GYNET - Safety and efficacy of anti-netrin 1 (NP137) in combination with chemotherapy and/or pembrolizumab in patients with pretreated locally advanced / metastatic endometrial carcinoma or cervix carcinoma: an adaptive multi-arms randomized Phase I/II

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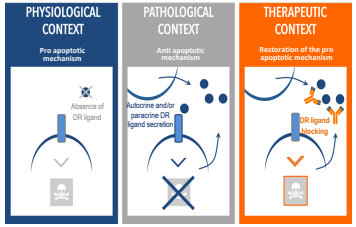
BACKGROUND

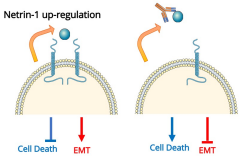
Dependence receptors (DRs) and their respective ligands play a key role in the control of cancer development and DRs are recognized as tumor suppressors. In order to escape from cell death, aggressive cancer cells are selecting mechanisms to silence the death pathway normally induced by DRs. The therapeutic strategy is thus to generate candidate drugs blocking the interaction between the ligand and its DR, to treat patient suffering from cancer displaying production of the ligand to restore cancer cell death and consequently induce tumor regression.

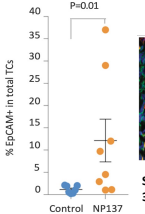


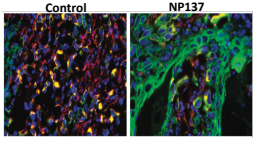
NP137 (Netris Pharma) is a humanized IgG1 targeting a conserved epitope located in the 2nd EGFR-like domain of netrin-1, blocking interaction with :UNC5 In preclinical studies, targeting netrin-1 with the humanized anti-netrin-1 antibody NP137 inhibits tumor growth, metastasis in cervical cancer mouse model. In preclinical studies, targeting netrin-1 with the humanized anti-netrin-1 antibody NP137 inhibits tumor growth and metastasis.
In First in Man clinical trial (NCT02977195), NP137 single agent (IV, Q3W from 1 to 20mg/kg) was well-tolerated and preliminary evidence of clinical activity was observed in gynecological cancer patients (P. Cassier ESMO 2019). Main related AE were infusion-related reactions (IRR), mainly of moderate intensity and manageable by premedication. No Dose Limiting Toxicity were reported, but the Recommended Phase II Dose was fixed at 14 mg/kg due to a Grade 3 IRR in a patient treated at 20mg/kg.

RATIONALE

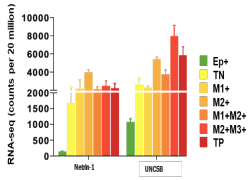
EMT is a key process in cancer cell progression and a key mechanism of drug resistance. Netrin-1 & UNC5B are key genes up-regulated during tumoral early phase of EMT to protect EMT engaged cells from cell death.
In preclinical models, NP137 treatment induced a shift of the engrafted tumors toward a more epithelial phenotype. RNA sequencing performed on tumors from mice treated with NP137 revealed an increased expression of epithelial genes. This effect could be envisioned as a driver of the increase response to immune-checkpoint inhibitors.





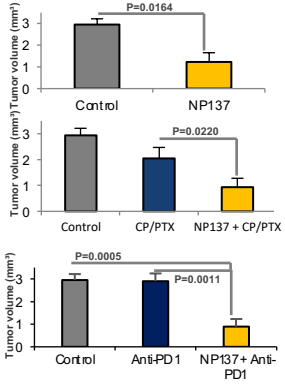


SC graft EpCAM- + NP137 or Control (NP001) 3x/week, 21d



Latil et al., 2017, Cell Stem Cell; Pastushenko et al., 2018, Nature; Pastushenko and Blanpain, 2018, Trends Cell Biol.

PRECLINICAL PROOF OF CONCEPT



Significant tumor growth inhibition in K14-HPV16/E2 cervical cancer mouse model.

Respectively 10 (NP137) and 12 (Control) tumor-bearing HPV16/E2 mice were treated for 1 month 3 times a week. NP137 inhibited by 58% tumor volume compared to control treated mice (Mann Whitney test).

NP137 increases sensitivity to chemotherapy in K14-HPV16/E2 cervical cancer mouse model.

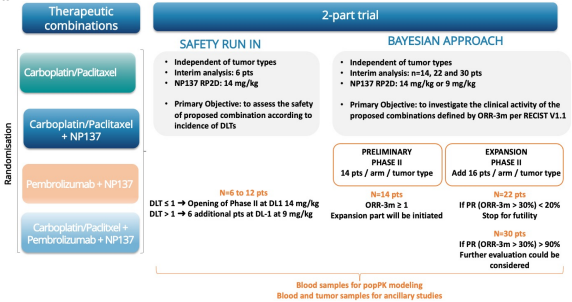
Respectively 10 (CP/PTX) , 9 (NP137+CP/PTX) and 12 (Control) tumor-bearing HPV16/E2 mice were treated for 1 month 3 times a week. NP137 associated to CP/PTX inhibited by 54% tumor volume compared to CP/PTX treated mice and by 68% compared to control treated mice (Mann Whitney test)

NP137 increases sensitivity to ICPI (anti-PD-1) In K14-HPV16/E2 cervical cancer mouse model.

Respectively 8 (Anti-PD-1) , 8 (NP137+Anti-PD-1) and 12 (Control) tumor-bearing HPV16/E2 mice were treated for 1 month 3 times a week. NP137 associated to Anti-PD-1 inhibited by 69% tumor volume compared to Anti-PD-1 treated mice and by 70% compared to control treated mice (Mann Whitney test)

DESIGN

GYNET (**NCT04652076**) is a multicentrer, Phase I/II clinical trial aiming to investigate the safety and the clinical activity of NP137 when combined with pembrolizumab and/or chemotherapies in patients with advanced/metastatic gynecological cancers: endometrial carcinoma and cervix carcinoma.
First, a safety run is planned on first 6 to 12 pts in each arm to assess the safety of the therapeutic combinations. Second, an adaptive Bayesian approach will allow to quickly stop treatment cohorts without evidence of efficacy and/or select promising treatment cohorts according to Objective Free Rate at 3months (ORR-3M) assessed per RECIST 1.1 with an independent central review.
A maximum of **30 patients will be enrolled in each arm** for both tumor type for a total sample size of **240 patients.**



OBJECTIVES

- **Primary objective**
  - Safety Run in part: To assess the safety of the proposed therapeutic combinations according to the incidence of DLT.
  - Phase II part: To investigate the clinical activity of the proposed therapeutic combinations as defined by the 3-month objective response rate (ORR-3m) as per RECIST V1.1 assessment by Blinded independent central review (BICR).
- **Secondary objectives**
  - To further document the safety profile of the proposed therapeutic combinations.
  - To assess the PK parameters of NP137.
  - To further assess the anti-tumor activity of the proposed combination (in terms of Best overall response, Duration of response, Clinical Benefit rate at 3 months [CBR-3m], PFS and OS.
  - Overall Tumor response will be assessed using RECIST V1.1 and iRECIST assessment by both BICR and investigator.

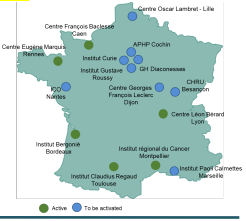
POPULATION

- Patient with histologically confirmed locally advanced / metastatic endometrial carcinoma (Endometrial sarcoma are excluded) or patient with histologically confirmed locally advanced / metastatic cervix adeno- or epidermoid- carcinoma
- Previously treated by at least one line of platinum based chemotherapy, but no more than 3 lines. If the last chemotherapy was given as neoadjuvant or adjuvant chemotherapy for a local disease (stage I or II), inclusion must be performed no more than one year after the end of the chemotherapy. In all cases, a minimal wash-out period of 6 months after completion of last chemotherapy with [platinum + paclitaxel] is required prior to entering the study.
- Documented disease progression as per RECIST V1.1 after prior systemic chemotherapy regimen and presence of at least one lesion evaluable for response according to RECIST 1.1.
- Patients with progression during chemotherapy with platinum and paclitaxel first-line treatment are not eligible.

CURRENT STATUS (end of july 2021)

As of today, Safety run part is ongoing: 13 patients have been enrolled and treated (DL1: 14 mg/kg).
No DLT and no major safety issue were reported to date.
6 sites are currently under recruiting and 6 additional sites will be activated at Q3/Q4 2021.

GYNET investigational sites are detailed on https://rhu-depgyn.com



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DISCLOSURE STATEMENT

First author, Pr. Isabelle Ray Coquard declares that she has no conflict of interest.