# PIWIL1 ISH ASSAY CLINICAL PERFORMANCE STUDY IN FFPE SPECIMENS FROM SUBJECTS WITH ADVANCED TUMORS FOR ENROLMENT WITHIN THE CLINICAL TRIAL IMC-R117C-1004

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To evaluate the clinical utility of the PIWIL1 ISH assay for predicting response of patients with Advanced PIWIL1-Positive Cancers within the Immunocore clinical study. To determine the role of PIWIL1 expression as a potential predictor of efficacy...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON57615

**Source**
ToetsingOnline

**Brief title**
N/A

### Condition

- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
Cancer, late-stage cancer

**Health condition**

Advanced colorectal, esophageal, gastric, and ovarian cancers

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Immunocore Limited
**Source(s) of monetary or material Support:** Industry

## Intervention

**Keyword:** ADVANCED TUMORS, IMC-R117C-1004, PIWIL1 ISH ASSAY

## Outcome measures

### Primary outcome

Primary: Clinical Utility Of PIWIL1 ISH Assay

Objective: To evaluate the clinical utility of the PIWIL1 ISH assay for

predicting response of patients with Advanced PIWIL1-Positive Cancers within

the Immunocore clinical study

Endpoint: Identify the clinical utility based on the ORR for evaluable samples

tested using the PIWIL1 ISH assay

### Secondary outcome

N/A

# Study description

### Background summary

STUDY PURPOSE
The purpose of this study is to prospectively screen FFPE human tissue tumor

cell samples from study subjects with advanced colorectal, esophageal, gastric, and ovarian cancers with the PIWIL1 ISH assay to establish patient eligibility for the Immunocore clinical trial, *A Phase 1/2 First-in-Human Study of the Safety and Efficacy of IMC-R117C (PIWIL1 × CD3 ImmTAC® Bispecific Protein) as a Single Agent and in Combination in HLA-A*02:01-Positive Participants with Selected Advanced PIWIL1-Positive Cancers*. For the evaluation of patient specimens for the Immunocore Limited clinical study LoQ/cut-off was set at 10% positivity by the Sponsor based on in-house data on PIWIL1 ISH expression and peptide levels. It was determined that 10% is the lowest amount concentration where the level of target peptide fragment of PIWIL1 presented by HLA-A*02:01 can be identified. A result of >=% 10 is considered positive for PIWIL1 expression, and a result of <10% is considered negative.

The purpose of this study is to evaluate the clinical utility of the PIWIL1 ISH assay as a CDx, as well as screening for inclusion in the Immunocore clinical study.

ASSAY UNDER EVALUATION
NeoGenomics PIWIL1 ISH Clinical Trial Assay

INCLUSION CRITERIA FOR IMC-R117C-004
1. Participant must be >=18 years of age, inclusive, at the time of signing the ICF
2. ECOG status of 0 or 1 at start of treatment
3. HLA-A*02:01-positive (testing at central laboratory).
4. PIWIL1 expression in >=10% of tumor cells must be established in patient specimen.
5. Histologically confirmed advanced (i.e., either locally advanced or metastatic disease that is unresectable) colorectal, esophageal, gastric, or ovarian carcinoma.
6. Participants must meet tumor PIWIL1 testing requirements:
a. ALL COHORTS: An archival or newly collected tumor biopsy must be sent to the study central laboratory. An archival biopsy may be provided as an FFPE tissue block, or an FFPE pre-cut slide.
b. MONOTHERAPY COHORTS: a tumor biopsy sample must be sent to the study central laboratory and a positive result must be received prior to enrolling. If data indicate that clinical activity is restricted to participants with higher tumor PIWIL1 expression, subsequent enrollment may be restricted to participants whose tumors are confirmed as having higher PIWIL1 expression; details will be documented in the SPM.
c. COMBINATION COHORTS: An archival or newly collected tumor biopsy must be confirmed as adequate (as defined in the study Laboratory Manual) locally prior to completion of Screening and subsequently sent to the study central laboratory. If data indicate that clinical activity is restricted to participants with higher tumor PIWIL1 expression, subsequent enrollment may be restricted to participants whose tumors are confirmed as having higher PIWIL1 expression; details will be documented in the SPM.

7. Participants must meet RECIST v1.1 criteria for evaluable/measurable disease based on investigator assessment:
a. In dose-escalation, regimen optimization, and Phase 2, participants must have evaluable disease (at least 1 non-target or target lesion),
b. In expansion, all participants must have at least 1 target lesion.
c. Tumors in irradiated areas are acceptable only if there is subsequent documented radiographic progression
8. Participants must meet the histology, biomarker, and prior treatment requirements specified in Table 9 of the Immunocore study protocol for the applicable arm and study part. Required therapies must have been given for unresectable/metastatic disease or in the neoadjuvant or adjuvant setting with disease progression during or within 6 months of completing neoadjuvant or adjuvant therapy.
9. Male and female participants of childbearing potential who are sexually active with a non¬ sterilized partner must agree to use highly effective methods of birth control from the study screening date until 6 months after the final dose of the study treatment; cessation of birth control after this point shall be discussed with a responsible physician. Highly effective methods of contraception are described in Section 10.5 of the Immunocore study protocol.
a. Pregnant or lactating women are prohibited from enrolling in this study.
b. Male participants are not allowed to donate sperm from the time of enrollment until 6 months post-administration of study treatments.
10. Capable of giving signed informed consent as described in Section 10.1.3 of the Immunocore study protocol, which includes compliance with the requirements and restrictions listed in the Immunocore ICF and protocol.

EXCLUSION CRITERIA FOR IMC-R117C-004
1. Presence of untreated or symptomatic CNS metastases, leptomeningeal disease, or cord compression. NOTE: Participants with treated CNS lesions may enroll provided all the following apply:
a. Treated CNS lesions must be radiographically stable for >=2 weeks after intervention (surgery and/or radiation).
b. Participants must be neurologically stable off systemic corticosteroids for at least 2 weeks prior to enrollment.
2. Bowel obstruction within 3 months prior to the planned first dose of study treatment
3. Participants at high risk for vital organ perforation, fistula formation, or hemorrhage, defined as:
a. History of gastrointestinal perforation, abdominal fistula, intra-abdominal abscess, or active gastrointestinal bleeding within 6 months of the first dose of study treatment OR
b. Single tumor lesion with diameter > 100 mm, tumor adjacent to or directly involving the surface of a vital organ (e.g., serosal surface of the bowel, airway, or major vessel), AND treatment with an anti-angiogenic agent within 3 months of the first dose of study treatment
4. Ongoing ascites or effusion requiring recurrent drainage (i.e, at least twice within 28 days prior to the planned first dose of study treatment). NOTE:

Participants with an indwelling catheter in place for at least 14 days prior to the planned first dose of study treatment may be eligible following discussion with the study medical monitor.
a. For combination with bevacizumab, any ascites or effusion requiring drainage within 28 days prior to the first dose of study treatment is exclusionary
5. Participants with presence of NCI CTCAE >=Grade 2 toxicity due to prior cancer therapy, with the following exceptions:
a. Participants with Grade 2 alopecia, Grade 2 endocrine disorder (on stable replacement doses and asymptomatic), Grade 2 hypophosphatemia (on appropriate replacement therapy), Grade 2 ototoxicity, or Grade 2 peripheral neuropathy may enroll in any arm.
b. Participants with other stable Grade 2 toxicities due to prior anticancer therapy, that are anticipated to have minimal risk of worsening due to treatment with IMC-R117C and applicable combination partner(s), may enroll only with prior written approval from the study medical monitor.
6. Hypersensitivity to:
a. IMC-R117C or any associated excipients (all arms),
b. Bevacizumab, Chinese Hamster Ovary cell products, other recombinant human or humanized antibodies, 5-FU, capecitabine, or any associated excipients (Arm Band Arm D)
c. Cetuximab, encorafenib, or any associated excipients (Arm C)
7. Receipt of anticancer therapy for the disease under study within the following times prior to the first planned dose of study treatment (NOTE: washout periods do not apply to therapies that will be continued as combination partners. For maintenance arms, washout periods do not apply to therapies given for induction):
a. Cellular therapies (e.g., T-cell therapies): 90 days. NOTE: The investigator must discuss any prior cellular therapy treatment with the medical monitor, provide evidence (if possible) confirming that no residual biological/immunological activity remains, discuss any associated potential risks, and determine whether any additional monitoring is indicated. In additi

## Study objective

To evaluate the clinical utility of the PIWIL1 ISH assay for predicting response of patients with Advanced PIWIL1-Positive Cancers within the Immunocore clinical study. To determine the role of PIWIL1 expression as a potential predictor of efficacy based on the ORR for evaluable samples tested using the PIWIL1 ISH assay

## Study design

This is an interventional first-in-human study of the safety and efficacy of IMC-R117C as a single agent and in combination with other therapeutic agents in HLA-A*02:01-positive participants with advanced PIWIL1-positive cancers. This

study is designed to assess the safety, tolerability, PK, immunogenicity, pharmacodynamics, and antitumor activity of IMC-R117C as a monotherapy and in combination with other agents. This study is a minimally invasive surgical procedure, containing prospective collection of tumor biopsy samples to test for expression of PIWIL1.

## Intervention

N/A

## Study burden and risks

1. SUMMARY OF RISKS
1. POTENTIAL RISKS OF THE CLINICAL PERFORMANCE STUDY

NeoGenomics Laboratories has assessed the potential patient risks associated with the use of the PIWIL1 ISH assay for the detection of the PIWIL1 tumor cell expression in FFPE specimens from patients with a diagnosis of advanced colorectal, esophageal, gastric, and ovarian cancer as part of inclusion criteria within the Immunocore Limited clinical study. The PIWIL1 ISH assay does not provide a primary disease diagnosis, it provides the PIWIL1 expression status in patients previously diagnosed with advanced solid tumors.
Patients will be enrolled based on stringent inclusion/exclusion criteria and those who are evaluated for entry into the study will be informed of the risks of treatment with the investigational therapy that has not yet proven to provide therapeutic benefit. The collection of a FFPE specimens is part of routine clinical practice for evaluation of solid tumor malignancies and risks associated with a FFPE specimen biopsy are defined in the patient informed consent form. For this central laboratory testing of PIWIL1 expression status, there are no direct patient risks. Therefore, patients who sign the informed consent forms are considered by their physicians to be suitable for accepting these risks. The controls put in place to monitor and conduct the study will also help to ensure the safety, rights, and welfare of the subjects enrolled into the trial.
Given the nature of this device study and the mitigation of identified risks, the residual risk to patients whose sample specimen is tested is acceptable. A failure mode and effect analysis were conducted to ensure that risks relating to the design and use of the device use are as low as reasonably possible. A risk management report will summarize the outcome of the risk assessment including a risk-benefit assessment for patients participating in this device study.

NeoGenomics has assessed the risks associated with the use of the PIWIL1 ISH assay to be utilized within the Immunocore clinical study IMC-R117C-1004 as presented within this CPSP. NeoGenomics believes the potential benefits outweigh patient risks based on the following criteria:

• Risks associated with device design and use have been reduced to be as low as possible.

• The PIWIL1 ISH assay is not intended to provide a primary disease diagnosis, it is intended to be used to confirm PIWIL1 expression status in patient specimen with a confirmed diagnose of advanced solid tumors.
• The PIWIL1 ISH assay is being utilized as a CTA for the detection of the PIWIL1 expression in FFPE tumor specimens. All specimen testing will be performed solely at NeoGenomics Laboratories which are high-complexity CLIA and/or CAP accredited facilities.
• The PIWIL1 ISH assay is NOT a near patient device, therefore, there are no direct risks to patients or healthcare workers.
• The PIWIL1 ISH assay has been validated according to Clinical Laboratory Standards Institute (CLSI) standards, and the validation testing satisfied all the pre-defined acceptance criteria.
• The PIWIL1 ISH assay is NOT a packaged and distributed IVD kit, the assay is performed at high complexity clinical laboratories which have validated the assay for its intended purpose for the Immunocore clinical study.
• Each PIWIL1 ISH assay result is reviewed and signed by a NeoGenomics Laboratories board-certified pathologist.

2. RISK ASSOCIATED WITH BIOPSY PROCEDURES
For subjects who will be enrolled in the study, tumor material (FFPE block, slides, or wet tissue) is requested at screening for confirmatory and biomarker testing. Risk associated with a tumor biopsy are defined in the Immunocore protocol and ICF. Left-over specimen banks, genetic or tissue bank are not applicable for this study. Therefore, no biorepositories requirements for this study and all left-over specimens will be destroyed/ discarded at the end of the study.
3. INVESTIGATIONAL THERAPY RELATED RISK
Risk associated to IMC-R117C-1004 are defined in Immunocore clinical protocol and investigators brochure.
4. RISKS ASSOCIATED WITH THE PIWIL1 ISH ASSAY
A Failure Modes and Effect Analysis (FMEA) has been conducted to ensure that the risks associated with the PIWIL1 ISH assay related to the design and use of the device use are as low as reasonably possible. Details of that FMEA will be included in the final risk management report. Additionally, PIWIL1 ISH assay risks and anticipated adverse device effects only includes false positive and false negative test results provided to clinical study site.
5. POTENTIAL BENEFITS OF THE PIWIL1 ISH ASSAY
The objective of this study is to screen PIWIL1 expression by ISH in FFPE patient specimens with a confirmed diagnosis of advanced solid tumors to establish study eligibility for the Immunocore clinical study. Given the encouraging preliminary efficacy and the acceptable safety profile in IMC-R117C the benefit/risk of IMC-R117C in patients with PIWIL1+ solid tumor warrants continued investigation.

# Contacts

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**Scientific**
Immunocore Limited

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Participant must be >=18 years of age, inclusive, at the time of signing the ICF
2. ECOG status of 0 or 1 at start of treatment.
3. HLA-A*02:01-positive (testing at central laboratory).
4. PIWIL1 expression in >=10% of tumor cells must be established in patient specimen
5. Histologically confirmed advanced (i.e., either locally advanced or metastatic disease that is unresectable) colorectal, esophageal, gastric, or ovarian carcinoma.
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a. Pregnant or lactating women are prohibited from enrolling in this study.

b. Male participants are not allowed to donate sperm from the time of enrollment until 6 months post-administration of study treatments.
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## Exclusion criteria

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or cord compression. NOTE: Participants with treated CNS lesions may enroll provided all the following apply:

a. Treated CNS lesions must be radiographically stable for >=2 weeks after intervention (surgery and/or radiation).
b. Participants must be neurologically stable off systemic corticosteroids for at least 2 weeks prior to enrollment.
2. Bowel obstruction within 3 months prior to the planned first dose of study treatment
3. Participants at high risk for vital organ perforation, fistula formation, or hemorrhage, defined as:
a. History of gastrointestinal perforation, abdominal fistula, intra-abdominal abscess, or active gastrointestinal bleeding within 6 months of the first dose of study treatment OR
b. Single tumor lesion with diameter > 100 mm, tumor adjacent to or directly involving the surface of a vital organ (e.g., serosal surface of the bowel, airway, or major vessel), AND treatment with an anti-angiogenic agent within 3 months of the first dose of study treatment
4. Ongoing ascites or effusion requiring recurrent drainage (i.e, at least twice within 28 days prior to the planned first dose of study treatment). NOTE: Participants with an indwelling catheter in place for at least 14 days prior to the planned first dose of study treatment may be eligible following discussion with the study medical monitor.
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a. Participants with Grade 2 alopecia, Grade 2 endocrine disorder (on stable replacement doses and asymptomatic), Grade 2 hypophosphatemia (on appropriate replacement therapy), Grade 2 ototoxicity, or Grade 2 peripheral neuropathy may enroll in any arm.
b. Participants with other stable Grade 2 toxicities due to prior anticancer therapy, that are anticipated to have minimal risk of worsening due to treatment with IMC-R117C and applicable combination partner(s), may enroll only with prior written approval from the study medical monitor.
6. Hypersensitivity to:

a. IMC-R117C or any associated excipients (all arms),
b. Bevacizumab, Chinese Hamster Ovary cell products, other recombinant human or humanized antibodies, 5-FU, capecitabine, or any associated excipients (Arm Band Arm D)
c. Cetuximab, encorafenib, or any associated excipients (Arm C)
7. Receipt of anticancer therapy for the disease under study within the following times prior to the first planned dose of study treatment (NOTE: washout periods do not apply to therapies that will be continued as combination partners. For maintenance arms, washout periods do not apply to therapies given for induction):

a. Cellular therapies (e.g., T-cell therapies): 90 days. NOTE: The investigator must discuss any prior cellular therapy treatment with the medical monitor, provide evidence (if possible) confirming that no residual biological/immunological activity remains, discuss any associated potential risks, and determine whether any additional monitoring is indicated. In addition, the investigator and medical monitor must agree that the participant has recovered adequately from the prior cellular therapy and that no unacceptable potential risks are anticipated.
b. BRAF inhibitor: 28 days.
c. CTLA-4-targeted immunotherapies (e.g., ipilimumab): 28 days.
d. All other immunotherapies, including PD-(L)1-targeted immunotherapies (e.g., atezolizumab, pembrolizumab), and bispecific T-cell engager monoclonal antibody therapies: 21 days.
e. All other systemic therapies: 14 days.
f. Radiotherapy: 14 days (excepting palliative radiotherapy to a limited field, which may be administered within 14 days, e.g., for a focally painful tumor mass).
8. Participants must not have received prior treatment with an lmmTAC molecule, including tebentafusp, IMC-F106C, IMCnyeso, or IMC-C103C.
9. In all arms any other contraindication for the applicable combination partner based on local prescribing information.

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-11-2024 |
| Enrollment: | 40 |
| Type: | Anticipated |

### Medical products/devices used

| | |
|---|---|
| Generic name: | NeoGenomics PIWIL1 ISH Clinical Trial Assay |
| Registration: | No |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 02-06-2025 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |

## 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 |
|---|---|
| CCMO | NL88013.000.24 |