A first-in-human dose-escalation and expansion study with the antibody-drug conjugate BYON3521 to evaluate the safety, pharmacokinetics and efficacy in patients with c-MET expressing locally advanced or metastatic solid tumours.

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The primary objective of this trial is:• Part 1 (dose-escalation): To evaluate the safety of BYON3521 and to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE); • Part 2 (expansion): To evaluate the objective tumour…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON56017

Source
ToetsingOnline

Brief title
Phase1 study in patients with advanced or metastatic solid tumours

Condition

- Metastases

Synonym
cancer, carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Fortrea Belgium SRL
Source(s) of monetary or material Support: Byondis BV

Intervention

Keyword: dose escalation, dose expansion, first-in-man, solid tumours

Outcome measures

Primary outcome

The primary endpoint for Part 1 of the trial is:

• Incidence of DLTs.

The primary endpoint for Part 2 of the trial is:

• ORR (Cohort A-D).

ORR is defined as the percentage of patients with a best overall tumour

response of complete response (CR) or partial response (PR) according to RECIST

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Secondary outcome

12.2.2. Secondary endpoints

12.2.2.1. Safety endpoints

The endpoints related to safety include:

• Incidence and severity of (serious) AEs;

• Changes in vital signs and weight;

• Changes in ECOG performance status;

• Changes in laboratory parameters;

• Percentage of patients with confirmed anti-BYON3521 antibodies;

• Number of patients with dose modifications due to AEs.

12.2.2.2. Efficacy endpoints

Preliminary efficacy will be assessed by:

• ORR (Part 1);

• Clinical benefit rate (CBR);

• Best overall response (BOR);

• Best percent change in target lesion measurements;

• Time to response;

• Duration of response (DOR);

• Progression-free survival (PFS);

• Overall survival (OS) (Part 2).

CBR is defined as the percentage of patients with CR, PR, SD or non-CR/non-PD (SD or non-CR/non-PD for 6 or more months). BOR is defined as the number of patients with CR, PR, stable disease (SD) and progressive disease (PD), patients must have a valid tumour assessment of SD at least 35 days after their first dose of study treatment for this to be considered as their best response; Time to response is defined as the time from first day of IMP treatment to first observation of CR or PR. DOR is defined as the duration from first

observation of response (CR or PR) to the time of disease progression or death from any cause. PFS is defined as the time from first day of IMP treatment to disease progression or death from any cause. OS is defined as the time from first day of IMP treatment to death from any cause.

12.2.2.3. Pharmacokinetic endpoints

PK endpoints will include standard parameters such as Cmax, tmax, area under the curve (AUC), Cmin (trough-levels), terminal half-life (t*), volume of distribution, and drug clearance.

12.2.2.4. Other endpoints

Genetic tumour analysis and SLFN11 analysis will be summarized and correlated, if feasible, with response data.

Study description

Background summary

BYON3521 has not yet been tested in humans.
BYON3521 is a so called antibody-drug conjugate and consists of two parts. The antibody part binds to a protein that is overexpressed on different types of cancer cells (c-MET protein). When BYON3521 binds to this cancer cell, it will be taken up by the cancer cell. The second part of the drug, a toxin, will be cleaved in the cell by an enzyme and subsequently kills the cancer cell. You can see it as a sort of chemotherapy that is brought into the cancer cell. There may also be some cleavage of the drug outside the cancer cell but in the tumour mass, so that cancer cells that do not have the c-MET protein may also be killed.

Study objective

The primary objective of this trial is:

• Part 1 (dose-escalation): To evaluate the safety of BYON3521 and to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE);
• Part 2 (expansion): To evaluate the objective tumour response rate (ORR).

The secondary objectives of this trial are:
• Safety (Part 2);
• Pharmacokinetic (PK) parameters;
• Immunogenicity;
• Preliminary efficacy.

Study design

This is the first-in-human trial with BYON3521, an antibody-drug conjugate (ADC) comprising a humanized IgG1 monoclonal antibody directed against the c-MET receptor covalently conjugated to a duocarmycin-containing linker-drug.

This trial includes a dose-escalation part (Part 1) in which the MTD and RDE will be determined, and an expansion part (Part 2) to evaluate efficacy and safety in specific patient cohorts. Eligible patients will receive BYON3521 infusions once every three weeks until disease progression or unacceptable toxicity. In Part 1 of the trial all tumour types with highc-MET expression or MET-amplification or already known MET-mutation (excluding exon14 mutation - exon14m) may be included. In Part 2 of the trial patients with specific solid tumours with high c-MET expression will be included. For the following tumour types literature and micro-array data indicate that the c-MET pathway is more often activated (Table 1).

Table 1: Selected solid tumour types with possible c-MET pathway activation (based on literature).
Papillary renal cell cancer (PRCC) Clear cell ovarian and endometrial cancer
Uveal melanoma (UM)
Clear cell renal cell cancer (CCRCC) Cervix cancer Salivary gland cancer
Gastric cancer Germ-cell cancer Glioblastoma multiforme
Head and neck squamous cell carcinoma (HNSCC) Urothelial cell cancer
Soft-tissue sarcoma
Papillary thyroid cancer Prostate cancer
Non small cell lung cancer Colorectal cancer

• Dose-escalation (Part 1)
The starting dose will be 0.8 mg/kg BYON3521. In the first cohort one patient will be enrolled. If a drug-related adverse event Grade >= 2 is observed 2 more patients will be enrolled (excluding infusion-related reaction controlled with appropriate supportive measures such as medication and/or reduced infusion rate and/or infusion interruption). Subsequent cohorts will enroll at least 3 patients. There should be at least 1 week between dosing of the 1st patient and dosing of the next patient(s) at each dose level. To estimate the MTD, an adaptive approach using the Continual Reassessment Method of Neuenschwander et

al (N-CRM model) will be used with a dose-limiting toxicity (DLT) period of 1 treatment cycle (21 days). The MTD and/or RDE will be defined by the safety committee, based on all available safety, PK, and preliminary efficacy data.

• Expansion (Part 2)
This part of the trial will consist of 4 cohorts in which patients will receive BYON3521 at the RDE. Patients with specific c-MET expressing solid tumours (IHC score >= 2+) will be enrolled:

A. Non-squamous non small lung cancer (nonsquamous NSCLC);;
B. Specific gynaecological cancers: ovarian cancer, endometrial cancer, cervical cancer;
C. Pancreatic adenocarcinoma (PA); Uveal melanoma (UM);

In total up to 120 eligible and evaluable patients will be enrolled. Futility will be monitored separately for each cohort using a Bayesian model that predicts the probability of success after 30 patients. Futility monitoring will begin after 12 patients have evaluable endpoint data in any of the cohorts. If the predictive probability is below 5%, the sponsor may choose to terminate a cohort.

Intervention

Dose escalation schedule
To determine the MTD of BYON3521, an adaptive approach using a Continual Reassessment Method (N-CRM) model will be used. The standard dose selection in a N-CRM model is based on point estimates for the probability of a DLT at each dose.

Doses will be investigated from 0.8 mg/kg up to 10.0 mg/kg. One patient will be enrolled in the first cohort unless a drug-related adverse event Grade >= 2 is observed, in which case 2 more patients will be enrolled (excluding infusion-related reaction controlled with appropriate supportive measures, such as medication and/or reduced infusion rate and/or infusion interruption). Subsequent cohorts will enroll at least 3 patients. If deemed necessary, additional patients may be included per cohort to make informed dosing decisions. Dose-escalation or de-escalation decisions will be determined following review of all available safety, PK, and efficacy data, and the dosing recommendations will be primarily guided by the N-CRM. The key decisions of dose-escalation or de-escalation and identification of the MTD will be made by the safety committee and will occur during the dose-escalation teleconferences, which will be held once all patients in a given dose cohort have completed DLT evaluation. The maximum escalation limit will depend on the dose level:
• Dose strengths up to 3.2 mg/kg: 100%;
• Dose strengths above 3.2 up to 4.8 mg/kg: 50%;

• Dose strengths above 4.8 mg/kg: 33%.

Study burden and risks

Taking part in the study can have these cons:
- possible side effects or adverse effects of BYON3521.
- possible discomfort from the measurements during the study (eg: blood samples)
- taking part in the study will cost extra time.
- compliance with the study agreements

If the study drug is effective, patient may benefit by improvement of their health condition. It is possible that patients do not personally benefit from t their participation in this study. Patient's condition may remain the same or worsen due to ineffective treatment or underlying disease, and may even lead to death. However, by taking part, patient will provide new information that will help to learn more about BYON3521 as a treatment for cancer. This information could help future cancer patients.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

D4a Inclusion criteria
In English
1. Male or female, age >=18 years at the time of signing first informed consent;
2. Patient with histologically-confirmed, locally advanced or metastatic cancer who has progressed on standard therapy or for whom no standard therapy exists:
* Part 1 (dose-escalation): solid tumours of any origin;
* Part 2 (expansion):
• Cohort A: Non-squmous non small cell lung cancer (non-squamous NSCLC) (see exclusion 1.f);;
• Cohort B: Specific gynaecological cancers: ovarian cancer, endometrial cancer, cervical cancer;
• Cohort C: HNSCCPancreatic adenocarcinoma (PA););
• Cohort D: Uveal melanoma (UM).;

3. Part 1: Tumour c-MET positive membrane staining by immunohistochemistry (IHC)a and/or MET amplification by dual In Situ Hybridization (dISH)a and/or known MET-mutation (excluding exon14m)b on most recent available/obtained tumour material from a site not previously irradiated;
a as determined by the central laboratory, b in agreement with sponsor
art 2: Tumour c-MET membrane expression by immunohistochemistry (IHCor tumour c-MET positive membrane staining by immunohistochemistry (IHC) and MET-mutation (excluding exon14m) score >= 2+) as determined by the central laboratory on most recent available/obtained tumour material from a site not previously irradiated;
4. Presence of a tumour lesion accessible for biopsy and patient should be willing to undergo a fresh tumour biopsy, unless adequate biopsy material is available obtained not more than 6 months prior to signing main informed consent;
5. Eastern Cooperative Oncology Group (ECOG) performance status <= 1;
6. Adequate organ function, evidenced by the following laboratory results:
- Absolute neutrophil count >= 1.5 x 109/L;
- Platelet count >= 100 x 109/L;
- Hemoglobin >= 9.0 g/dL or 5.6 mmol/L;
- Total bilirubin <= 1.5 x the upper limit of normal (ULN);

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 3.0 x ULN (or <= 5.0 x ULN in the presence of liver metastases);
- Serum creatinine <= 1.5 x ULN;
- Estimated Glomerular Filtration Rate (eGFR)* >= 60 ml/min/1.73 m2;
*preferably calculated with CKD-EPI formula
7. Highly effective contraception must be used during the trial and up to at least 8 months after last IMP treatment for women of childbearing potential and up to at least 6 months after last IMP treatment for male patients with a female partner of childbearing potential. This is not required in case the patient or sole partner is surgically sterilized or in case the patient truly abstains from sexual activity;

Additional inclusion criteria for Part 2 only
8. At least one measurable cancer lesion as defined by the Response Evaluation Criteria for Solid Tumours (RECIST version 1.1);

D4a Main inclusion crititeria
In Dutch
1Man of vrouw, leeftijd >= 18 jaar op het moment van ondertekening van de eerste geïnformeerde toestemming;
2Patiënt met histologisch bevestigde, lokaal gevorderde of gemetastaseerde kanker die progressie heeft vertoond met standaardbehandeling of voor wie geen standaardbehandeling bestaat:
*Deel 1 (dosisescalatie): solide tumoren van elke oorsprong;
*Deel 2 (uitbreiding): • Cohort A: Niet-squameuze, niet-kleincellige longkanker (niet-squameus NSCLC) (zie uitsluiting 1.f);
• Cohort B: Specifieke vormen van gynaecologische kanker: eierstokkanker, baarmoederkanker, baarmoederhalskanker;
• Cohort C: Pancreasadenocarcinoom (PA);
• •Cohort D: Uveaal melanoom (UM);
3Deel 1: Tumor c-MET-positieve membraankleuring door immunohistochemie (IHC)a en/of MET-amplificatie door dubbele In Situ Hybridisatie (dISH)a en/of bekende MET-mutatie (exclusief exon14m)b op het meest recent beschikbare/verkregen tumormateriaal van een plaats die niet eerder bestraald is;
a zoals bepaald door het centraal laboratorium, b in overeenstemming met de sponsor
eel 2: Tumor c-MET-membraanexpressie door immunohistochemie (IHC(IHC-score >= 2+) zoals bepaald door het centraal laboratorium op het meest recent beschikbare/verkregen tumormateriaal van een plaats die niet eerder bestraald is;

4Aanwezigheid van een tumorlaesie die toegankelijk is voor biopsie en bereidheid van de patiënt om een nieuwe tumorbiopsie te ondergaan, tenzij er voldoende biopsiemateriaal beschikbaar is dat niet meer dan 6 maanden voorafgaand aan ondertekening van het hoofdtoestemmingsformulier verkregen is;

5Eastern Cooperative Oncology Group (ECOG) performancestatus van <= 1;
- 6 Voldoende orgaanfunctie, zoals aangetoond door de volgende laboratoriumuitslagen:
Absolute neutrofielentelling >= 1,5 x 109/l;
- Plaatjestelling >= 100 x 109/l;
- Hemoglobine >= 9,0 g/dl of 5,6 mmol/l;
- Totale bilirubine <= 1,5x de bovengrens van het normale bereik (ULN);
- Alanine-aminotransferase (ALT) en aspartaat-aminotransferase (AST) <= 3,0 x bovengrens van normaal (of <= 5,0 X ULN in aanwezigheid van uitzaaiingen in de lever);
- Serumcreatinine <= 1,5 x ULN;
- Geschatte glomerulaire filtratiesnelheid (eGFR)* >= 60 mL/min/1,73 m2;
*bij voorkeur berekend met de CKD-EPI-formule
7. Zeer effectieve anticonceptie moet worden gebruikt tijdens het onderzoek en tot ten minste 8 maanden na de laatste IMP-behandeling voor vrouwen die zwanger kunnen worden en tot ten minste 6 maanden na de laatste IMP-behandeling voor mannelijke patiënten met een vrouwelijke partner die zwanger kan worden. Dit is niet vereist in het geval dat de patiënt of de enige partner chirurgisch is gesteriliseerd of in het geval dat de patiënt zich waarlijk onthoudt van seksuele activiteit;
Aanvullend inclusiecriterium alleen voor deel 2
8. Ten minste één meetbare kankerlaesie zoals gedefinieerd door de Response Evaluation Criteria for Solid Tumors (RECIST versie 1.1);

Exclusion criteria

D5. Exclusion criteria
In English
1. Having been treated with:
a. DUBA-containing antibody-drug conjugates (ADCs) at any time;
b. c-MET targeting cytotoxic agents at any time, including ADC with cytotoxic payload;
c. Other anticancer therapy including chemotherapy, immunotherapy, c-MET targeting agent or investigational agent within 4 weeks prior to start IMP treatment or within 5 times the elimination half-life of the therapy, whatever is shorter;
d. Radiotherapy within 4 weeks prior to start IMP treatment, or within 1 week for palliative care (as long as the lungs were not exposed);
e. Hormone therapy (except for gonadotropin-releasing hormone (GnRH) agonists for prostate cancer or premenopausal breast cancer) within 1 week prior to start IMP treatment;
f. Cohort A (non-squamous NSCLC) only: EGFR inhibitors or eligible for EGFR inhibitors at any time;
The patient must have sufficiently recovered from any treatment-related toxicities to CTCAE Grade <=1 or baseline, except for toxicities not considered

a safety risk for the patient at the investigator*s discretion; (e.g. alopecia or skin hyperpigmentation);
2. History of hypersensitivity or allergic reaction to any of the excipients of the IMP treatment which led to permanent discontinuation of the treatment;
3. Known presence of a tumour harboring MET exon14 mutation; (Part 1 only);
4. History or presence of keratitis;
5. History or presence of glomerulonephritis, acute tubular necrosis and/or interstitial nephritis, or clinically significant findings as determined by urinalysis at screening (see Section 9.12, Figure 1);
6. History or presence of idiopathic pulmonary fibrosis, organizing pneumonia (e.g. bronchiolitis obliterans), drug-induced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan;
7. History (within 6 months prior to start IMP) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure, myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication;
8. Severe, uncontrolled systemic disease (e.g. clinically significant renal, cardiovascular, pulmonary, metabolic disease, skin disease, or autoimmune disease including
Sjogren*s syndrom)) at screening;
9. Symptomatic brain metastases, brain metastases requiring steroids to manage symptoms, or treatment for brain metastases within 8 weeks prior to start IMP treatment;
10. Known active Hepatitis B, C or E infection at screening; (prior infections are not
excluded);
11. Major surgery within 4 weeks prior to start IMP treatment;
12. Pregnancy or lactation;
13. Other condition that in the investigator*s opinion is likely to jeopardize patient safety or interfere with the patient*s ability to comply with study requirements.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-07-2022
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BYON3521
Generic name:	BYON3521

Ethics review

Approved WMO Date:	27-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-04-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	12-08-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-003846-19-NL
CCMO	NL79308.091.21