Project Plan Summary

Official Title	**AIO-BNHO Co**mprehe**n**sive Cli**n**ico-genomi**c**s database ne**t**work – **AIO-BNHO CONNECT**
Study Acronym	CONNECT
Version	FINAL 2.0
Date	23.09.2022
Steering Board	Prof. Dr. Dr. Sonja Loges Dr. C. Benedikt Westphalen Prof. Dr. Anke Reinacher-Schick Dr. Eray Gökkurt Prof. Dr. Wolfgang Knauf Prof. Dr. Thomas Illmer Prof. Dr. Wilko Weichert Prof. Dr. Andrea Tannapfel Prof. Dr. Ulrich Mansmann Prof. Dr. Frank Griesinger Isabel Reinhardt
Primary Study Sponsor	AIO-Studien-gGmbH
Study Type	National, retro- and prospective, observational, multicenter clinical research platform to connect clinical and genomic data
Study Indication	Adult patients with advanced (locally advanced, inoperable, or metastatic) solid tumors (excluding NSCLC, SCLC, and mesothelioma) ineligible for curative treatment and with results available from multi-gene next-generation sequencing (NGS) panels (>30 genes)
Study Design	Multicenter: Yes International: No Planned countries: Germany Biobank: Decentral Patient-reported outcomes: No
Study Treatment	Not applicable. Routine care as per site standard/ physician's choice according to patient's needs.
Planned Number of Subjects	3000 subjects; of those, 1000 subjects with targeted therapy based on NGS results. Inclusion of deceased patients is possible. Recruitment will be terminated when both subject numbers are reached, respectively.
Number of Sites	Up to 50
Study Site(s)	Office- and hospital-based medical oncologists/ gynecologists/ urologists/ gastroenterologists
Study Rationale	The growing understanding of cancer biology paired with the acceleration of diagnostic development and the expanding availability of targeted cancer therapies have dramatically changed cancer treatment. Current treatment guidelines already include the strong recommendation for testing on specific

	predictive biomarkers to guide treatment decision making. Apart from entity-specific testing for certain predictive markers, there is also growing use of comprehensive genomic profiling to identify potential biomarkers (e.g., actionable alterations) irrespective of the original tumor histology, so called tumor-agnostic approaches. Next-generation sequencing (NGS) that offers scalability, speed, and high accuracy to evaluate genes of interest, is increasingly feasible in German clinical routine and has become a cornerstone of therapy guidance in precision oncology. However, precision oncology still meets significant challenges, such as timely molecular profiling and treatment assignment. Some fundamental aspects of precision oncology still need to be better understood. The European Society for Medical Oncology (ESMO) has developed a scale for clinical actionability of molecular targets (ESCAT) to guide treatment decisions based on evidence level from available clinical trial and real-world data.[1] Still, the biological role of some alterations, e.g., discriminating driver and passenger mutations, is unclear. Thus, it remains challenging to choose an alteration/ therapy match that will actually prove effective in the individual patient.[2] To meet this challenge, multidisciplinary molecular tumor boards (MTB) have been implemented to support treating physicians in molecular-informed treatment decisions. Real-world evidence will play a pivotal role in improving our understanding and employment of precision oncology.[3] To date, however, the tools for structured documentation of real-world NGS-driven treatment decisions and outcome research are limited due to the inherent diversity of the German health care system. The AIO-BNHO CONNECT research platform is a clinic-genomic database collecting data on NGS results and corresponding clinical outcomes in patients with advanced solid tumors (excluding NSCLC, SCLC, and mesothelioma). Data of deceased patients will be included. The platform will provide insight into the current state of precision oncology in Germany by compiling real-world data encompassing a broad spectrum of care providers including but not limited to practice-based oncologists, community hospitals, and university hospitals. The platform also comprises a decentral tissue repository with clinically annotated tumor specimens retrieved within routine clinical care that can be used in future collaborative research projects. The project will be extended by an AIO-BNHO molecular tumor board as well as an outreach and education program dedicated to precision oncology. In summary, CONNECT is designed as a knowledge-generating platform of real-world precision oncology data and will prospectively serve as a launchpad for future translational, educational, and clinical activities.
Inclusion Criteria	• Diagnosis of advanced (i.e., locally advanced, inoperable, or metastatic) solid tumor, ineligible for curative surgery and/or curative systemic therapy • Available results of commercial or non-commercial RNA- and/or DNA-based multi-gene NGS panels with >30 genes analyzed; for non-commercial panels a list of all tested genes and multiple gene biomarkers (e.g., tumor mutational burden (TMB), microsatellite status) must be provided • Age ≥ 18 years • Signed and dated informed consent form (not applicable for inclusion of deceased patients)
Exclusion Criteria	• Diagnosis of NSCLC/SCLC (C34) or mesothelioma (C45) • NGS results older than two years at the date of patient inclusion
Objectives	<u>For all included patients</u> (according to minimal data set, in the following referred to as Data Set^{MIN}):

	• To assess utilization of MTBs • To investigate treatment reality after NGS analysis by describing the proportions of patients a. for whom a targeted therapy was reasonable /not reasonable according to NGS results b. for whom a targeted therapy based on NGS results was planned/ not planned c. who received at least one targeted therapy based on NGS results/ who exclusively received therapies other than targeted therapies based on NGS results/ who did not receive any therapy • To set up a decentralized biobank of clinically annotated tissue samples for optional future translational projects <u>Additional objectives for patients receiving a targeted therapy based on NGS results</u> (according to extended data set, in the following referred to as Data Set^{EXT}): • To determine types of NGS assays, tissue of origin used for NGS analysis, and genomic alterations yielded by multi-gene NGS panels • To investigate the MTB-based therapy recommendations, their implementation rate, and reasons for non-implementation • To assess effectiveness of targeted therapies administered after NGS analysis, individually and in relation to preceding treatments (if applicable)
Minimal versus extended data set	For all included patients a minimal data set will be collected (Data Set^{MIN}). The following criterion will trigger documentation of the extended data set (Data Set^{EXT}): • Start of a targeted therapy based on NGS results outside of a clinical trial. This means: • For patients included after start of a targeted therapy based on NGS results (outside of a clinical trial) full documentation (Data Set^{MIN} and Data Set^{EXT}) will be applicable. • For patients included before start of a targeted therapy based on NGS results (outside of a clinical trial), first, only the minimal data set will be applicable. Only if the patient ultimately receives a targeted therapy based on NGS results the electronic Case Report Form (eCRF) pages for extended documentation will be activated. If the patient never receives a targeted therapy based on NGS results, only the minimal data set will be captured. Data on all systemic therapies will be documented retrospectively after end of treatment.
Data on Patient Characteristics	*Data Set^{MIN} (data collected for all included patients):* • Basic demographic patient characteristics *Data Set^{EXT} (data collected in addition to Data Set^{MIN} for patients receiving a targeted therapy based on NGS results):* • Further demographic patient characteristics • Clinical patient characteristics
Data on Disease Characteristics	*Data Set^{MIN}:* • Date of primary tumor diagnosis • Tumor type with ICD-10 code *Data Set^{EXT}:*

	• Details on tumor type

Data on the Utilization and Implementation of Molecular Tumor Boards	*Data Set^{MIN}:*
	Physician questionnaire Q^{MIN} (answers to be documented in eCRF):
	• Was the patient's case (with regard to NGS analysis) discussed in an MTB?; If yes: Was a treatment recommendation given?
	Data Set^{EXT}:
	MTB reports will be pseudonymized by study sites with the study-specific patient identifier (ID) and sent to iOMEDICO for central documentation by specialized staff:
	• MTB setting
	• Date of MTB discussion
	• Details on treatment recommendations for targeted therapies
	Physician questionnaire Q^{EXT} (answers to be documented in the eCRF):
	• Implementation of treatment recommendation including reasons for non-implementation
	• Recommendation for additional tumor biopsies
	  ○ If yes: Reason for re-biopsy
	  ○ If yes: Biopsy done?
	  ▪ If yes: Biopsy successful?
	  ▪ If yes: Further NGS analysis conducted?
	  • If yes: Documentation of the (new) NGS analysis
	• Recommendation to see geneticist
	• Recommendation to re-evaluate initial diagnosis

Data on NGS Analysis and Results	*Data Set^{MIN}:* • Name of (pathological) institute/ company, where NGS was performed Physician questionnaires Q^{MIN} and $Q^{BIOMARKER}$ (answers to be documented in the eCRF): Q^{MIN}: • Is/ was it reasonable to give a targeted therapy according to NGS results? • Is/ was it planned to give a targeted therapy based on NGS results? $Q^{BIOMARKER}$: • Only for patients receiving a targeted therapy: Provide the biomarker(s) decisive for targeted therapy NGS reports will be pseudonymized by study sites with the study-specific patient ID and sent to iOMEDICO for central documentation by specialized staff: • Information on NGS modalities, i.e., test panel • Test results *Data Set^{EXT}:* Extended central documentation of NGS reports by specialized staff: • Date of testing request • Date of NGS report • Information on tested tissue • Further information on NGS modalities • Further information on test results
Treatment Data	*Data Set^{MIN}:* • Participation in a clinical trial • Substance(s) administered in treatment line(s) after NGS analysis (only for patients not participating in a clinical trial)

	Data Set^{EXT}: • Key details on previous treatment line(s), i.e., treatment lines that started prior to NGS analysis • Details on last preceding treatment line before start of targeted therapy based on NGS results • Details on targeted therapy(ies) based on NGS results • Key details on therapy(ies) other(s) than targeted therapies based on NGS results • Details on previous and concomitant surgeries • Details on previous and concomitant radiotherapies

Effectiveness Data	Investigator-assessed response evaluations will be performed as per site standard.
	Data Set^{EXT}:
	Planned data collection/ analyses:
	a) Last preceding treatment line before start of targeted therapy
	• Best response to calculate
	  ○ Overall response rate (ORR)
	  ○ Disease control rate (DCR)
	• Date of treatment start, date of progression, and start date of subsequent therapy (i.e., targeted therapy based on NGS results) to calculate
	  ○ Time to progression (TTP)
	b) Targeted therapy(ies) after NGS analysis
	• Best response to calculate
	  ○ ORR
	  ○ DCR
	• Date of diagnosis of advanced disease, date of treatment start, date of progression, date of last contact, and date of death to calculate
	  ○ Progression-free survival (PFS)
	  ○ Time to next treatment (TTNT)
	  ○ Overall survival (OS)
	a) and b)
	• PFS ratio, i.e., PFS interval associated with targeted therapy(ies) administered after NGS analysis divided by the TTP interval associated with the last prior treatment(s)

Data on Reimbursement	*Data Set^{MIN}:*
	• Request for cost coverage by health insurance company
	  ○ If yes:
	  ▪ Date of request
	  ▪ Date of response
	  ▪ Response (approval, disapproval)
	  - If disapproval: rebuttal with outcome

Assessment of Patient-Reported Outcomes (PROs)	NA
Safety Data	NA
Decentralized Biobank	All patients will be asked to give additional informed consent that their routinely collected tissue samples will be assigned to the biobank and may be used for future translational research (not applicable for deceased patients' samples). For the decentralized biobank, pathological samples will remain with the local pathologist until scientific translational question arise. The identification number of the sample and the contact details of the pathologies, where the sample is stored, will be documented in the eCRF. Future translational research projects that will develop during the project will be described in detail in

	independent research proposals and submitted to an ethics committee for review and approval.
Visit Schedule on Treatment and Follow-up	Not applicable. Routine care as per site standard.
Statistics and Data Analysis	Sets of analyses: The Full Analysis Set $(FAS)^{MIN}$ consists of all included patients, excluding screening failures. The FAS^{EXT} consists of all FAS^{MIN} patients who have passed the eligibility check for extended documentation (i.e., patients who have received a targeted therapy based on NGS results outside of a clinical trial). Once either 3000 patients are included or 1000 patients have passed the eligibility check for extended documentation, an additional analysis set will be provided for analysis of treatment reality (FAS^{MINREL}). This set will cover patients included before one of the scenarios occur. Interim analyses: Annual interim analyses (IA-1: 2023, IA-2: 2024) and a final analysis at the end of the study (FA: 2025) will be conducted. IA-1 will cover descriptive data on patient and disease characteristics, data on prior treatments (including data on tumor response of last preceding treatment line before start of targeted therapy, if applicable), data on treatment reality after NGS analysis, data regarding the utilization and implementation of MTBs, data on biomarker(s) decisive for targeted therapy, and data on substance(s) administered in treatment line(s) after NGS analysis. IA-2 will additionally describe details on NGS analysis and test results, outcome of targeted therapies including time-dependent analyses (i.e., best overall response, ORR, DCR, PFS, PFS ratio, TTNT, OS), and data on reimbursement. FA will cover all analyses and objectives. Subgroup analyses: Patient subgroups based on the different substance classes will be analyzed separately. If numbers are sufficient, further subgroups, e.g., by tumor entity and biomarker will be analyzed. All subgroup analyses are exploratory. In case of an a priori defined hypothesis to be tested on a certain subgroup, such subgroup analysis including the rationale and statistical techniques applied will be defined in a dedicated statistical analysis plan (SAP). General principles: Categorical variables will be presented as absolute and relative frequencies, continuous variables with number, mean and standard deviation or median and 25th and 75th percentiles. Time-to-event variables, such as PFS and OS, will be analyzed using the Kaplan-Meier method and displayed with median, quartiles, 95%-confidence interval (CI), and frequencies of events/censored patients. Kaplan-Meier plots will be provided. If required, models will be applied for exploratory analyses. In general, all analyses are of descriptive nature and no p-values will be provided unless there is a specific hypothesis to be tested defined and planned in a dedicated SAP. Optional investigational translational projects will be defined according to latest scientific knowledge and analyzed separately. Further details will be defined in the SAP.
Quality assurance	Data are collected from patients' medical records, physician questionnaires, NGS reports, and MTB reports. Data are transferred into an electronic documentation system (EDC) with implemented automatic plausibility and completeness checks (automated queries). Quality checks on specific parameters are regularly performed by the data and medical management (manual queries) and centers asked to complete and/or verify data if

	necessary. In addition, an eligibility check for extended documentation will be performed by specialized staff of iOMEDICO by mutual reconciliation of the physician-reported biomarker(s) decisive for targeted therapy and the NGS results.		
Monitoring	Automatic checks for plausibility and completeness of documented data are implemented in the EDC. Furthermore, centralized monitoring is regularly performed by data and medical management.		
Reports and Interim Analyses	Status reports	monthly	steering board, supporting companies
	Interim reports	annually	Steering board, supporting companies
Language	Protocol	English	
	eCRF	English	
	Interim report	English	
	Publication	English	
Planned Study Duration	First Patient In (FPI):	Q2 2022	
	Duration recruitment phase:	24 months	
	Last Patient In (LPI)	Q2 2024	
	Duration documentation phase (including treatment and survival follow-up):	Max. until 12 months after LPI	
	Last Patient Out (LPO):	Q2 2025	
	Final Analysis (FA)	6 months after LPO	
	Abstracts and presentations	After each pre-specified IA or FA (in total 4).	
	Publication	After pre-specified IA or FA (in total 3).	