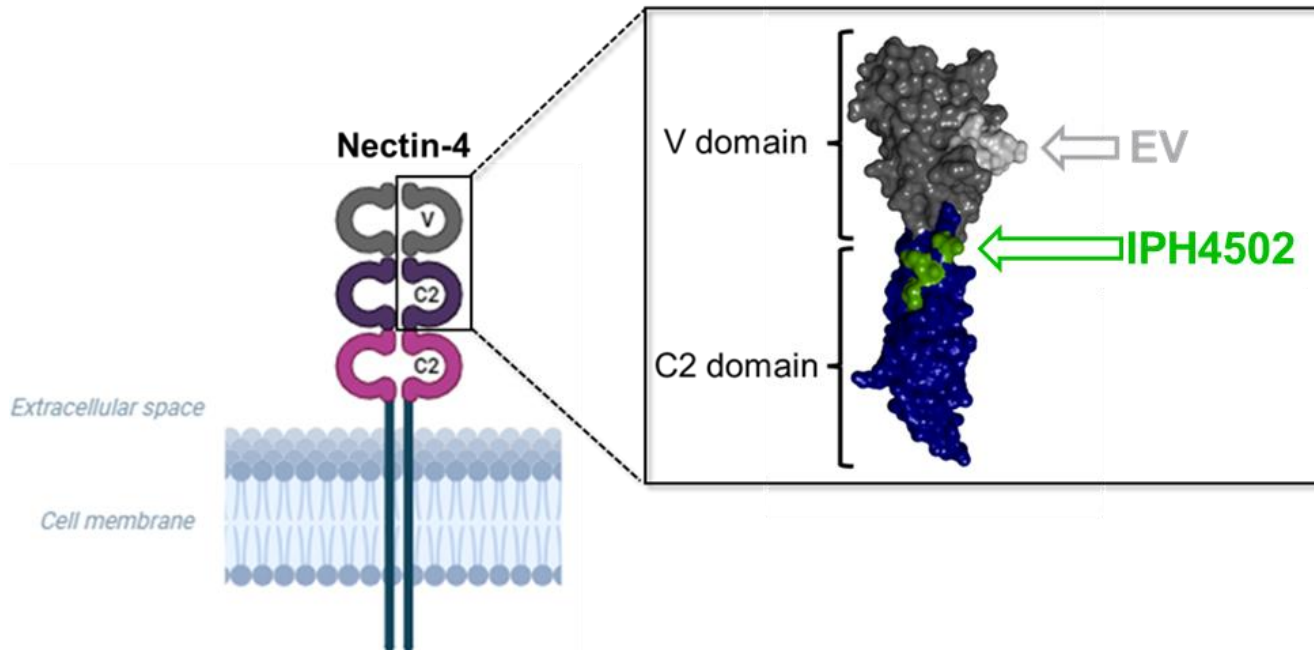
Linker

Cleavable

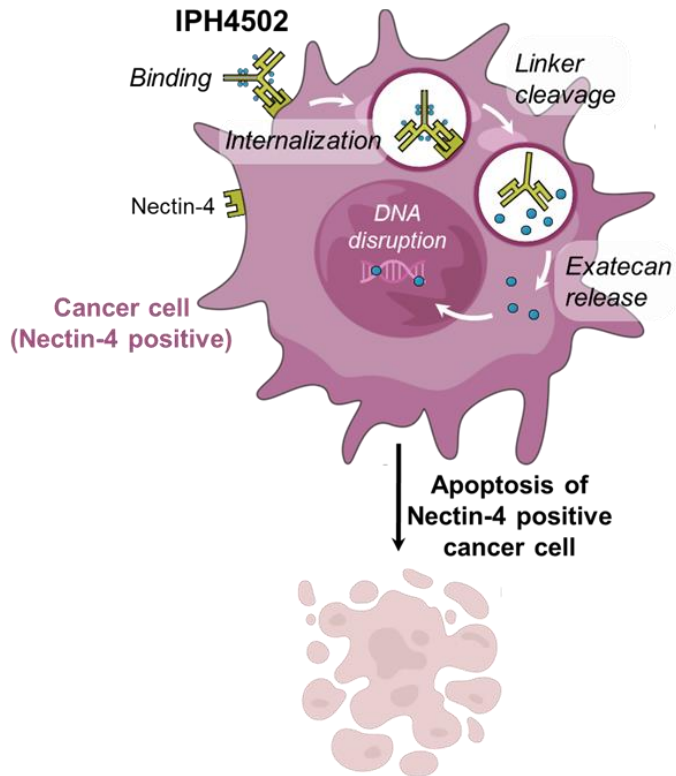
- **Hydrophilic** → improved half-life, low clearance
- **Stable** → improved safety with low release of free drug
- **Excellent conjugability** → high yield manufacturing process

* EV = Enfortumab Vedotin

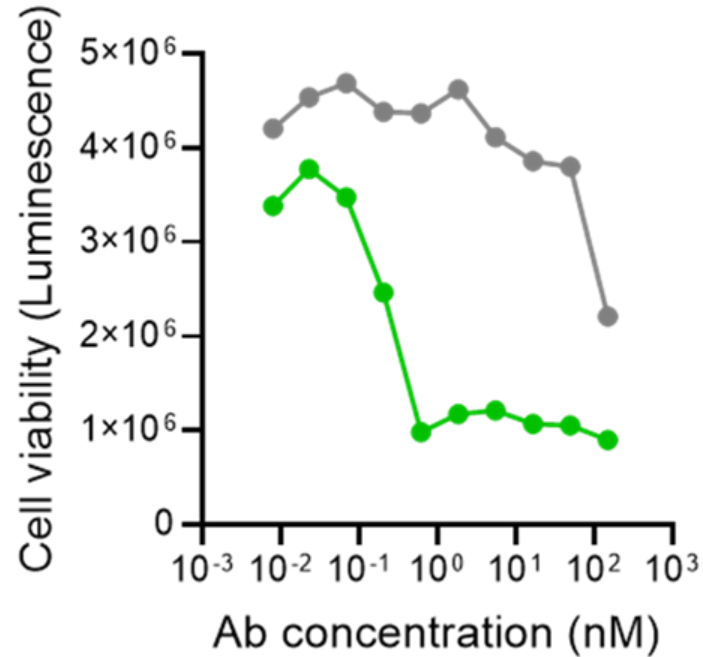
IPH4502 recognizes Nectin-4 on a different epitope and exhibits higher solubility than EV



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

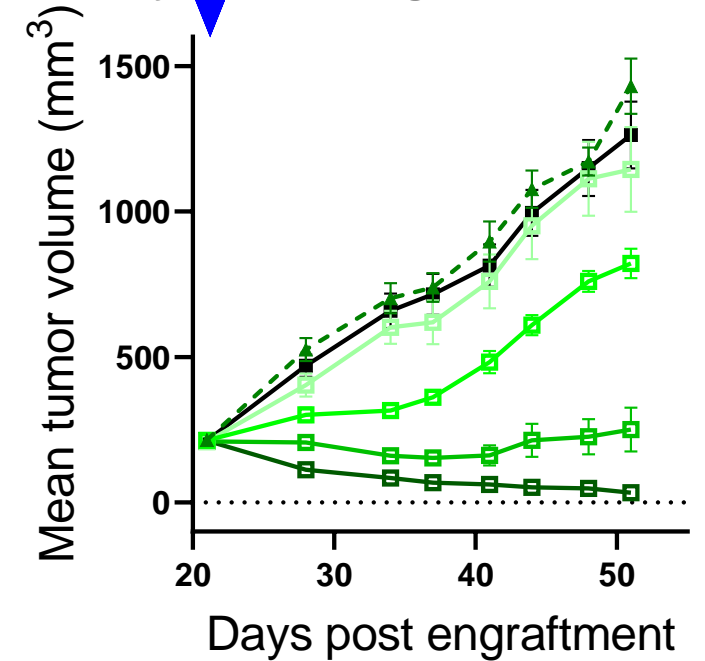


IPH4502 induces Nectin-4+ cell killing *in vitro*



● IPH4502
● IC-exatecan

IPH4502 demonstrates robust efficacy in a xenograft model



▼ Treatment

■ Vehicle (n=8)

▲ IC-Exatecan 3 mg/kg (n=8)

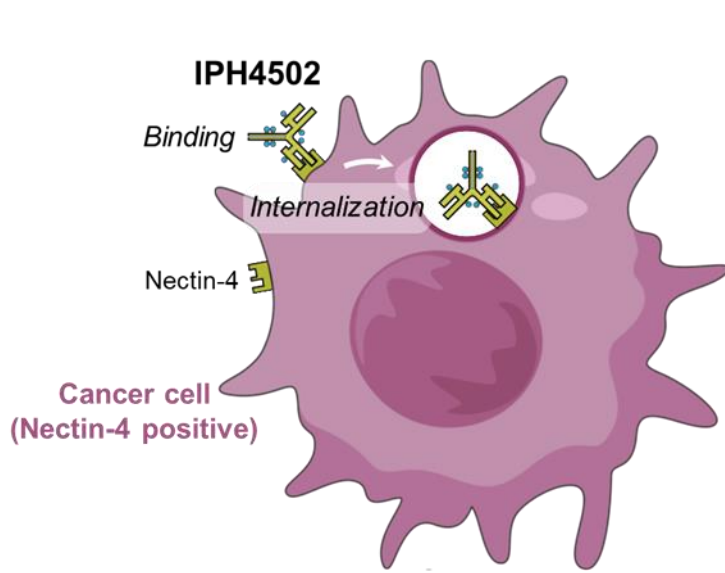
□ IPH4502 0.25 mg/kg (n=8)

■ IPH4502 0.5 mg/kg (n=8)

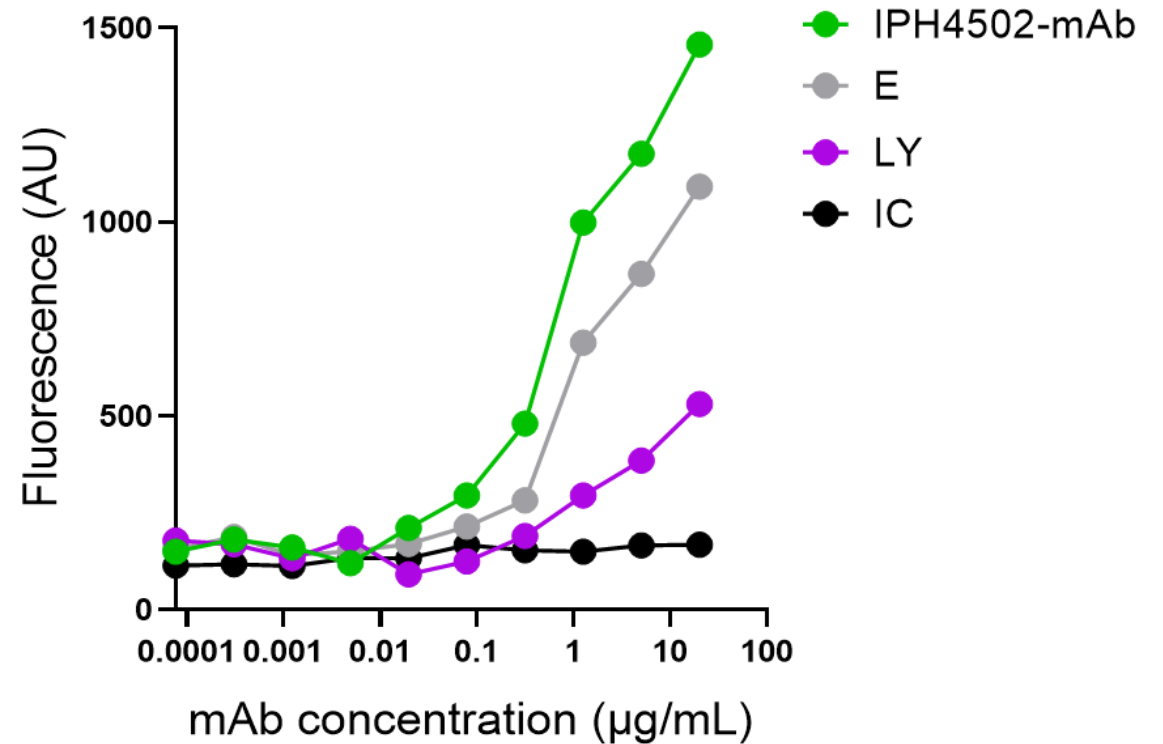
■ IPH4502 1 mg/kg (n=8)

■ IPH4502 3 mg/kg (n=8)

IPH4502 demonstrates more efficient internalization than other Nectin-4 ADC



mAb
internalization



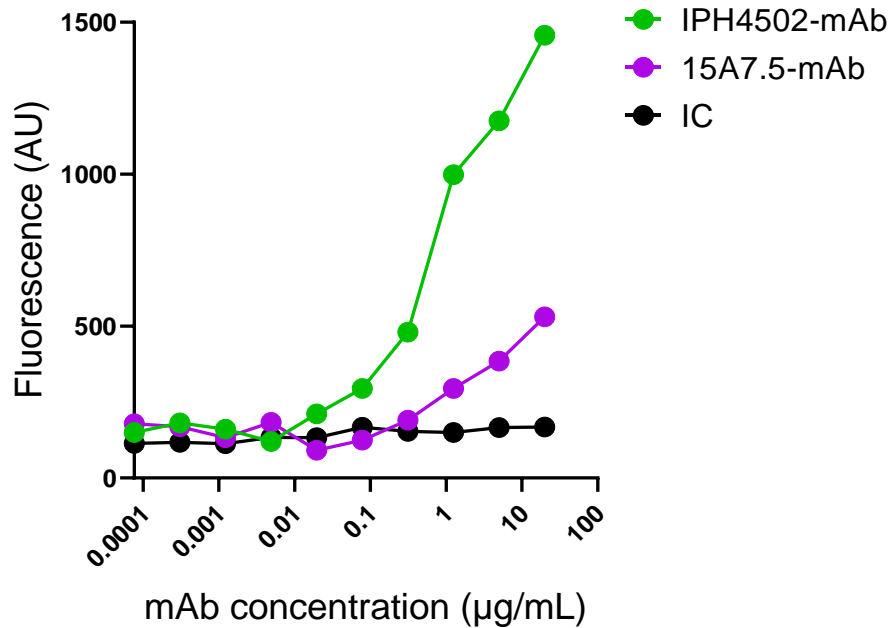
Internalization of naked antibodies coupled to pHAb amine in Nectin-4 expressing SUM190 PT cells was monitored at 24h

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)

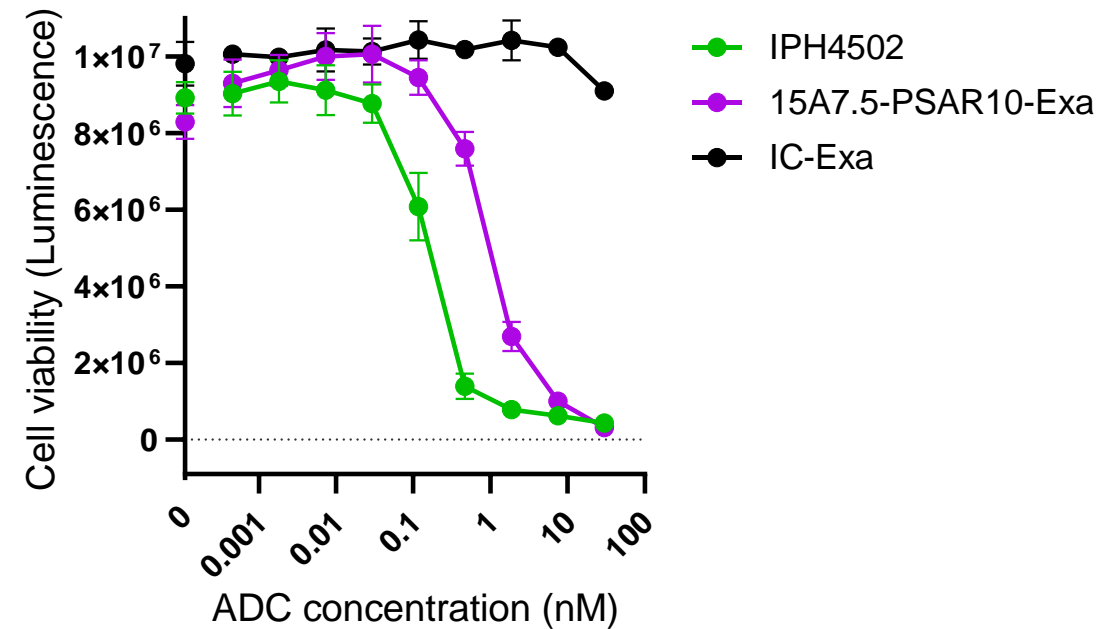
pHAb = pH sensitive dye that increases fluorescence upon internalization

IPH4502 demonstrates higher internalization and cytotoxicity than 15A7.5-PSAR10-exatecan

Internalization



Cytotoxicity



Internalization of naked mAbs coupled to pHAb amine in Nectin-4 expressing SUM190 PT cells was monitored at 24h

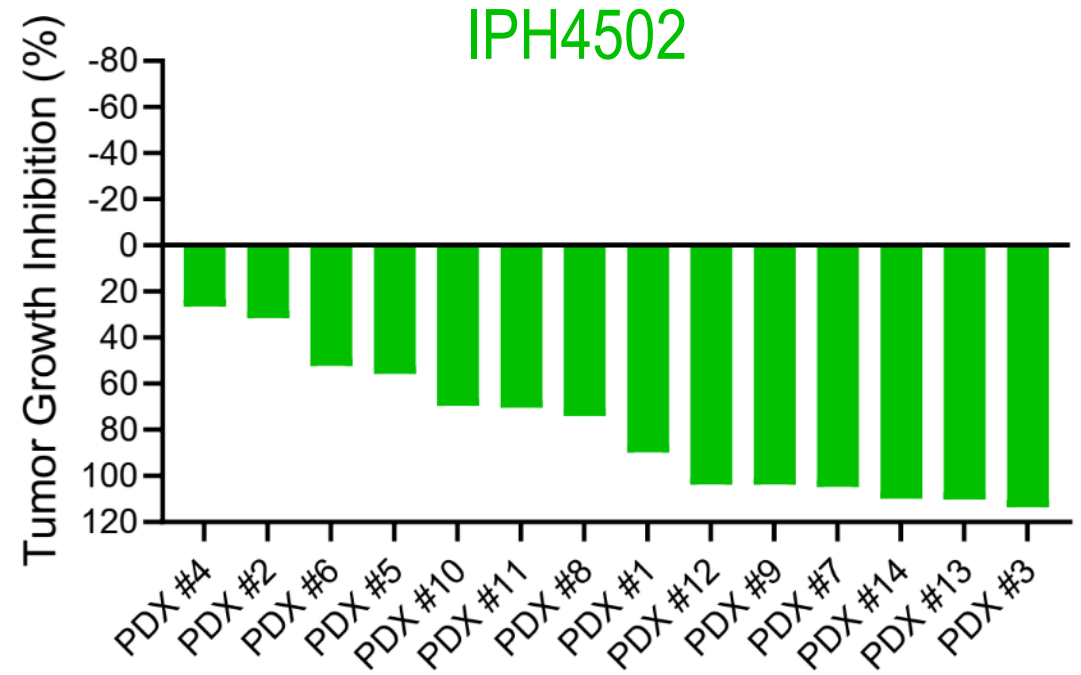
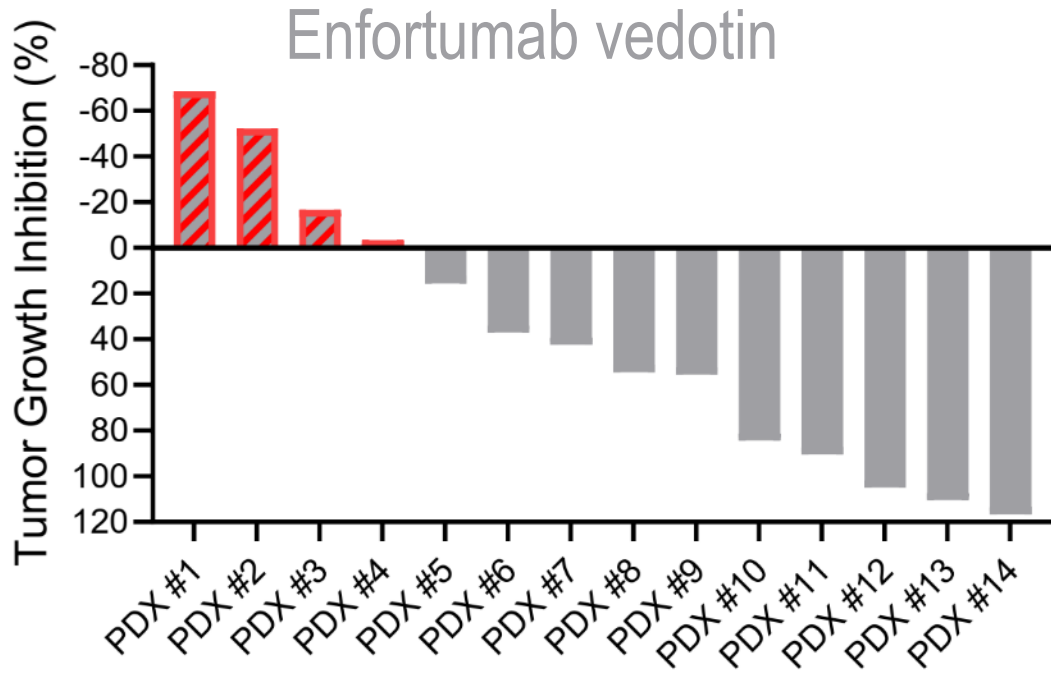
15A7.5 = humanized mAb from patent EP4086284A1 (ETX-22 / LY4101174-mAb)

pHAb = pH sensitive dye that increases fluorescence upon internalization

ADCs were incubated for 10 days with SUM190 PT cells and cell viability was evaluated with CellTiter-Glo® assay.

15A7.5-PSAR10-Exa = humanized 15A7.5 coupled to exatecan at DAR 8 with PSAR10 linker (Lopez et al., 2024; ETX-22 / LY4101174)

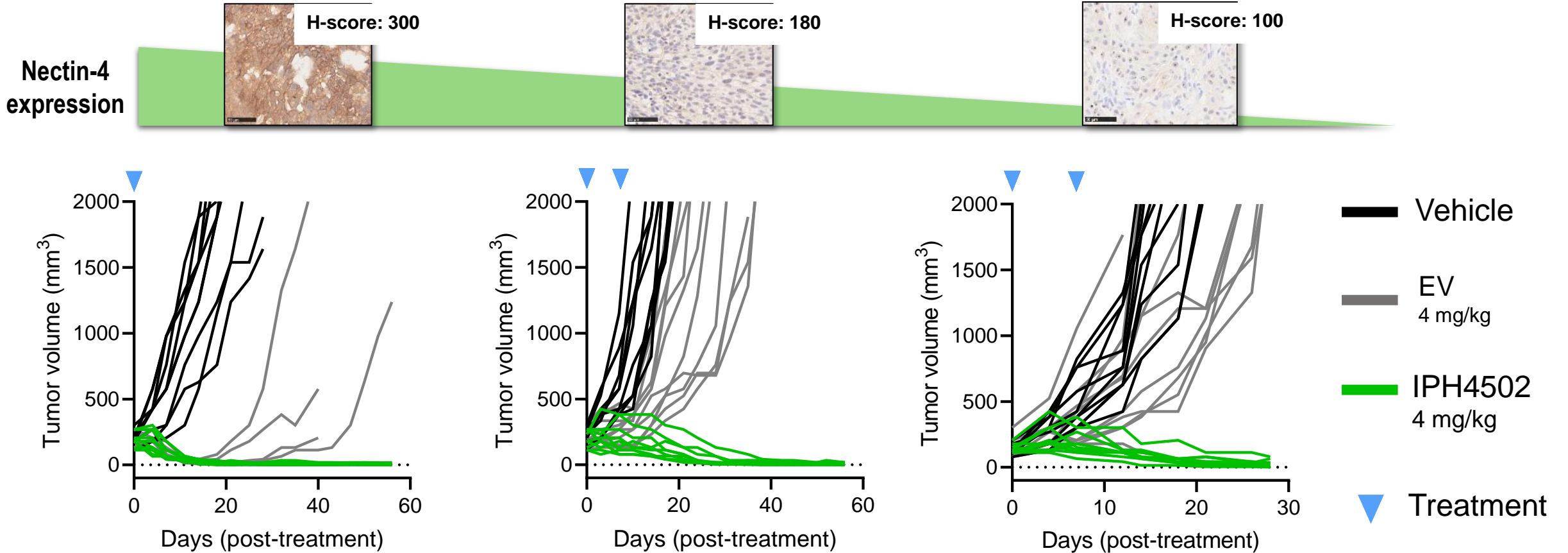
IPH4502 shows stronger anti-tumor activity than EV in multiple PDX models from UC patients



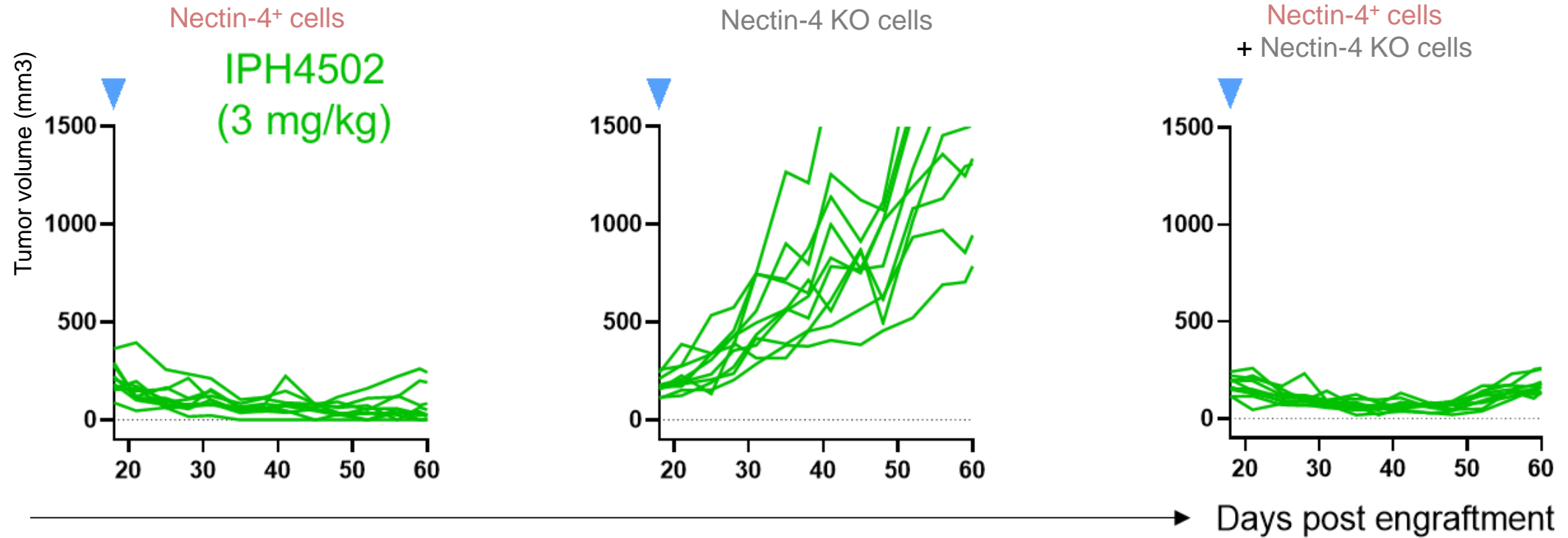
Mice were treated with the same dose (4mg/kg) for both ADCs at day 0 (randomization) and day 7

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 across various Nectin-4 expression levels and demonstrates superior activity to EV in bladder PDX models



IPH4502: Demonstrates in vivo potential for efficacy in heterogeneous Nectin-4 expressing tumors via target-dependent bystander effect



In vivo bystander killing



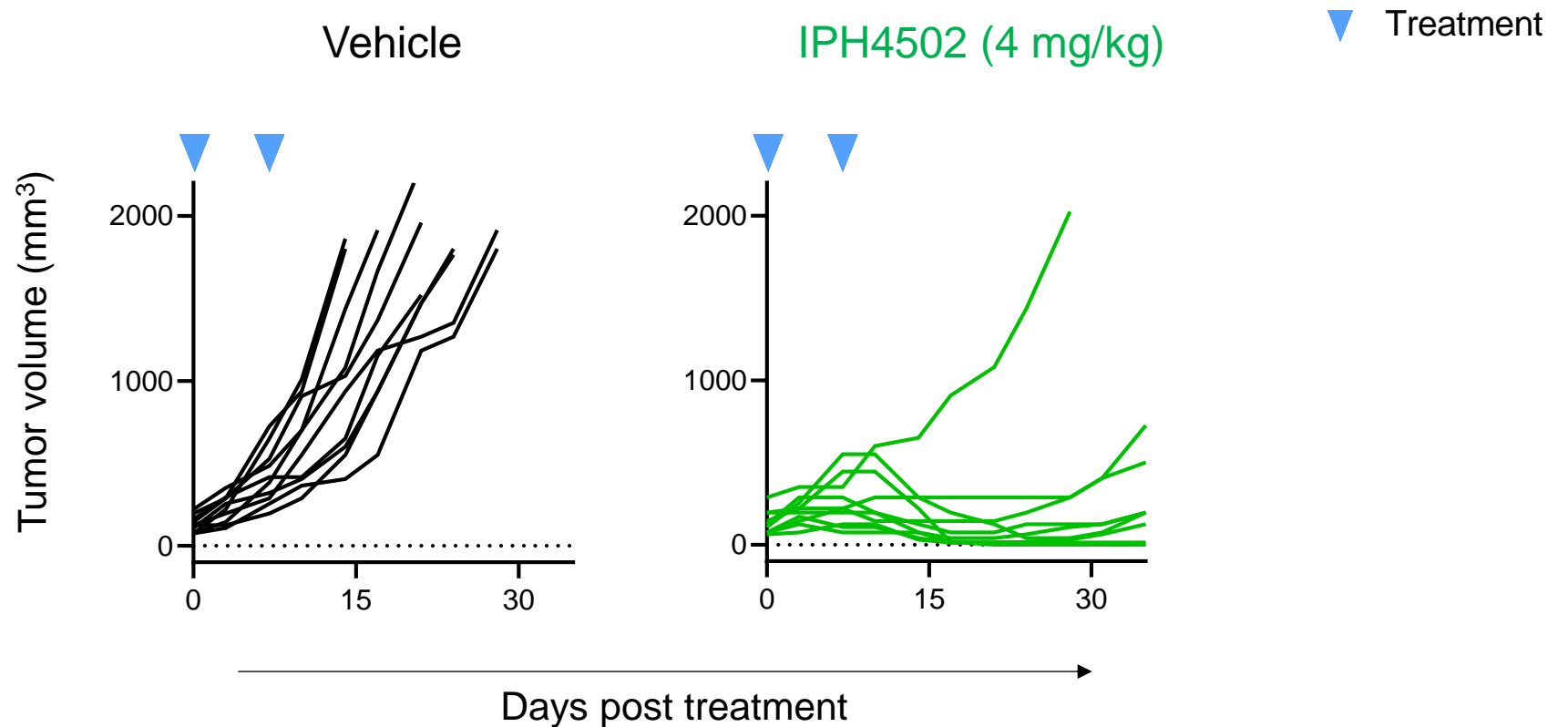
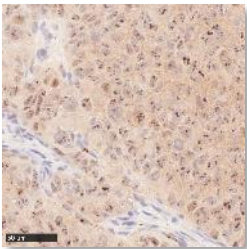
Address heterogeneous Nectin-4 expression

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

PDX model of TNBC

TNBC

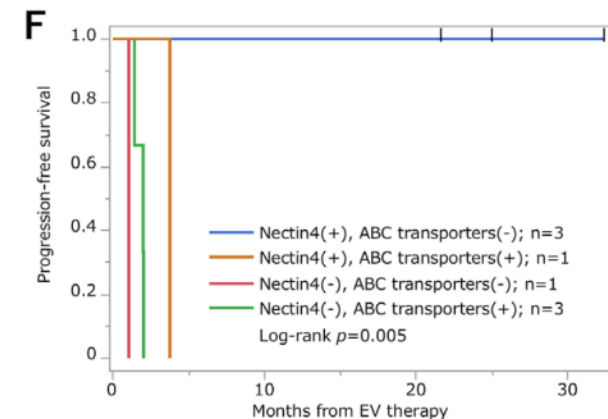
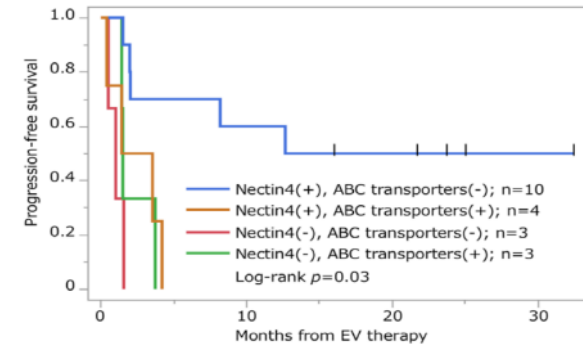
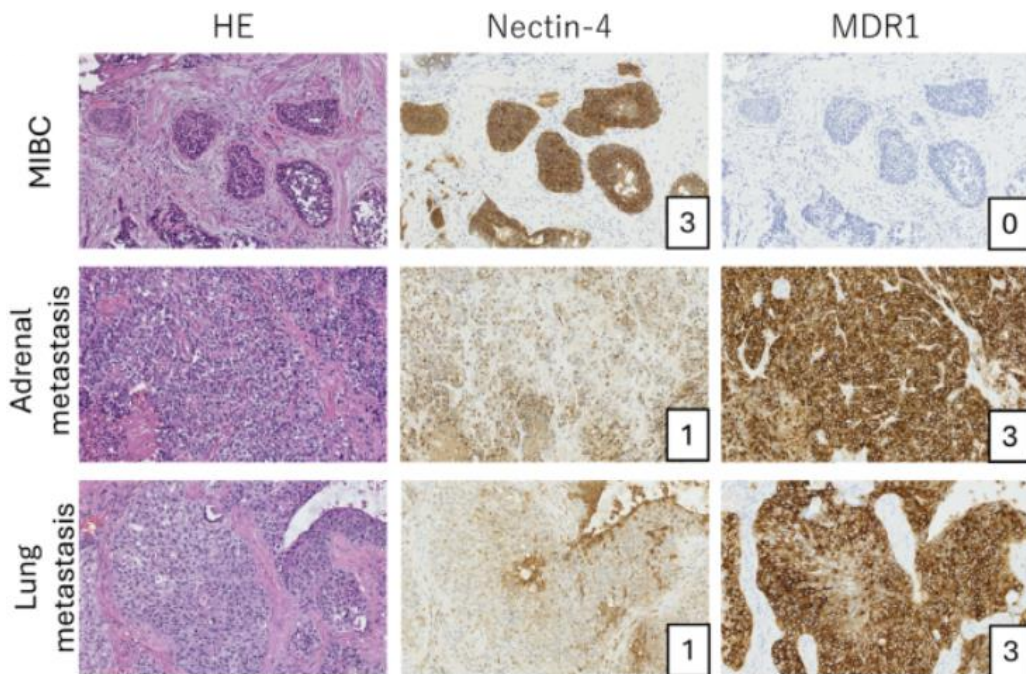
Nectin-4
H-score: 200



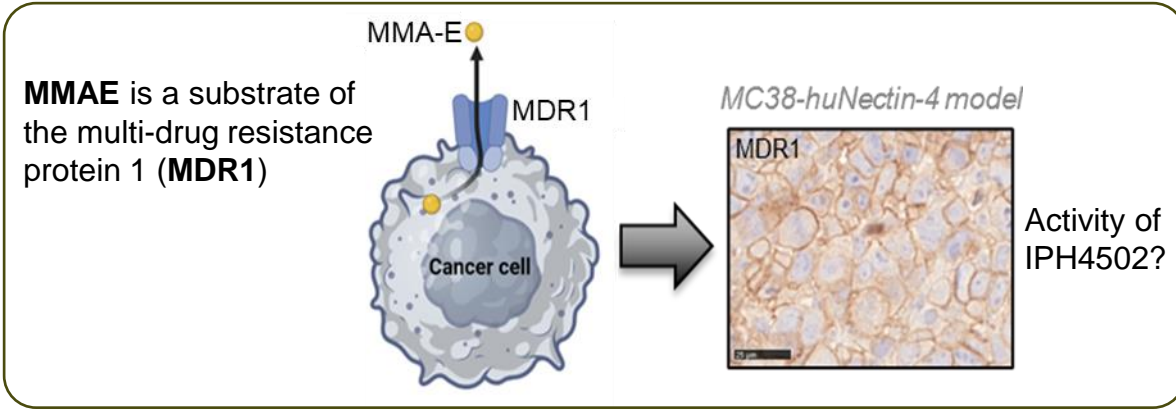
ABC transporters expression correlates with resistance to enfortumab vedotin in urothelial carcinoma

In metastatic lesions, Nectin-4 is lower and ABC transporter expression is increased

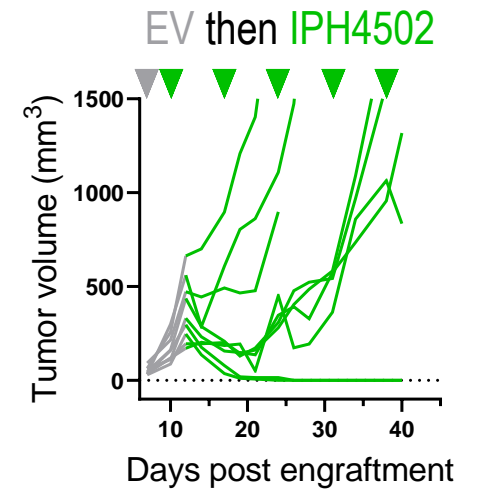
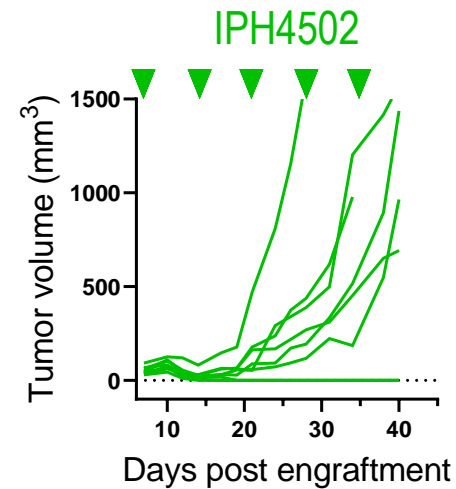
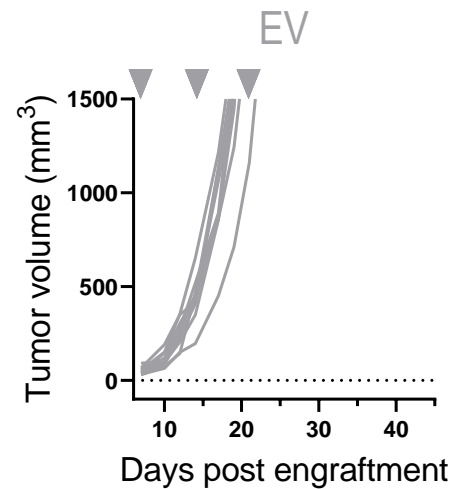
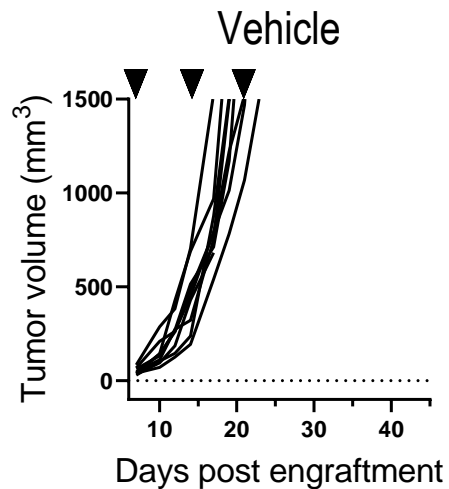
ABC transporter expression in primary tumor or metastasis correlates with resistance



IPH4502 demonstrates efficacy in EV-primary refractory model



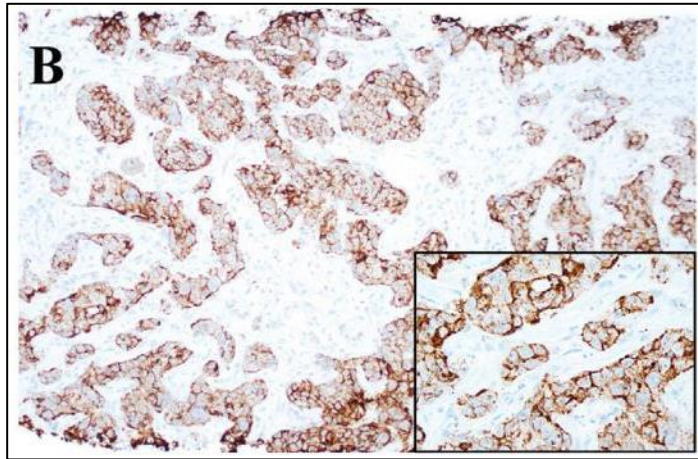
▼ Treatment



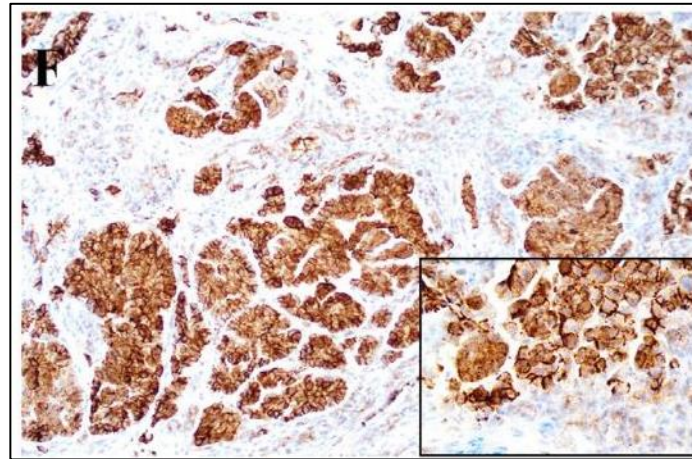
Nectin-4 remains highly expressed in EV-relapsed cancer patients

Nectin-4 expression was assessed by IHC in fresh biopsies from sites of tumor progression following EV from 3 patients

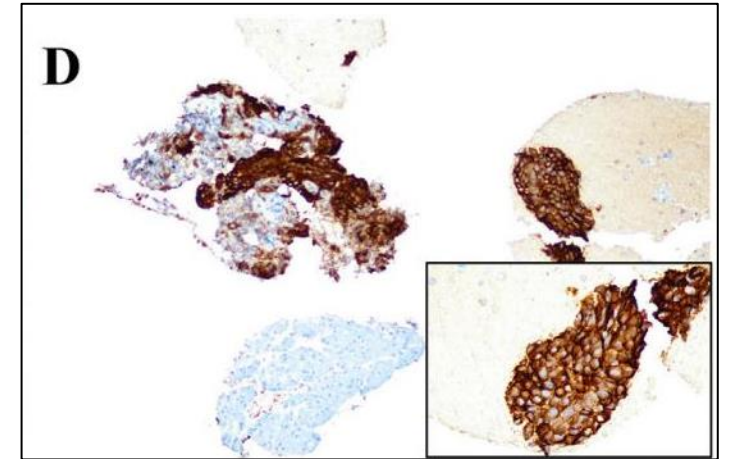
Liver metastasis



Lymph node metastasis



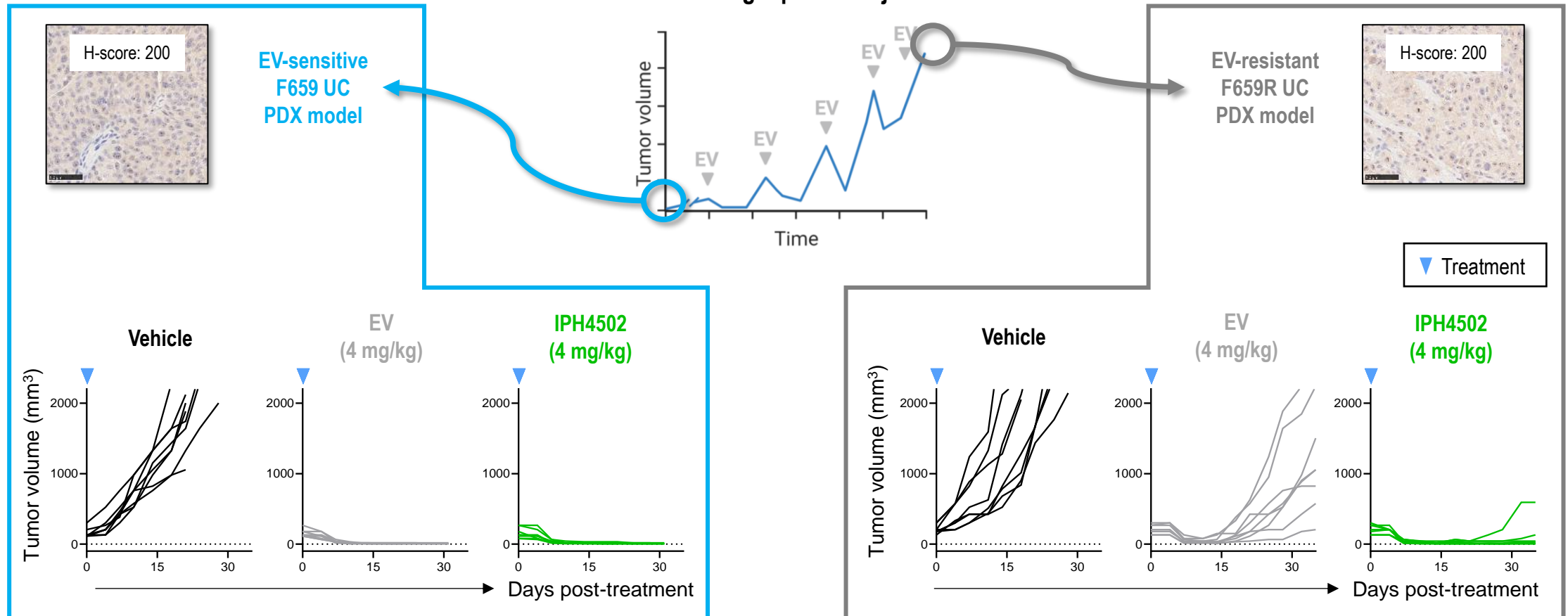
Duodenal metastasis



Nectin-4 expression is conserved in high grade UC patients with disease progression after treatment with EV (between 4-8 cycles)

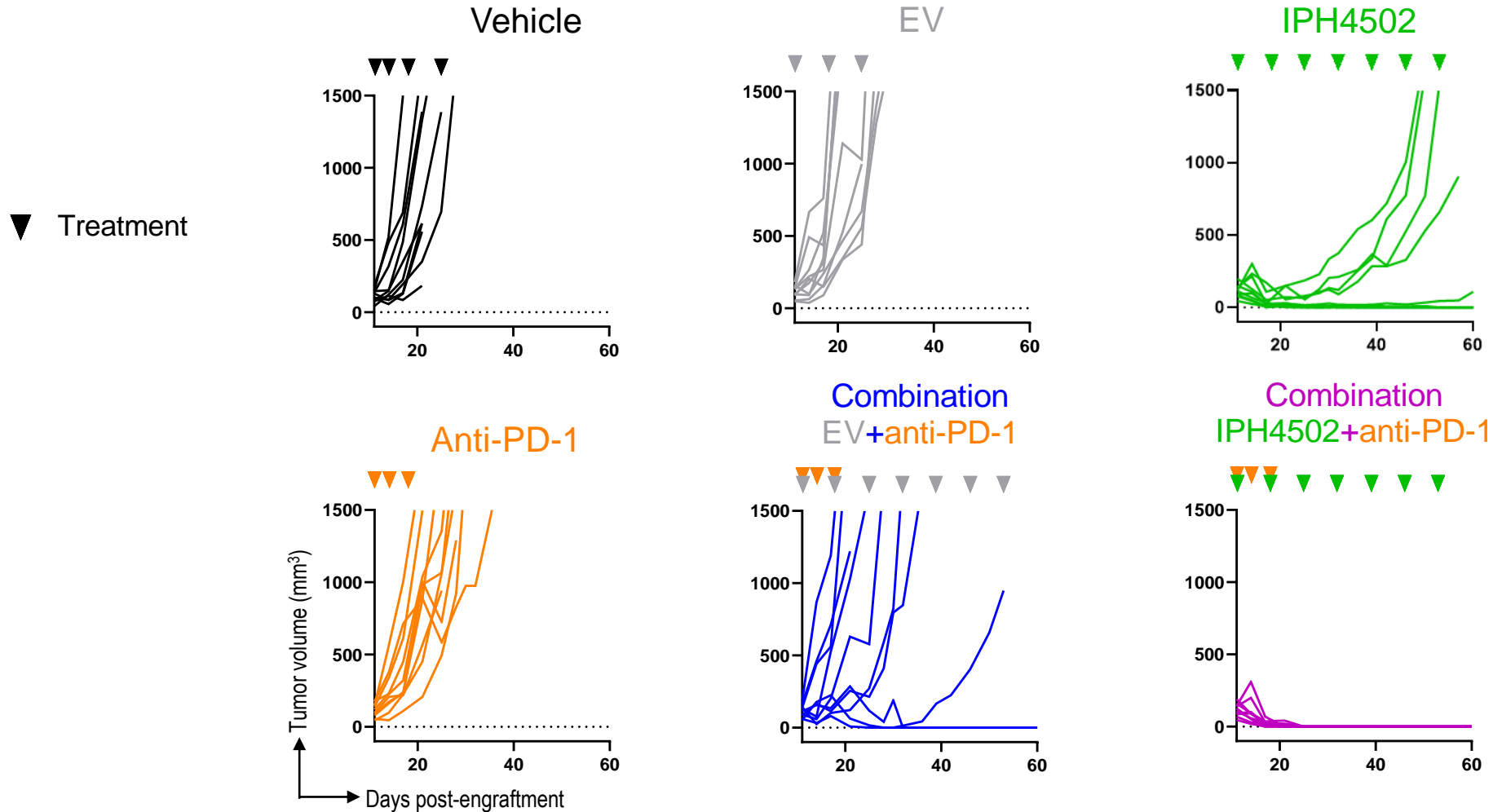
IPH4502 has anti-tumor activity in a PDX-model of acquired EV-resistance

Generation of a UC PDX model acquiring resistance to EV following repetitive injections:

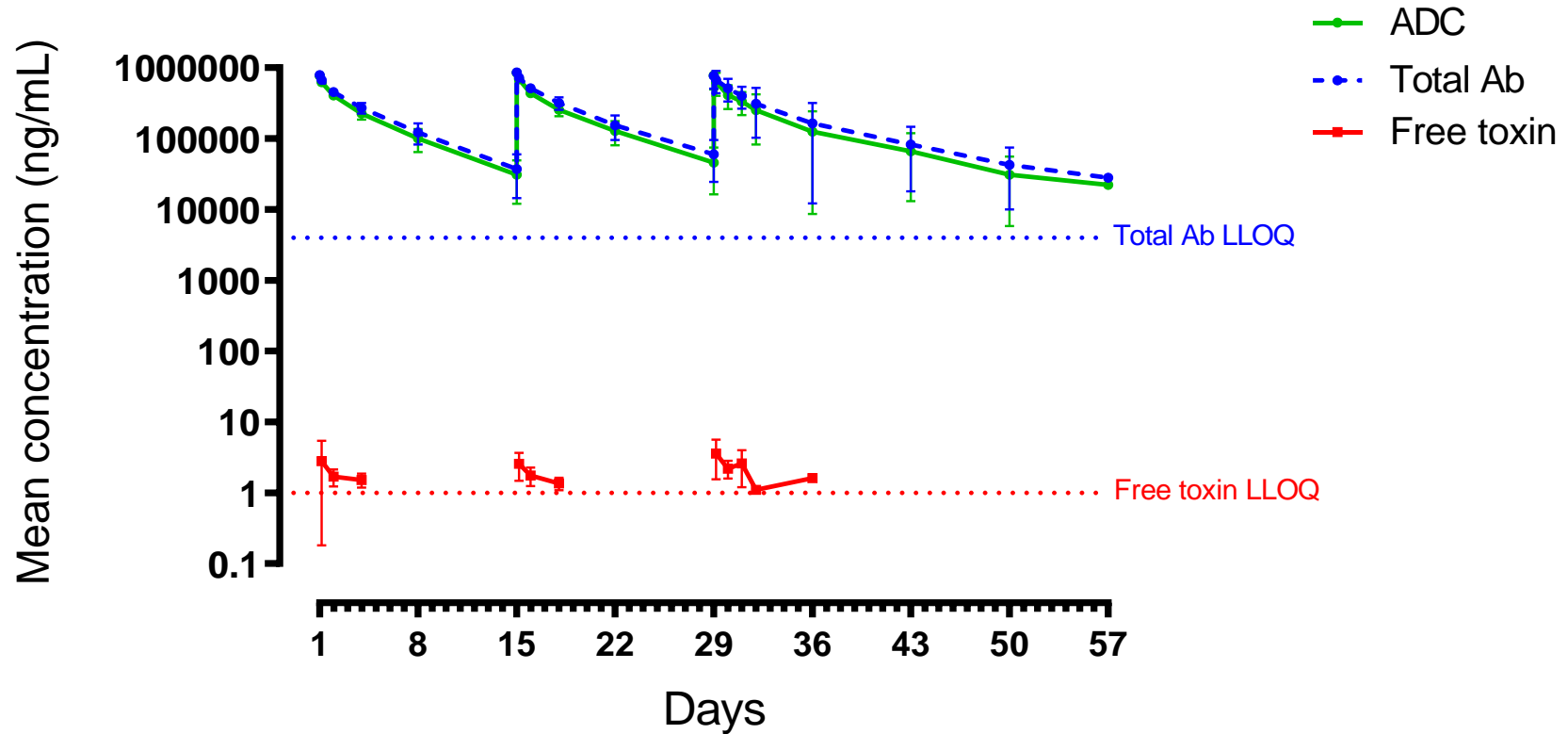


NMRI-Nude mice were subcutaneously implanted with tumor fragments. The F659R PDX model was generated through the repetitive in vivo treatment of the F659 PDX model with EV, which was repeated until the model exhibited resistance to EV. (n=8 mice/group)

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



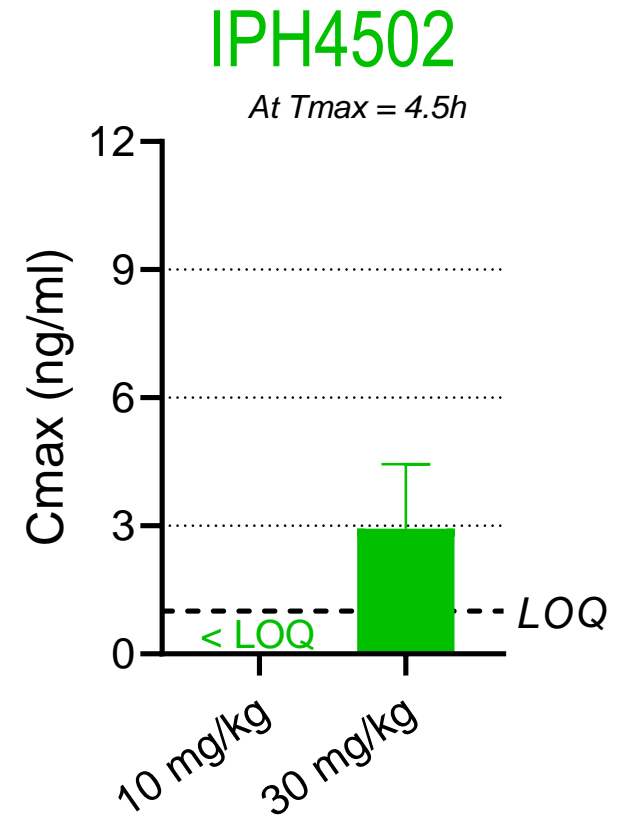
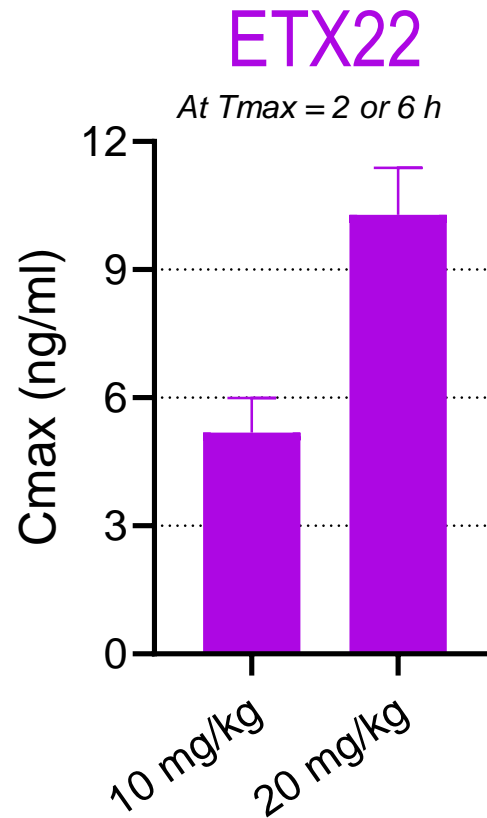
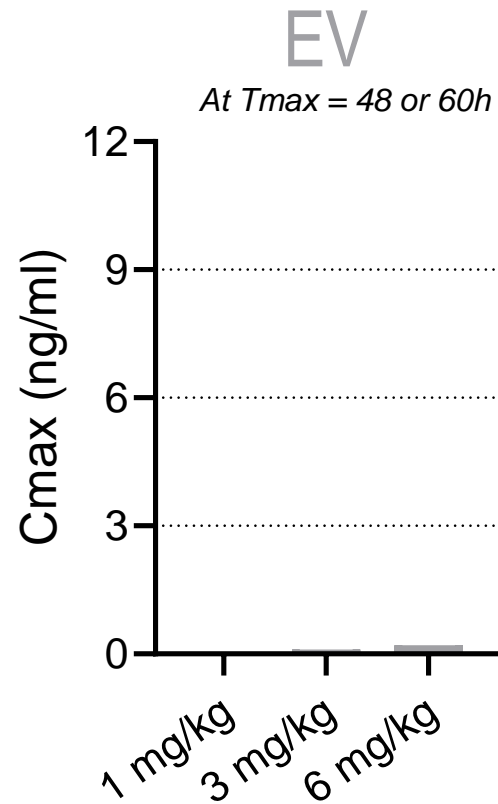
IPH4502 has high ADC exposure and minimal exatecan systemic release in NHP



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 (\pm 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

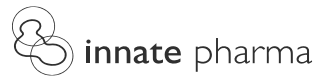
IPH4502 has minimal exatecan systemic release in NHP

Free-toxin: Cmax



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 – Clinical development plan



IPH4502 Assumptions for IPH4502 Clinical plan

**IPH4502 to overcome
Nectin-4 ADCs limitations**

Broader therapeutic window

Potential beyond Bladder

↑ activity in low and heterogeneous
Nectin-4 expressors

**Target resistant populations to
standard of care EV**

Favorable safety profile

- High Bystander effect
- High Internalization
- Non-competitive epitope vs EV
- Superior efficacy to EV in bladder cancer models with low and heterogeneous Nectin-4 expression
- Stable Linker with low release of free exatecan into cynomolgus monkey plasma
- Overcome MDR1-mediated resistance to MMAE
- Activity in secondary resistance to EV models

IPH4502 potential in solid tumors: UC and Beyond

IPH4502 potential benefit vs MMAE ADCs



UC

Address growing unmet need of **post-Padcev mUC patients***

Move up to **1L mUC** in combination with PD1 with less toxicity expected than EV



Expand beyond UC

High potential in **several tumor types not responsive nor addressed by MMAE ADCs** with low/med and heterogeneous expression of Nectin-4

**Stable N4 expression in refractory tumors from patients treated with EV*

Large addressable market with significant upside

Indications included in the Phase 1 dose escalation

>200K US/EU patients

Bladder
NSCLC
Breast
CRC
Prostate

100-200K US/EU patients

HNSCC
Ovarian
GEJ

<100K US/EU patients

Cervical
Esophageal
Melanoma

IPH4502 Phase 1 study design

US and EU

DOSE ESCALATION

STUDY POPULATION

Solid tumor types known to express Nectin-4*

Bladder, Cervical, Breast, NSCLC, GEJ, Esophageal, HNSCC, Prostate, Melanoma, Ovarian, CRC

DESIGN FEATURES

- Step-wise dose escalation to determine MTD for further dose optimization
- Bayesian optimal interval design (BOIN) to optimize MTD identification
- Backfill (BF) cohorts between dose escalation cohorts to increase # treated patients at active dose

Up to 30 pts in dose escalation
Up to 15 pts in Backfill cohorts

DOSE OPTIMIZATION

DESIGN FEATURES

- Randomize at least 2 dosing schedules with clinical activity to optimize dose and determine the recommended phase 2 dose (RP2D)
- Explore indications with signs of anti-tumor activity

Up to 30 pts per indication

OBJECTIVES

Primary Objectives:
Safety (DLT, MTD) and tolerability of IPH4502
Determine RP2D

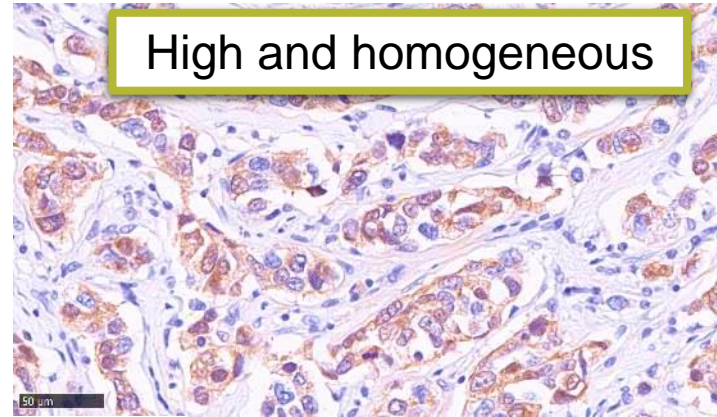
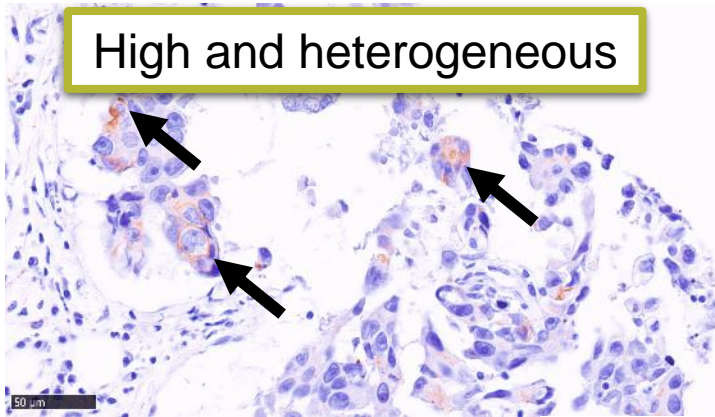
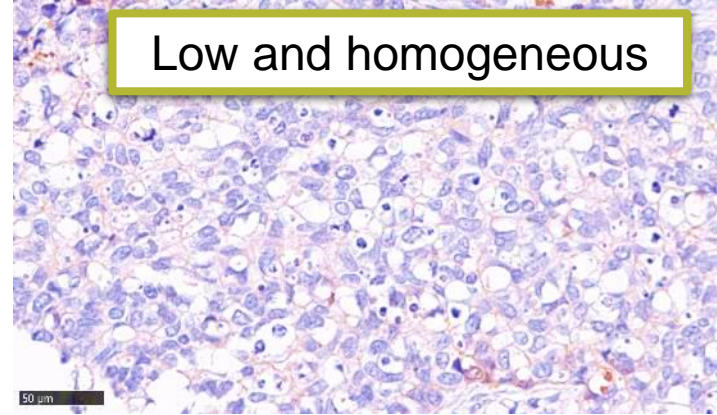
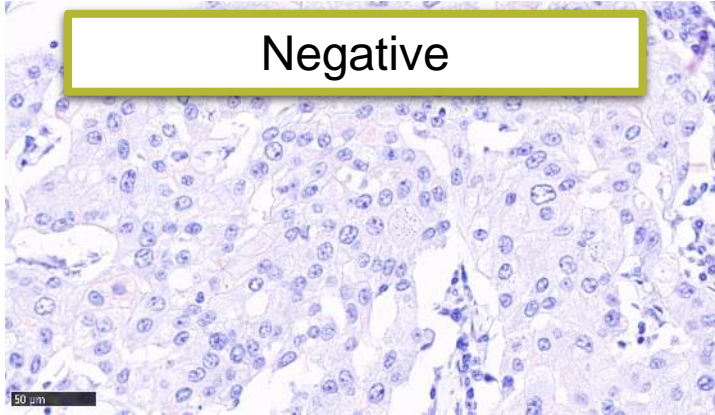
Secondary Objectives:

- PK
- Immunogenicity
- Preliminary efficacy

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IPH4502 Biomarker plan

Nectin-4 expression

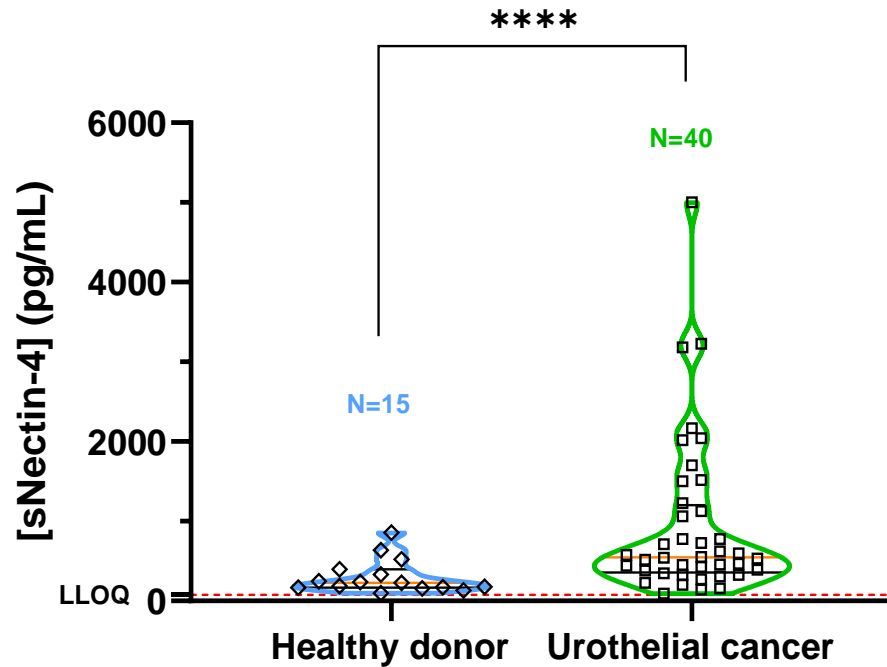


Breast cancer

The clinical program includes a biomarker plan to identify patient populations who most benefit from the IPH4502 treatment

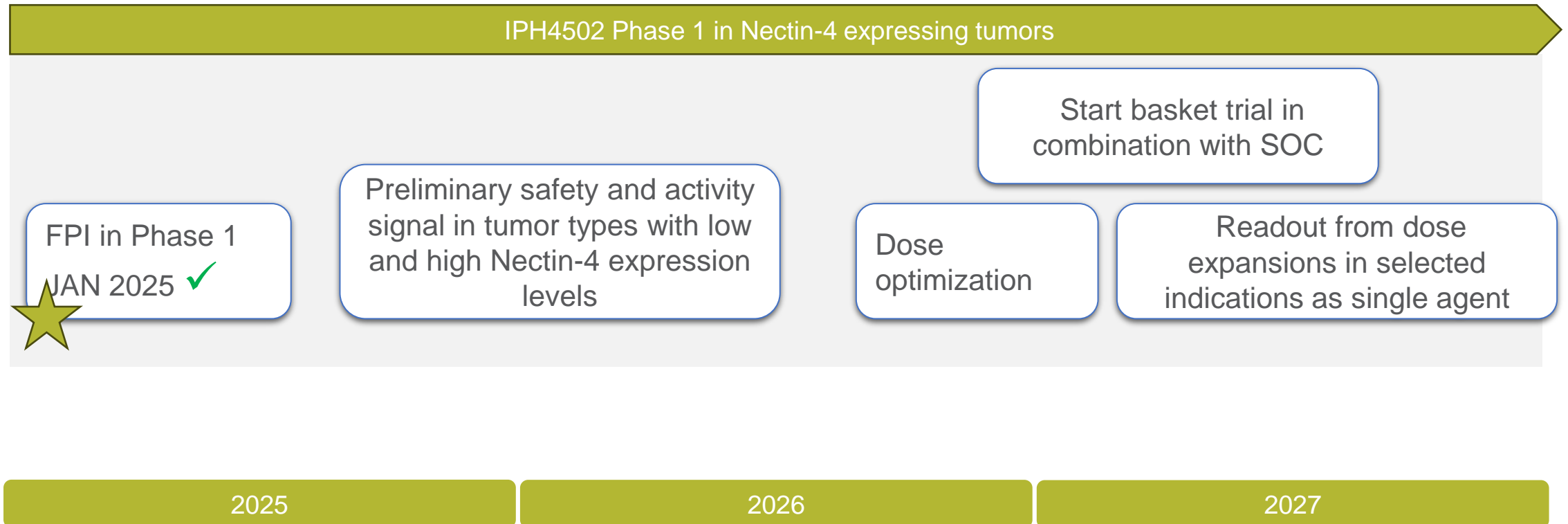
- Analysis of Nectin-4 expression in cancer tissue from study patients
- Soluble biomarkers
- Analysis of clinical features and exposure-response analysis

Soluble Nectin-4 is higher in cancer patients than in healthy donors



A soluble form of Nectin-4 (sNectin-4), has been identified in several other tumor types such as ovarian cancer (Derycke et al. 2010), breast cancer (Fabre-Lafay et al. 2007), or NSCLC (Takano et al. 2009).

IPH4502 Multiple Clinical Milestones to be Delivered in Mid-term



Data will inform next steps



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Thank you

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