IPH4502, a next-generation Nectin-4 exatecan antibody-drug conjugate

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SCAN ME

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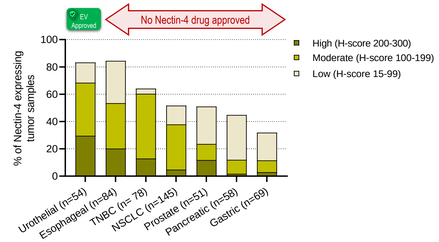
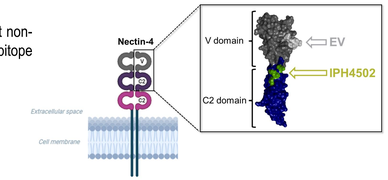
Background

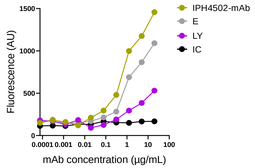
- Nectin-4 is overexpressed in multiple solid tumors including, but not limited to, urothelial carcinoma (UC), esophageal cancer, non-small cell lung cancer (NSCLC), or triple negative breast cancer (TNBC).
- Enfortumab vedotin (EV), an antibody-drug conjugate (ADC) targeting Nectin-4 with a monomethyl auristatin E (MMAE) payload, has been approved for the treatment of UC, which exhibits the highest Nectin-4 expression among all solid tumor types. EV and other ADC targeting Nectin-4 are currently being investigated in clinical studies for UC and other malignancies.



- To address the unmet medical need of UC patients who discontinue EV for toxicities, lack of efficacy, or ineligibility for this approved therapy, and to expand Nectin-4 targeting in tumor indications beyond UC with lower Nectin-4, we developed IPH4502, a differentiated anti-Nectin-4 ADC conjugated to exatecan with a cleavable hydrophilic linker, and a drug-to-antibody ratio of 8.
- IPH4502 has a distinct non-overlapping binding epitope of EV:

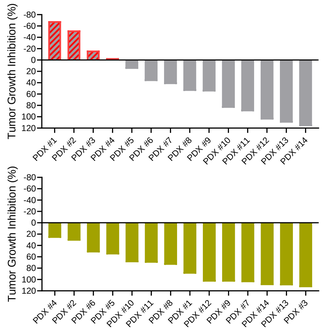


1. IPH4502 demonstrates more efficient internalization than other Nectin-4 ADC



Internalization was evaluated by coupling pHAb amine-reactive dye (Promega) to monoclonal antibodies (mAbs) without linker-payload. E corresponds to a mAb having the amino acid sequence of enfortumab, and LY is the humanized 15A7.5 mAb from patent EP4086284A1, believed to correspond to LY4101174-mAb. Isotype control (IC) was used as negative control. SUM190-PT cells expressing Nectin-4 were incubated with a dose range of mAb-pHAb, and fluorescence was quantified at 24h with a fluorescence plate reader (Enspire; PerkinElmer). Data presented are representative of 2 independent experiments.

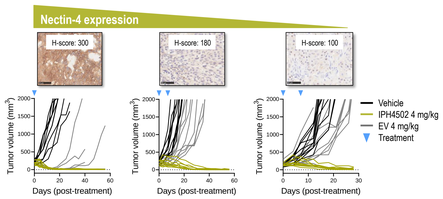
2. IPH4502 shows stronger anti-tumor activity than EV in multiple PDX models from UC patients



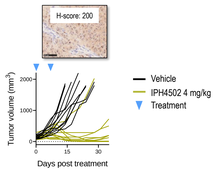
NMRI-Nude mice were subcutaneously implanted with tumor fragments from 14 different UC PDX models. On days 1 and 8 post-randomization, mice (n=3/group/model) were administered intravenously (IV) with IC-Exatecan, IPH4502, or EV at a dose of 4 mg/kg. Experiments were performed at Urosphere, France. Tumor Growth Inhibition = 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 the IC-Exatecan group were still alive.

3. IPH4502 shows anti-tumor activity across a range of Nectin-4 expression levels in UC PDX models and beyond UC

A. UC PDX model with various Nectin-4 expression levels:



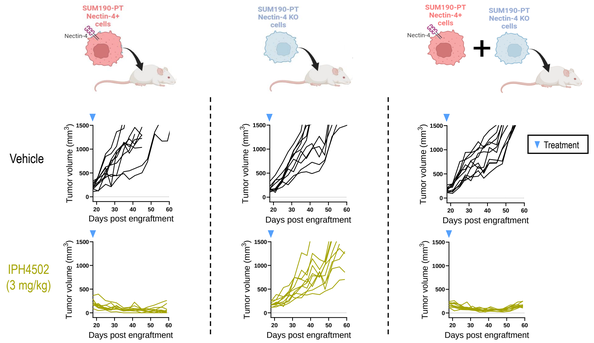
B. TNBC PDX model:



A. NMRI-Nude mice were subcutaneously implanted with tumor fragments from 3 UC PDX models. At the designated time points (blue arrowheads), mice (n=10/group) were administered IV with vehicle, IPH4502, or EV at a dose of 4 mg/kg. Experiments were performed at Urosphere, France. For each model, the Nectin-4 histochemical-score (H-score = percentage x intensity (ranging from 0 to 3) of staining), and a representative image of Nectin-4 IHC staining of the tumor are presented.

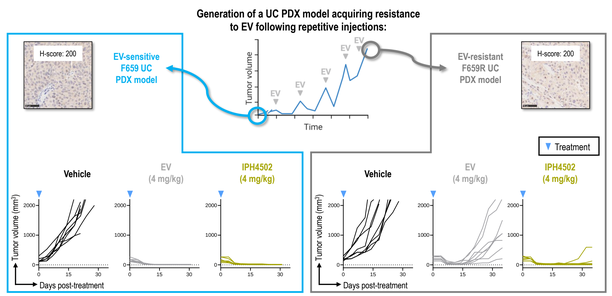
B. Nude mice were subcutaneously implanted with tumor fragments from one TNBC PDX model. At the designated time points (blue arrowheads), mice (n=10/group) were administered IV with vehicle or IPH4502 at a dose of 4 mg/kg. Experiments were performed at Xentech, France. The Nectin-4 H-score and a representative image of IHC staining of the tumor are presented.

4. IPH4502 has a strong bystander killing effect *in vivo*



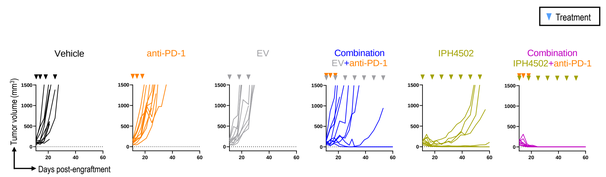
CB17-SCID mice were subcutaneously engrafted with SUM190-PT cells (Nectin-4 positive), SUM190-PT Nectin-4 KO cells (CRISPR-Cas9 KO cell line generated at Innate Pharma), or a mix of SUM190-PT cells and SUM190-PT Nectin-4 KO cells (ratio 1:1). Mice were treated once with either vehicle, or IPH4502 at 3 mg/kg at day 18 post tumor engraftment (n=10 mice/group).

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



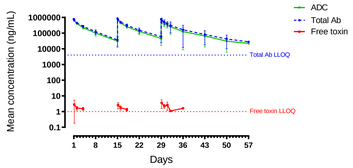
NMRI-Nude mice were subcutaneously implanted with tumor fragments. The F659R PDX model was generated through the repetitive *in vivo* treatment of the F659 PDX model with EV, which was repeated until the model exhibited resistance to EV. Subsequently, F659R tumor fragments were implanted into new NMRI-Nude mice. At the indicated time point (blue arrowheads), mice implanted with either F659 or F659R tumor fragments were injected IV with vehicle, IPH4502 or EV at the dose of 4 mg/kg (n=8 mice/group). For each model, the Nectin-4 H-score and a representative image of Nectin-4 IHC staining of the tumor are shown. Experiments were performed at Urosphere, France.

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



B cell-depleted C57Bl6/J mice were subcutaneously engrafted with the murine colon adenocarcinoma cell line MC38 cells transfected with human Nectin-4, which represents an aggressive tumor model. MC38 huNectin-4 cells express high levels of multidrug resistance protein 1 (MDR1), and exhibit resistance to EV. At the designated time points (arrowheads), mice were administered IV with vehicle, anti-PD-1, EV, IPH4502, EV+anti-PD-1, or IPH4502+anti-PD-1 (all molecules at 10 mg/kg) (n=10 mice/group).

7. IPH4502 has high ADC exposure and minimal exatecan systemic release



In a GLP toxicology study in cynomolgus monkey, IPH4502 was administered at a dose of 30 mg/kg IV with 30 minutes infusion once every two weeks for a total of 3 doses. ADC, total Ab and free toxin mean concentrations (±standard deviations) in plasma were determined using validated LC-MS/MS methods. Lower limits of quantification (LLOQ) are indicated for total Ab, and free toxin. The molecular weight (MW) of IPH4502 is 163 kDa, the MW of IPH4502-mAb (naked antibody) is 149 kDa, and the MW of exatecan is 531.6 Da.

Conclusions

IPH4502 is a differentiated exatecan-based Nectin-4 ADC with potential for improved clinical benefit:

- Improved anti-tumor activity across a spectrum of Nectin-4 expression levels (ranging from low to high) in UC PDX models, in comparison to EV, attributed to its high internalization and bystander killing effect.
- Anti-tumor activity beyond UC in PDX models.
- Anti-tumor activity in EV-resistant models (primary resistance and acquired resistance).
- Increased anti-tumor activity *in vivo* when combined with anti-PD-1.
- ADC linker stability and low release of free exatecan in cynomolgus monkey plasma.

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