UNIKLINIK KÖLN

CIO Centrum für Integrierte Onkologie Aachen Bonn Köln Düsseldorf

Title of Study:

Gazyvaro Targeting Tumor Promoting, Regulatory B-cells in Solid Tumors

Short Title / Acronym: **GASOLINE**

Eudra-CT Number: 2019-000914-12

Protocol Code: UNI-KOELN-3719

Start of Study – Completion of Study

First patient enrolled on July 05, 2021 - last study visit of last patient September 24, 2021

Final Short Study Report

Sponsor of Clinical Trial:

University of Cologne (Universität zu Köln)

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Signatures

By their signatures the authors approve of the content of the present final report. The clinical trial described herein was conducted in compliance with the principles of the Helsinki Declaration, Good Clinical Practice (GCP), and pursuant to all applicable legislation.

Sponsor / Representative	Professor Dr. med. Thomas Zander	15.6.22 Cologne,
Principal Investigator	Professor Dr. med. Thomas Zander	15.6.22 Cologne,
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Name of Sponsor/Company	Universität zu Köln Albertus-Magnus-Platz, 50923 Köln Vertreten durch: Universitätsklinikum Köln (AöR) Kerpener Str. 62, 50937 Köln
Name of Finished Product	• Gazyvaro® • Tecentriq®
Name of Active Substance	• Obinutuzumab • Atezolizumab
Individual Study Table: Referring to Part of the Dossier (Volume, Page) *Anmerkung: Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich*	n/a
Title of Study *Anmerkung: Es muss klar hervorgehen, dass die letzte Protokollversion einschließlich aller Amendments gemeint ist, die Amendments sind anzugeben und zu identifizieren*	GASOLINE: Gazyvaro Targeting Tumor Promoting, Regulatory B-cells in Solid Tumors • Protocol Code: UNI-Koeln-3719 • EudraCT: 2019-000914-12 • Latest protocol version voted: V04_0 • Initial Ethics Committee Vote: 12.06.2020
Investigators	Prof. Dr. med. Thomas Zander
Study centre(s)	Zentrum für Integrierte Onkologie (CIO) Universitätsklinikum Köln (AöR) Joseph-Stelzmann Str. 9, 50931 Köln
Publication (reference)	n/a
Studied period (years): date of first enrolment, date of last completed *Anmerkung: Hier sollen auch Studienunterbrechungen und vorzeitige Studienbeendigungen/Studienabbrüche unter Angabe der Gründe aufgeführt werden*	• Official authority approval: 12/2020 • Inclusion first patient (FPFV): 07/2021 • Inclusion last patient: 07/2021 • Last patient last visit (LPLV): 09/2021 • Interruption of Study 12/21 to 01/22 because of substantial amendement of the trial protocol • Premature termination: 03/2022 (No further financial support from Roche) Closure of database: 14/JUNE/2022

<table>
<tr><td>Phase of development</td><td>Phase 1b trial</td></tr>
<tr><td>Objectives</td><td>• Clinical response (CR, PR or SD) until staging after 4 cycles and immunological response after cycle 2 or 6.
OR
• Immunological response after 2 cycles (monotherapy) and clinical response (CR, PR or SD) after cycle 6.</td></tr>
<tr><td>Methodology</td><td>• Prospective, single arm, open label, basket, monocentric

<u>Study design:</u>
<table>
<tr><td>Day -29 and -15</td><td>obinutuzumab 100mg IL in accessible lesions of melanoma or CTCL</td></tr>
<tr><td>Cycle 1, day 1</td><td>obinutuzumab 100mg IV</td></tr>
<tr><td>Cycle 1, day 2</td><td>obinutuzumab 900mg IV</td></tr>
<tr><td>Cycle 2, day 1</td><td>obinutuzumab 1000mg IV</td></tr>
<tr><td>Cycle 3-4, (interim staging after 2 cycles)</td><td>Non-responders: obinutuzumab 1000mg IV, atezolizumab 1200mg IV, day 1, repetition every 21 days, also if clinically apparent PD after 1st cycle
Responders: 2 more single-agent cycles obinutuzumab 1000mg IV (cycle 3/4)</td></tr>
<tr><td>From cycle 5 onward</td><td>atezolizumab 1200mg IV day 1, repetition every 21 days until PD or loss of clinical benefit</td></tr>
</table>
CTCL = cutaneous T-cell lymphoma IL = intralesional administration
IV = intravenous administration PD = progressive disease</td></tr>
<tr><td>Number of patients (planned and analysed)</td><td><u>Planned:</u>
• Stage I: 27 patients (approximately: 10 melanoma, 11 prostate, 6 CTCL)
• Stage II: 34 patients per selected indication (entities or biological subgroups), maximally 3x34 patients

Screened: 2 patients
Enrolled: 1 patient (1 screening failure)
<u>Analysed for efficacy:</u>
• none
<u>Analysed for safety and demography:</u>
• 1</td></tr>
</table>

Diagnosis and main criteria for inclusion	1. 18 years of age or older 2. Written, signed, and dated informed consent before conduct of any study-specific procedure 3. ECOG performance status of 0-2 4. Life expectancy of more than 6 months 5. Advanced disease: a. **Prostate Cancer:** Castration resistant metastatic disease,at least 2 prior lines of treatment have failed, known PSA serum level at baseline b. **Melanoma:** Unresectable stage III melanoma with N3 macroscopic lymph nodes or in-transit/satellite metastases or stage IV melanoma after standard therapy Known PD-L1, PD-1 and BRAF status at baseline level. c. **CTCL:** ≥ stage IIB, ≥ 2 previous lines of treatment (1 skindirected, 1 systemic); continuing skin directed therapy Measurable lesion according to RECIST 1.1/iRECIST and CTCL according to consensus criteria 6. Recent biopsy confirming the diagnosis (≤ 4 weeks old) 7. Adequate organ function a. WBC ≥ 2500/µL b. ANC ≥ 1000/µL c. Platelets ≥ 50 x 103/µL d. Hemoglobin ≥ 8 g/dL e. Estimated glomerular filtration rate > 30mL/min/1.73m2 calculated with CKD-EPI or FAS f. AST ≤ 2.5 x ULN for patients without liver metastasis, ≤ 5 x ULN for patients with liver metastasis g. Bilirubin ≤ 1.5 x ULN, (except patients with Gilbert's Syndrome), Total bilirubin less than 3.0 mg/dL) 8. Reproductive Status a. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception and must agree to use adequate method to avoid pregnancy for at least 5 months after the last dose of Atezolizumab and 18 months after the last dose of Obinutuzumab. b. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of ß-HCG) within one until two weeks prior to the

	start of obinutuzumab / atezolizumab at time of treatment. c. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving obinutuzumab / atezolizumab and who are sexually active with WOCBP must be willing to adhere to contraception for a period of 5 months post tezolizumab treatment and 18 months post obinutuzumab treatment completion. d. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply additionally: • Women < 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). • Women ≥ 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
Test product, dose and mode of administration, batch number	Investigational study drugs: • obinutuzumab • atezolizumab **Immunotherapy:** • obinutuzumab IV infusion, cycle (1; 2; 3; 4) repetition every 21 days (Table 2). • atezolizumab IV infusion, cycle 3 and 4 for non-responder, 5; 6; 7 and 8; repetition every 21 days

Duration of treatment	The one treated patient received 2 cycles of obinotuzumab in a dose of 1000mg each and after detection of progressive disease patient received one cycle of obinotuzumab 100mg and atezolizumab 1200mg as comination treatment. No further application of Obinotuzumab or atezolizumab was given because of progressive disease. Patient received study treatment over a period of nearly 2 months from 22th July to 07th September 2021
Reference therapy, dose and mode of administration, batch number	Not applicable. Open label trial not randomized to standard treatment was given.
Criteria for evaluation: Efficacy, Safety	Planned key efficacy endpoint (as per protocol): • Clinical response (CR, PR or SD) until staging after 4 cycles and immunological response after cycle 2 or 6. OR • Immunological response after 2 cycles (monotherapy) and clinical response (CR, PR or SD) after cycle 6. As only one patient was enrolled in the study and received the study treatment, a statistical analysis of efficacy endpoints is not possible. A listing of the safety parameters is given in section 'Summary'.
Statistical methods	Descriptive, please see explanation above.

Summary – Conclusions: Efficacy Results, Safety Results, Conclusion	Descriptive analysis (for n= 1 study participant). 6 adverse events (AE) and 2 serious adverse events (SAE) are detected. **<u>Analysis for:</u>** Demographics: • Female • Age 48 • caucasion Efficacy: - not possible, not done <u>Safety and toxicity</u> Adverse events: - infusion related reaction grade 2 caused by obinutuzumab - percutaneous endoscopic gastrostomy grade 2, not related to study medication - diarrhea grade 2, not related to study medication - jejunal ileus 3, not related to study medication caused by progressive disease AE was also assessed as SAE because it required hospitalization of the patient. - jejunal ileus 2, not related to study medication caused by progressive disease - trush grade 2, - worsening of jejunal ileus grade 5 not related to study medication caused by progressive disease. Also assessed as SAE with fatal outcome. Overall, the therapy was well tolerated. The occurrence of infusion reactions caused by obinutuzumab is well known. All other AE´s and SAE´s are related to the tumor disease itself.
Date of report	15/JUNE/2022