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CONDITION	Patients with metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (stage IV) and no prior chemotherapy for stage IV disease.
OBJECTIVE(S)	→ **Primary objective(s)** → The primary objective of the study, including the dose escalating part (Part 1a), the dose expansion part (Part 1b) as well as the consolidation part (Part 2), is to determine the safety and tolerability of Azacitidine (Arm B) and/or Romidepsin (Arm A) in combination with nab-Paclitaxel/Gemcitabine in patients with advanced PDAC (Part 1a and 1b), followed by sequential immune targeting with PD-L1 blockade in combination with low-dose Lenalidomide (Part 2) in patients with controlled disease after 3 cycles (Part 1). → Moreover, in the dose escalating part of the study (Part 1a), the recommmended dose for expansion (RDE) and dose-limiting toxicity (DLT) of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine will be identified. → **Secondary objective(s)** → to assess ORR, CA19-9 response and disease control rate (=1st DCR after 3 cycles), progression free survival (PFS) and overall survival (OS) in patients treated at the recommended dose and regimen of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine (Part 1a and Part 1b) → to show a promising clinical activity of the selected epigenetic and chemotherapeutic targeting approach from Part 1a with regard to the disease control rate (Part 1b) → to assess 2nd ORR, 2nd CA19-9 response and 2nd DCR (after start of Part 2), PFS and OS in patients treated with Durvalumab and Lenalidomide as consolidation treatment (Part 2) → to assess OS in all patients treated at the recommended dose and regimen **Exploratory Translational Sub-studies** 1. Exploratory analyses on tumor biopsy samples may include but will not be limited to: Genetic, epigenetic and expression profiling of tumor cells and immune phenotyping before and after therapy initiation including next generation sequencing (NGS)-based DNA/RNA-seq, genome-wide methylation profiling, immune cells infiltrate characterization (e.g. CD8, CD4, Treg, Macrophages and DC), immune phenotyping (e.g. interferon-stimulating genes such as IFI16, IFI27, IFI44, IFI44L, MX1 and OASL; induction of endogenous retroviral sequences (=ERVs) such as Syncytin-1-3, ERV-3, env-K, env-H and env-Fc1-2) by epigenetic treatment. 2. An exploratory objective of this study is to evaluate biomarkers in liquid biopsies, including but not limited to tracking oncogenic mutations such as KRAS in cell free DNA (ctDNA analysis), cytokines, chemokines, circulating receptors or ligands, other

	immune-related biomarkers (e.g. interleukin 2, interferon-γ) and immuno-phenotyping (e.g. CD8, CD4, Treg, Macrophages).
INTERVENTION(S)	The dose escalation part of the study will employ a standard 3 + 3 design to test safety and tolerability of histone deacetylases (HDAC) inhibition with Romidepsin (Arm A), DNA methyltransferases (DNMT) inhibition with Azacitidine (Arm B) or both agents (Arm C), in combination with nab-Paclitaxel/Gemcitabine **(Part 1a).** Study treatment is given until intolerable toxicity of Romidepsin and/or Azacitidine for a maximum of 3 cycles, whereas in the Standard arm nab-Paclitaxel/Gemcitabine will be administered exclusively. Treatment will escalate until the recommended dose for expansion (RDE) is identified. In the event that dose level 1 has 2 dose-limiting toxicities (DLT) the dose will be reduced and a dose level -1 will be included. DLT, defined as any of the following toxicities occurring during treatment cycle 1 of a respective dose level and regarded to be related to the studied drug combination. Common terminology criteria for adverse events (CTCAE) 5.0 will be used to assess toxicities: Arm A • Absolute neutrophil count < 1 x 10^9/L for ≥7 days • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • > Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Romidepsin: • Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion • ≥ Grade 2 non-hematologic toxicity, except alopecia Arm B • Absolute neutrophil count < 1 x 10^9/L for ≥7 days • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • > Grade 2 non-hematologic toxicity Only if deemed related to Azacitidine: • unexplained reductions in serum bicarbonate levels to less than 20 mmol/l • unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2-fold above baseline values and above ULN Arm C • Absolute neutrophil count < 1 x 10^9/L for ≥7 days 1) • Platelets < 50 x 10^9/L for ≥7 days (severe thrombopenia) • ≥ Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Romidepsin: • Grade 4 febrile (≥ 38.5ºC) neutropenia or thrombocytopenia that requires platelet transfusion • ≥ Grade 2 non-hematologic toxicity, except alopecia Only if deemed related to Azacitidine: - unexplained reductions in serum bicarbonate levels to less than 20 mmol/l - unexplained elevations in serum creatinine or blood urea nitrogen to ≥ 2-fold above baseline values and above ULN 2) For the dose expansion part (Part 1b) of the study, one of the treatment arms (Arm C over B over A) will be continued using a Simon Two-stage design to a maximum of 35 patients. Selection of the expansion arm will be as follows in

	case of successful determination of the RDE: Arm C preferred over Arm B over Arm A. In case of no determination of RDE in Arm C, Arm B will be prefered over Arm A. In case of no determination of RDE in Arm B, Arm A will be selected. In case of no determination of RDE in Arm A, patients will be treated with standard nab-Paclitaxel/Gemcitabine for up to 41 patients with controlled disease after 3 cycles to enter Part 2 of the trial. (but a maximum of 75 patients in total). All patients from Part 1a and 1b will be treated for a total of three cycles and will then enter the second part of the study in case of disease control, but still measurable disease (PR, SD). Patients without DCR will enter a 12 month long-term follow-up. Because of our aim to study a consolidation concept in the second part of the study, a sufficient number of patients with controlled disease after 3 cycles of therapy is needed based on the statistical considerations. Thus, in addition to the patients undergoing Part 1a (dose escalation) and Part 1b (dose expansion), patients treated with nab-Paclitaxel/Gemcitabine alone will be additionally recruited in this study (so-called “standard arm”). The number of patients in the standard group may vary on the recruited number of patients in Parts 1a and 1b (total target number of patients for Part 1 including standard group = 75), so that 41 patients will be available for Part 2 given a presumed 60% DCR after 3 cycles in Part 1 and a drop-out rate of 10%.
KEY EXCLUSION CRITERIA	→ **Principal exclusion criteria** 1. Patients who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse event from agents administered more than 4 weeks earlier 2. Patients may not be receiving any other investigational agents 3. Patients who have previously received Romidepsin, Azacitidine, Lenalidomide or Durvalumab or any PD1 or PD-L1 inhibitor or pacticipate currently on an other clinical trial, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study 4. Patients with untreated or uncontrolled brain metastases or leptomeningeal disease 5. Presence of other active illnesses 6. Any known cardiac abnormalities such as: • Congenital long QT syndrome • QTc interval ≥ 470 milliseconds. Calculated from 3 ECGs using Fridericias Correction 7. Myocardial infarction within 6 months prior to C1D1. Subjects with a history of myocardial infarction between 6 and 12 months prior to C1D1 who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event may participate 8. Other significant EKG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min) 9. Symptomatic coronary artery disease (CAD), e.g., angina Canadian Class II-IV. In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present 10. Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix IV) and/or known ejection fraction < 40% by MUGA or < 50% by echocardiogram and/or MRI 11. A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest unless currently addressed with an automatic implantable cardioverter defibrillator (AICD) 12. Concomitant use of any drug known to prolong QT interval

	13. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) 14. Lactating, pregnant or breast feeding 15. Patients with any other medical or psychological condition deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results 16. Diagnosis of immunodeficiency or any condition that requires systemic steroid therapy or other forms of immunosuppressive therapy; 17. Prior thromboembolic events 18. History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥ 5 years before the first dose of study drug and felt to be at low risk for recurrence by investigator. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. • Adequately treated carcinoma in situ without current evidence of disease (all treatment of which should have been completed 6 months prior to randomization) 19. Any uncontrolled active systemic infection 20. Major surgery within 4 weeks prior to first dose of study drug 21. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk 22. History of stroke or intracranial hemorrhage within 6 months prior to enrollment 23. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis 24. Unable to swallow oral medication or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction 25. Concomitant use of warfarin or other Vitamin K antagonists 26. Known allergy or hypersensitivity to any study drug or any of the study drug excipients 27. Unwilling or unable to participate in all required study evaluations and procedures. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information 28. Current or prior use of immunosuppressive medication within 14 days (use 28 days if combining Durvalumab with a novel agent) before the first dose of Durvalumab. The following are exceptions to this criterion: • Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection) • Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent • Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication) 29. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion: • Patients with vitiligo or alopecia • Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement • Any chronic skin condition that does not require systemic therapy

	• Patients without active disease in the last 5 years may be included but only after consultation with the study physician • Patients with celiac disease controlled by diet alone 30. Any unresolved toxicity NCI CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria • Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. • Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with Durvalumab may be included only after consultation with the Study Physician. 31. History of allogenic organ transplantation 32. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (HBV; known positive HBV surface antigen (HBsAg) result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. These patients will be closely monitored for signs and symptoms of active HBV or VZV infection throughout therapy. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA 33. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IMP and up to 30 days after the last dose of IMP 34. Subject is an employee of GWT-TUD GmbH
KEY INCLUSION CRITERIA	**Principal inclusion criteria** Subjects must fulfill all of the following criteria before inclusion in the study: 1. Patients must have histologically confirmed PDAC 2. Patients must have metastatic disease (stage IV) and not received prior chemotherapy for stage IV disease (adjuvant/additive chemotherapy is allowed if completed at least 6 months prior to study inclusion) 3. Patients must not have received the following drugs before: Azacitidine, Romidepsin, any checkpoint-inhibitor or immunomodulating agents such as IMiDs (Lenalidomide) 4. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension in accordance with RECIST criteria v. 1.1 5. Male or female, age ≥ 18 years 6. Body weight > 30 kg for inclusion into Part 2 (according to Durvalumab treatment) 7. ECOG performance status 0 or 1 8. Patients must have normal organ and marrow function as defined below • Leukocytes ≥ 2,5 x 10^9/L • Absolute neutrophil count ≥ 1,5 x 10^9/L • Platelets ≥ 100 x 10^9/L • Haemoglobin ≥ 9 g/dL • Total bilirubin ≤ 1.5 x upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician • Asparate aminotransferase/alanine aminotransferase (AST/ALT) (SGOT/SGPT) ≤ 2.5 x ULN and ≤ 5 in the case of liver metastasis • Measured creatinine clearance (CL) >60 mL/min or calculated creatinine CL>60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance

	9. Patients must be recovered from the effects of any prior surgery 10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up 11. All subjects must agree to refrain from donating blood while on study drug and for 90 days after discontinuation from this study treatment 12. All subjects must have a life expectancy of at least 12 weeks 13. All subjects must agree not to share medication 14. Females of childbearing potential (FCBP) must • Understand the potential teratogenic risk to the unborn child • Understand the need and agree to utilize two reliable forms of contraception simultaneously without interruption for at least 28 days before starting study drug, while participating in the study (including dose interruptions), and for at least 90 days after study treatment discontinuation • Understand and agree to inform the investigator if a change or stop of method of contraception is needed • Be capable of complying with effective contraceptive measures • Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy • Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test • Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocol • Acknowledges that she understands the hazards Lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of Lenalidomide • Females must agree to abstain from breastfeeding during study participation and for at least 90 days after study drug discontinuation 15. Males must • Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP • Agree to use a latex condom during any sexual contact with FCBP or a pregnant female while participating in the study and for 90 days following discontinuation from this study, even if he has undergone a successful vasectomy. For treatment with Gemcitabine and nab-Paclitaxel men must avoid fathering a child/ use condom up to 6 months after their last dose. Depending on duration of Lenalidomide/Durvalumab treatment this period can be loger than 90 days after study discontinuation. • Agree to refrain from donating semen or sperm while on the study drugs and for 90 days after discontinuation from this study treatment. For treatment with nab-Paclitaxel and Gemcitabine mal subject must agree not to fathering a child or donate semen for at least 6 month after last intake of medication. • Agree not to father a child during the course of the trial and for at least 90 days after last administration of study drugs For Gemcitabine and nab-Paclitaxel treatment up to 6 month after last drug intake. 16. Females of non-childbearing potential: • 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 amenorrhea for at least 24 consecutive months without an alternative medical cause. The following age-specific requirements apply: Women <50 years of age would be considered post-menopausal if they have been amenorrhea for at least 24 consecutive 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 post-menopausal if they have been amenorrhea for at least 24 consecutive 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))
OUTCOME(S)	→ **Primary endpoint(s)** The primary endpoint is the safety and tolerability of Azacitidine (Arm B) and/or Romidepsin (Arm A) in combination with nab-Paclitaxel/Gemcitabine, followed by sequential immune targeting with programmed death-ligand (PD-L)1 blockade in combination with low-dose Lenalidomide in patients with advanced PDAC (Part 1 and 2). Safety and tolerability will be determined by the following parameters: • Clinical laboratory (clinical chemistry, hematology, urinalysis) • Performance status according to Eastern Cooperation Oncology Group (ECOG) • Recording of AEs and concomitant medication • Physical examination • ECG • ECHO (Echocardiography) or MUGA (Multiple-Gated-Acquisition-(MUGA)-Radionuclide-Imaging) • Vital signs (pulse, blood pressure, body temparature) 4) Moreover, in the dose escalating part of the study (Part 1a/Phase I), the recommended dose for RDE and DLT of Azacitidine and/or Romidepsin in combination with nab-Paclitaxel/Gemcitabine will be identified after completion of 3 treatment cycles.
STUDY TYPE	This will be an interventional, multicenter, phase I/II clinical study of sequential epigenetic and immune targeting in combination with nab-Paclitaxel/Gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. The study will be accompanied by a broad translational research project with several aims.
STATISTICAL ANALYSIS	→ <u>Descriptive analyses</u> → Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by treatment group. Frequency tables for categorical data will be provided. Medical history findings will be summarized using MedDRA terms. → <u>Safety examinations</u> → Individual listings of AEs will be provided. The incidence of treatment-emergent AEs and drug-related AEs, respectively, will be summarized by treatment using MedDRA terms. All AEs starting or worsening after first study drug administration up to 90 days after last study drug administration will be considered as treatment-emergent. In summary, the trial design is based on the following assumptions:

	• The experimental therapy in Part 1b would be rated as insufficiently active, if the true DCR at > 12 weeks is 60% or lower, considered to be futile. • The experimental therapy would be considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true DCR amounted to 83% or more. • Probability to accept the experimental therapy as promising (> 83% DCR) with respect to efficacy, in spite of a true DCR of ≤ 60%: 0.05 (type I error) • Probability to reject the experimental therapy as not sufficiently efficient (≤ 60%), although the true DCR is promising (> 83%): 0.1 (type II error, corresponding to a power of 90%). For the Part 2 (consolidation treatment after three cycles of nab-Paclitaxel/Gemcitabine-based therapy with or without additional epigenetic treatment) sample size is based on continued safety evaluation and evaluation of (subsequent) overall response rate (ORR). ORR is defined using irRECIST1.1 (Wolchok, 2009) as the proportion of subjects with a response defined as confirmed CR or confirmed PR ≥ 16 weeks. Only patients with at least stable disease (SD by RECIST 1.1) and still measurable lesions will proceed from Part 1 to Part 2 of this study.
SAMPLE SIZE	*Up to 75 patients are planned to be enrolled. The sample size is based on disease control rate and ORR and these calculations are made without adjusting for multiplicity.* Because of our aim to study a consolidation concept in the second part of the study, a sufficient number of patients with controlled disease after 3 cycles of therapy is needed based on the statistical considerations. Thus, in addition to the patients undergoing part 1a (Dose escalation) and part 1b (Dose Expansion), patients treated with nab-Paclitaxel/Gemcitabine alone will be additionally recruited in this study (so-called “standard arm”). The number of patients in the standard group may vary on the recruited number of patients in Parts 1a and 1b (total target number of patients for Part 1 including standard group = 75), so that 41 patients will be available for Part 2 given a presumed 60% DCR after 3 cycles in part 1 (Goldstein 2015) and a drop-out rate of 10%. According to these parameters, and using the variant out of the class of optimal two-stage designs by SIMON (1989), that leads to the lowest maximum number of patients required (optimal approach), n = 13 patients have to be recruited in the first stage. The experimental combination will be rejected, if only 8 or less of these patients fulfill the criterion of clinical benefit. In the second step, further patients will be recruited up to a total number of 35 cases. A clinical benefit finding in 25 or more out of these will allow to reject the hypothesis of insufficient efficacy. The final conclusion of the trial will depend on the definite DCR (and its confidence interval) as well as the complete information on type, frequency and severity of toxicities.
TRIAL DURATION	→ **For the individual patient:** → Maximum 4 months induction (part 1), 12 months consolidation (part 2), after that 12 months Follow Up starting after completion of the consolidation therapy (part 2) with subsequent long-term Follow Up for SPMs. → **Planned study schedule** → First Patient First Visit → Q1/2020 → Last Patient First Visit → Q1/2022 → Last Patient End of Trial → Q1/2023 → Last Patient Last Active Follow up → Q1/2024 → Last Patient Last Follow Up of SPMs → Q1/2026

	→ Final Study report (primary data) → Q4/2024 → Report of SPMs → Q2/2026
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