IPH4502, a differentiated Nectin-4 exatecan antibody-drug conjugate with best-in-class potential

Abstract number: **PB-080**

Scan Me

Nicolas Viaud[1], Romain Remark[1], Séverine Augier[1], Léa Simon[1], Julie Lopez[1], Thomas Arnoux[1], Raja Noufir[1], Clément Jacquet[1], Paul Poizat[1], Maryline Agu[1], Marilyne Blemont[1], Camille Kosthowa[1], Robin Letay-Drouet[1], Cyril Perrier[1], Cédric Cesari[1], Angélique Palumbo[1], Guillaume Terral[1], Rachel Courtois[1], Marie-Laure Thibult[1], Agnès Represa[1], Benjamin Rossi[1], Angélique Boedec Herbette[1], Ariane Morel[1], Markus Jensen[1], Yannis Morel[1]

[1] Innate Pharma, Marseille, France

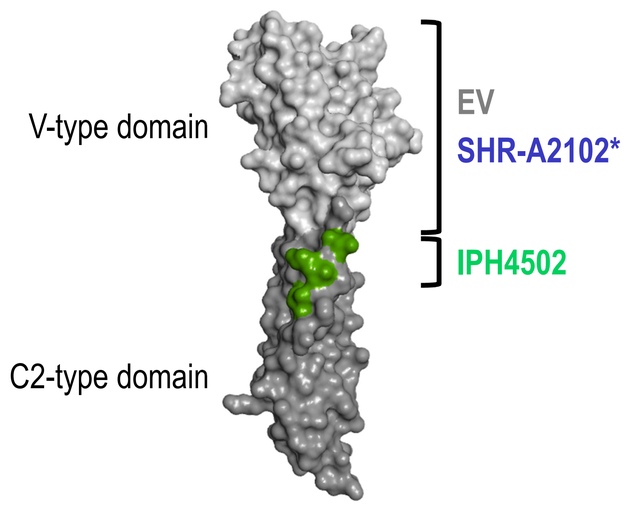
Background

Enfortumab vedotin (EV) has validated Nectin-4 as an ADC target in urothelial cancer; however, resistance, treatment-related toxicity, and reduced activity in tumors with low or heterogeneous Nectin-4 expression remain key challenges.

IPH4502 is a novel Nectin-4-targeted ADC designed with three differentiated components:

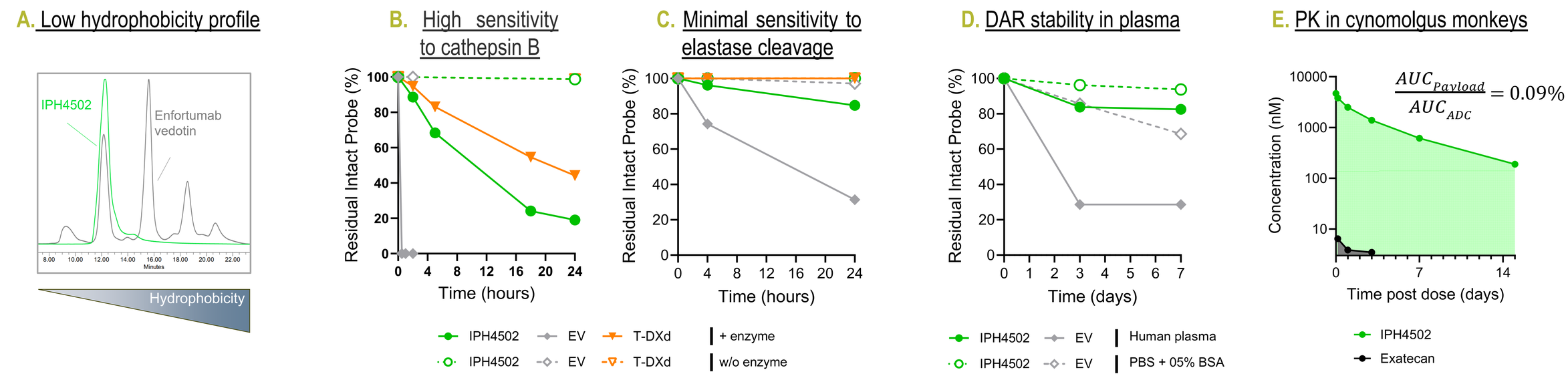
- **Proprietary anti-Nectin-4 antibody:** Targets a non-overlapping epitope relative to EV, with high internalization, potentially enabling activity in tumors with low or heterogeneous Nectin-4 expression
- **Proprietary stable linker:** Designed to limit premature systemic release of free exatecan and potentially reduce off-target payload exposure
- **Exatecan payload (DAR 8):** A potent topoisomerase I inhibitor with low susceptibility to MDR1-mediated efflux, to help overcome MMAE-related resistance associated with EV

1. IPH4502 binds to a distinct epitope



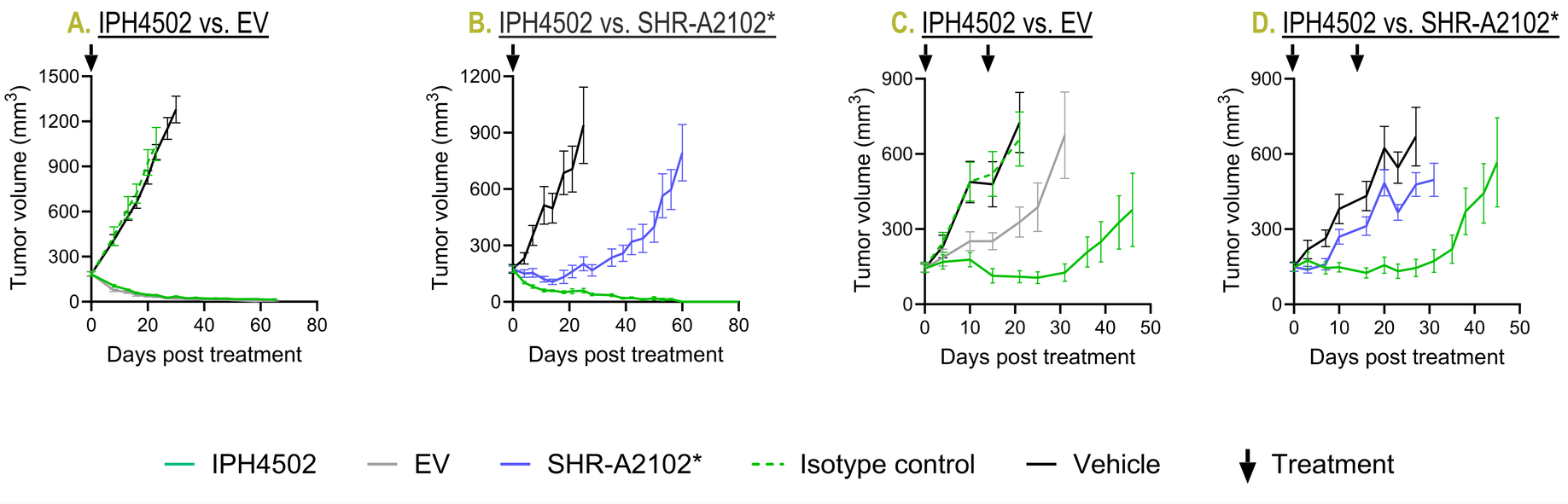
Flow cytometry experiments showed that EV and SHR-A2102* bind to the V domain of Nectin-4 and that IPH4502 binds at the junction of the V-C2 interdomain. Figure was created using the human Nectin-4 PDB 4FRW structure.

2. IPH4502 demonstrates high linker stability and selective intracellular exatecan release, minimizing systemic payload exposure



A. HIC chromatograms of IPH4502 (green) and EV (gray). **B, C.** DAR evolution of IPH4502 (green circles), EV (gray diamonds), and trastuzumab deruxtecan (T-DXd; orange triangles) after a 24-h incubation at 37°C with **(B)** cathepsin B (20 ng/µL) or **(C)** neutrophil elastase (1 ng/µL), expressed as the percentage of residual intact ADC. Filled symbols represent protease-treated conditions; open symbols indicate untreated controls. **D.** DAR evolution of IPH4502 (green) and EV (gray) monitored *ex vivo* for 7 days in human plasma at 37°C, expressed as the percentage of residual intact ADC. **E.** PK of IPH4502 in cynomolgus monkey following administration at 30 mg/kg. Graph shows the mean plasma concentrations of IPH4502 (green) and free exatecan (black) during cycle 1. After Day 3, free exatecan levels were below the limit of quantification.

3. IPH4502 exhibits superior *in vivo* antitumor activity vs. benchmark ADCs in high- and low-Nectin-4 CDX models



CB17-SCID mice were randomized and treated intravenously (i.v.) as indicated (arrows denote treatment days).

A, B. Two independent experiments in SUM190-PT tumor-bearing mice (treatment initiated at ~180 mm³). Mice received a single injection of vehicle (black), IPH4502 at 3 mg/kg (exatecan, DAR8; solid green line), matching isotype control at 3 mg/kg (exatecan, DAR8; dotted green line), EV at 3 mg/kg (MMAE, DAR4; gray), or SHR-A2102* at 6 mg/kg (rezetecan, DAR4; blue).

C, D. Two independent experiments in NCI-H322 tumor-bearing mice (treatment initiated at ~130 mm³). Mice were treated on day 0 and day 14 with vehicle (black), IPH4502 at 4 mg/kg (exatecan, DAR8; solid green line), matching isotype control at 4 mg/kg (exatecan, DAR8; dotted green line), EV at 4 mg/kg (MMAE, DAR4; gray), or SHR-A2102* at 8 mg/kg (rezetecan, DAR4; blue).
ABC: Antibody Binding Capacity.

***: SHR-A2102**: binder from Jiangsu Hengrui patent WO2022228406, conjugated to Mal-C-GGFG-rezetecan DAR4, believed to correspond to notiretatug rezetecan.

Conclusions & Takeaways

Differentiated target engagement

- IPH4502 targets an epitope in the V-C2 interdomain region of Nectin-4, distinct from approved and selected clinical benchmark ADCs

Stable, cleavable linker with efficient intracellular release

- Favorable hydrophobicity profile, high linker stability and minimal elastase-mediated cleavage, leading to minimal exatecan release *in vivo*
- Cathepsin B-mediated cleavage enables efficient, targeted intracellular release of exatecan

Superior *in vivo* efficacy vs approved and Topo-I clinical benchmarks in Nectin-4 low expressing model

- IPH4502 outperforms EV and a clinical-stage Topo-I benchmark ADC in a Nectin-4-low model

Clinical Outlook

Phase 1 ongoing
NCT06781983

Clinical data:
Poster PB-089

Scan Me

innate pharma

Copies of this poster are for personal use only and may not be reproduced without the permission of the authors