First in human dose-escalation trial with the c-MET targeting antibody-drug conjugate BYON3521

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BACKGROUND

BYON3521 is a proprietary novel c-MET targeting antibody-drug conjugate (ADC) with a cleavable linker-duocarmycin (vc-*seco*-DUBA) payload that causes irreversible alkylation of DNA in tumor cells. BYON3521 has demonstrated potent and selective killing of c-MET expressing tumor cells in preclinical models, even at low c-MET expression levels. In addition, *in vitro* studies showed that the active toxin can passively permeate the cell membrane and kill neighboring, c-MET negative cells as a bystander effect.

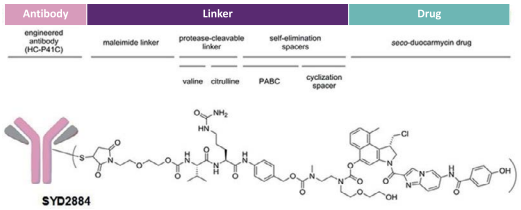

FIGURE 1 Schematic drawing of BYON3521

c-MET is expressed in several human organs and tissues, predominantly in epithelial cells. c-MET binds hepatocyte growth factor (HGF), which is the only known ligand for c-MET. The c-MET/HGF signaling pathway is essential in the processes of embryogenesis, wound healing and organ regeneration. c-MET/HGF dysregulation is associated with aggressive phenotypes and poor prognosis in various cancers.

FIGURE 2 BYON3521 efficiently binds and internalizes on c-MET expressing tumor cells and shows bystander killing *in vitro*.

IN VIVO STUDIES

Mouse clinical trial in PDX models

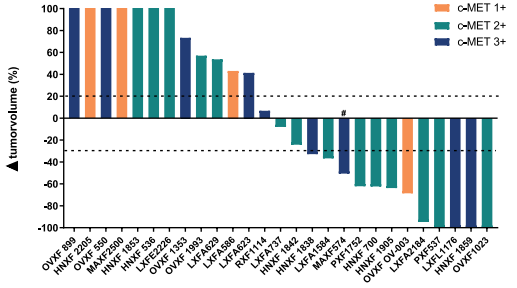

FIGURE 3 BYON3521 efficacy in non-*MET*-amplified patient-derived xenograft models (PDX) with low, moderate and high c-MET expression. Mice were treated with a single dose of 10 mg/kg. Partial and complete tumor remission was observed in several models, including models with moderate and low c-MET expression.

In vivo PKPD studies in mouse PDX models

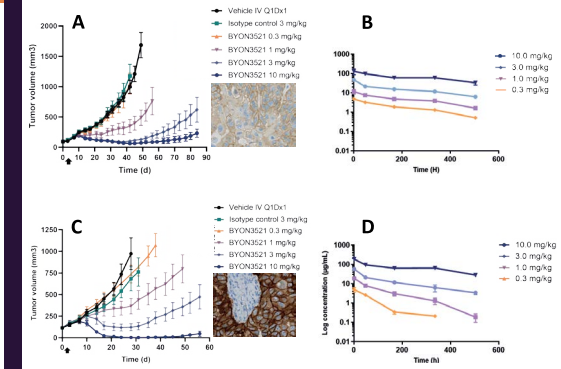

FIGURE 4 Efficacy of BYON3521 (A, C) and levels of conjugated BYON3521 (BYON3521 with at least 1 linker-drug), as measured with the anti-idiotype assay (Mesoscale) (B, D), in the non-*MET* amplified head & neck cancer PDX model HNXF1905 (A, B), and lung cancer PDX model LXFL1176 (C, D). Due to the very high c-MET expression levels in the LXFL1176, Target-Mediated Drug Disposition (TMDD) was observed at the lower doses. The arrow indicates the moment of randomization and dosing of the mice.

TRIAL DESIGN (NCT05323045)

Main inclusion criteria for dose-escalation part of this trial:

- Patients with previously treated progressive locally advanced or metastatic solid tumors;
- c-MET positive membrane staining and/or *MET*-amplified and/or known activating *MET*-mutation (excluding exon14m);
- ECOG performance status 0-1;
- Adequate organ function.

A central laboratory will assess:

- Expression of c-MET by using immunohistochemistry (IHC);
- Amplification of *MET* by using dual *In Situ* Hybridization (dISH).

BYON3521 is administered intravenously every three weeks until tumor progression or unacceptable toxicity. The Continual Reassessment Method of Neuenschwander (N-CRM model) is used to evaluate the safety of BYON3521 and to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE).

Primary objectives:

- Part 1 (dose-escalation): To evaluate the safety of BYON3521 and to determine the MTD and RDE;
- Part 2 (expansion): To evaluate the objective tumor response rate (ORR).

Part 1: Dose escalation	Part 2: Planned expansion cohorts*
Solid tumors of any origin	1. Non-squamous EGFRwt NSCLC 2. Gynecological cancers: • Ovarian cancer • Endometrial cancer • Cervical cancer 3. Pancreatic cancer 4. Uveal melanoma
c-MET positive membrane staining by IHC and/or *MET* amplification by dISH and/or known *MET*-mutation	c-MET positive membrane staining by IHC

* N=10-30 patients per cohort

STATUS

To date, four dose levels of BYON3521 were investigated. Patient enrollment is ongoing in Part 1 (dose escalation). There is no efficacy data available yet.

Patient characteristics*		Part 1 (N=10)
Male : Female		9 : 1
Median Age (range)		59 (43-69)
Primary tumor types	Colorectal Cancer	3
	Esophageal Cancer	1
	Gastric Cancer	1
	Non-Small Cell Lung Cancer	1
	Pancreatic Cancer	1
	Renal Cell Cancer	1
	Other	2
Prior regimens	1-3	6
	≥ 4	4
c-MET expression	0	1
	1+	0
	2+	8
	3+	0
	Not known	1
MET amplification	Positive	6
	Negative	3
	Not known	1
Known *MET* mutation	Yes	1
	No	9
BYON3521 dose (mg/kg)	0.8	1
	1.6	3
	3.2	3
	4.8	3

* cut-off 01MAR2023

SAFETY

Within the evaluated dose levels, **BYON3521 is well-tolerated with no Dose Limiting Toxicities (DLTs)**. The majority of drug-related AEs was mild or moderate in severity. Minimal hematological, liver or cardiac toxicity was observed. The table shows drug-related adverse events occurring in ≥2 patients (N=10).

Related treatment emergent AEs# (MedDRA Preferred Term)	Grade 1-2	Grade 3*	Total (N=10)
Nausea	2	1	3
Vomiting	2	1	3
Abdominal pain	2	-	2
Diarrhoea	2	-	2
Weight decreased	3	-	3
Decreased appetite	3	-	3
Back pain	2	-	2
Fatigue	2	-	2
Chills	1	1	2
Alanine aminotransferase increased	2	-	2
Blood alkaline phosphatase increased	1	1	2
Gamma-glutamyltransferase increased	1	1	2

The most severe event is counted if the patient reported multiple events.
* No Grade 4 or Grade 5 events were observed.

C-MET TUMOR ASSESSMENT

Prevalence of C-MET expression and/or *MET* amplification per tumor type as assessed by the central laboratory during prescreening (N=189).

Primary tumor types	C-MET expression	*MET* amplification	C-MET expr & *MET* ampl.	Total (N=189)
Lung cancer	4	1	3	8
Gynecological cancers	2	4	0	6
Pancreatic cancer	4	5	5	14
Uveal Melanoma	3	0	0	3
Colorectal cancer	14	7	8	29
Renal Cell Cancer	3	0	0	3
Other cancers	12	11	5	28
Total	**42**	**28**	**21**	**91**

PHARMACOKINETICS

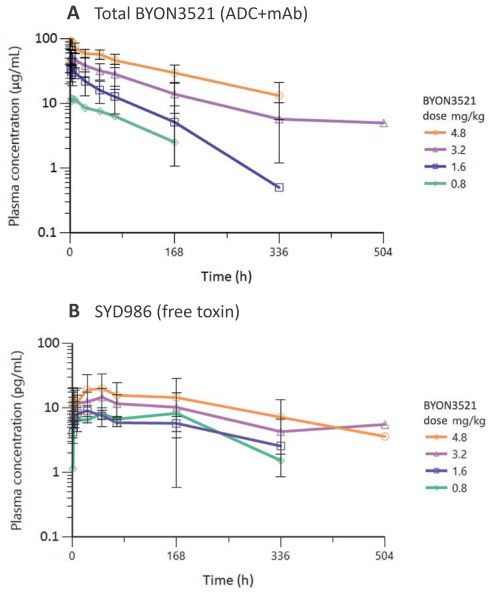

FIGURE 5 Pharmacokinetics of BYON3521. Mean plasma concentrations of total BYON3521 (A) and SYD986 (free toxin) (B) as measured with BYON3521-specific anti-idiotype assays. The 4.8 mg/kg dose is in the range of the predicted minimal efficacious dose in human (based on cynomolgus monkey study).

CONCLUSION

To date, the c-MET-directed ADC BYON3521 is well-tolerated with no DLTs at the investigated dose levels. Patient enrollment is ongoing.

Online poster:

byondis