Template: CTP-ONC-09

CLINICAL TRIAL PROTOCOL
BNT321-02

Document version:	2.0	**Document date:**	22 JAN 2024
Sponsor name:	BioNTech SE		
Sponsor address:	55131 Mainz, Germany		

Trial title:	A Phase I/randomized Phase II, open-label multicenter trial to evaluate the safety, tolerability, and efficacy of mFOLFIRINOX with or without BNT321 as adjuvant therapy following curative resection in patients with pancreatic adenocarcinoma
Brief lay title:	Safety, tolerability, and efficacy of mFOLFIRINOX ± BNT321 as adjuvant therapy following curative resection in patients with pancreatic adenocarcinoma
Trial phase:	Phase I/II
Indication:	R0 or R1 surgically resected pancreatic adenocarcinoma
Investigational medicinal products:	mFOLFIRINOX chemotherapy with or without BNT321 (human IgG monoclonal antibody against sialyl-Lewis A epitope of CA19-9)
Regulatory identifier:	IND: 126424 EU CT: 2023-506014-47-00
Trial sites:	Approximately 140 sites in Asia-Pacific, Europe, and North America. Additional sites may be included during the trial.
Trial Medical Monitor:	The name and contact details will be provided separately.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained. These personnel include the sponsor's medical expert for the trial and the person authorized to sign (approve) the protocol and any protocol amendments for the sponsor.

Some sponsor tasks in the conduct of this trial may be delegated, e.g., to contract research organization (CRO) personnel. Documentation of any delegation of responsibilities will be maintained.

Document history	Date	Version number
First sponsor approved version	19 JUN 2023	1.0
EU-CT Application Part I Assessment	22 JAN 2024	2.0

Statement of compliance: This trial will be conducted according to this protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice (GCP), and applicable regulatory requirements.

1 PROTOCOL SUMMARY

1.1 Synopsis

BNT321 is a fully human monoclonal antibody with high affinity and specificity for sialyl-Lewis A (sLe^a) carbohydrate antigen 19-9 (CA19-9), which is highly expressed in pancreatic ductal adenocarcinoma (PDAC). This is a two-part Phase I/randomized Phase II trial. Phase I dose escalation will investigate the safety and tolerability of BNT321 administered in patients with PDAC in combination with adjuvant modified (m)FOLFIRINOX followed by BNT321 monotherapy. The randomized Phase II part of the trial will investigate the efficacy of mFOLFIRINOX with or without BNT321 as PDAC adjuvant therapy.

Trial title

A Phase I/randomized Phase II, open-label multicenter trial to evaluate the safety, tolerability, and efficacy of mFOLFIRINOX with or without BNT321 as adjuvant therapy following curative resection in patients with pancreatic adenocarcinoma

Trial rationale

For early stage, non-metastatic PDAC, complete surgical resection can result in cure for some patients. mFOLFIRINOX is currently adapted as an adjuvant therapy for resectable PDAC, however, relapse in this setting is common, with a 3-year disease-free survival (DFS) realized in less than 40% of patients (Conroy et al. 2018). Improved PDAC adjuvant treatment options are therefore a high priority for clinical development.

BNT321-02 is planned as a Phase I/II clinical trial to evaluate the safety, multicycle tolerability, and efficacy of mFOLFIRINOX ± BNT321 as a novel combination adjuvant therapy for patients with R0 or R1 resected PDAC. The Phase I part of this trial will determine the safety and BNT321 recommended Phase II dose (RP2D) together with chemotherapy for previously untreated patients who are eligible to receive 24 weeks of PDAC adjuvant therapy. A key secondary pharmacodynamic endpoint in Phase I is determining the extent of complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) effects in peripheral blood longitudinally over an extended adjuvant therapy course. The safety and feasibility of continuing BNT321 monotherapy for 24 weeks beyond the initial 24 weeks of combination treatment will also be determined.

The BNT321-02 randomized Phase II part of this trial is a dedicated evaluation of the potential for mFOLFIRINOX + BNT321 combination therapy to provide meaningful clinical benefit over standard adjuvant mFOLFIRINOX. The Phase II part is designed to detect a substantial increase in median disease-free survival (mDFS), specifically with a target of 36 months mDFS which represents more than 12 months improvement over current chemotherapy. Overall survival (OS) is a secondary endpoint for Phase II, and demonstrated improvements will provide additional evidence of clinical benefit and further support the performance of additional follow-on trials in PDAC. Additional evaluations are limited pharmacokinetic and pharmacodynamic (ADCC, CDC, circulating tumor DNA [ctDNA], and CA19-9) assessments, which may help further characterize the clinical benefit and allow for more tailored designs in follow-on BNT321 trials.

Objectives and endpoints

OBJECTIVES	ENDPOINTS
PRIMARY	
Phase I	
To assess the safety and identify the RP2D of BNT321 in combination with mFOLFIRINOX as adjuvant therapy in patients with R0 or R1 resected PDAC.	The proportion (%) of patients who received at least one dose IMP reporting: • Incidence and occurrence of TEAEs including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of DLTs within a cohort during the DLT evaluation period.
Phase II	
To assess the efficacy of mFOLFIRINOX + BNT321 versus mFOLFIRINOX alone as adjuvant therapy in PDAC patients post R0 or R1 resection by mDFS.	In patients who are randomized into the trial: DFS defined as the time from randomization to occurrence of any of the following: • Locoregional recurrence or distant metastasis as determined by an independent central radiology assessment. • Occurrence of second primary (same or other) cancer as determined by an independent central radiology assessment. • Death from any cause.
SECONDARY	
Phase I and II	
To further assess the efficacy of mFOLFIRINOX + BNT321 or mFOLFIRINOX as adjuvant therapy in PDAC patients post R0 or R1 resection by OS.	In patients who are enrolled/randomized into the trial: • OS is defined as the time from first dose of trial treatment to death from any cause.
To further assess the efficacy of mFOLFIRINOX + BNT321 or mFOLFIRINOX as adjuvant therapy in PDAC patients post R0 or R1 resection by RFS and DFS rates.	In patients who are enrolled/randomized into the trial: RFS is defined as the time from randomization to occurrence of any of the following events, whichever occurs first: • Locoregional recurrence or distant metastasis as determined by the investigator. • Death from any cause.
To characterize the PK of BNT321 when co-administered with mFOLFIRINOX.	In patients who are dosed with at least one dose of IMP and who have evaluable PK data: • PK parameters derived from serum concentration of IMP, including mean AUC, mean C_{max}, and median t_{max} in Cycles 2 and 3 followed by sparse sampling through EOT.
To characterize immunogenicity of BNT321 when co-administered with mFOLFIRINOX.	In patients who are dosed with at least one dose of IMP: • Percentage of patients with detectable ADA formation in Cycles 1 and 3, followed by sparse sampling through EOT.

OBJECTIVES	ENDPOINTS
To describe the PD parameters of BNT321 co-administered with mFOLFIRINOX, including ADCC and CDC.	In all patients who are dosed with at least one dose of IMP: • Percentage of patients with detectable and durable (measurable throughout time on trial) ADCC and/or CDC activity in Cycles 2 and 4, followed by sparse sampling through EOT.
To assess self-reported HRQoL of patients receiving mFOLFIRINOX + BNT321 versus mFOLFIRINOX.	In all patients who are dosed with at least one dose of IMP: • Change from baseline at end of Cycle 12 for patient-reported HRQoL using EORTC QLQ-C30. • Change from baseline at end of Cycle 12 for patient-reported HRQoL using EORTC QLQ-Pan26 questionnaires. • Change from baseline at end of Cycle 12 in combined item scores from EORTC QLQ-C30 and EORTC QLQ-Pan26.
Phase II	
To evaluate the safety and tolerability of mFOLFIRINOX with and without BNT321 as adjuvant therapy in patients with R0 or R1 resected PDAC.	In patients receiving at least one dose of IMP: • Occurrence of TEAEs within a patient including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of dose reduction and discontinuation of IMP within a patient due to TEAE. • Occurrence of abnormal laboratory parameters within a patient.
EXPLORATORY	
Phase I and II	
To explore the CA19-9 peripheral and tumor expression level correlates with clinical outcome and PK.	CA19-9 levels measured from patient peripheral blood and tumor will be correlated with each other, with antibody clearance rates (PK), and with clinical activity (if data allowing).
To explore the immune correlates with clinical outcome (ADCC, CDC, and cytokines).	• ADCC and CDC measurements will be correlated with clinical activity (if data allowing). • Peripheral blood cytokine profiles will be measured to understand effects of treatment on peripheral immune milieu and will be correlated with clinical activity (if data allowing).
To explore the relationship between ctDNA and DFS to understand if freedom from relapse can be measured using liquid biopsy and/or predicted ahead of a clinical disease recurrence.	ctDNA will be measured longitudinally through targeted sequencing of peripheral blood to quantify specific gene mutations associated with the tumor (if data allowing).
To explore the relationship of clinical outcome with baseline* status of tumor resection classification R0 or R1, and resection nodal status pN0 or pN1.	Tumor resection classified for each patient as R0 (no tumor <1 mm from margin) or R1 (tumor within 1 mm from margin), RCP**. Tumor nodal status classified for each patient as pN0 (no nodal disease) or pN1 (nodal involvement in resection).

OBJECTIVES	ENDPOINTS
To determine mFOLFIRINOX dose intensity when administered with and without BNT321.	• The mFOLFIRINOX relative dose intensity (RDI), defined for each patient as the fraction of (cumulative chemotherapy dose received/ treatment duration) planned dose intensity. • Number of patients receiving RDI ≥70%.

* Baseline is defined as last value prior to initiation of trial treatment.

** RCP classification. Tumors designated R0 CRM+ (R0 narrow) according to CRM concept will be stratified as R1 tumor in this trial.

Abbreviations: AE = adverse event; ADA = anti-drug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; AUC = area under the curve; CDC = complement-dependent cytotoxicity; C_{max} = maximum serum concentration that the drug achieved after administration; ctDNA = circulating tumor deoxyribonucleic acid; CTCAE = US National Cancer Institute Common Terminology Criteria for Adverse Events; CRM = circumferential resection margin; DLT = dose-limiting toxicity; EOT = end of treatment; ECG = electrocardiogram; EORTC = European organisation for research and treatment of cancer; HRQoL = health-related quality of life; ICF = informed consent form; IMP = investigational medicinal product; mDFS = median disease-free survival; NA = not applicable; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; PD = pharmacodynamic; PK = pharmacokinetics; RCP = Royal College of Pathologists; RFS = relapse-free survival; RDI = relative dose intensity; RP2D = recommended Phase II dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time required to reach C_{max}.

Overall design

This trial is designed as a Phase I/randomized Phase II open-label trial of mFOLFIRINOX ± BNT321 for adjuvant therapy in PDAC patients post R0 or R1 resection.

Screening will occur ≤21 days prior to Cycle 1 Day 1. Patients will provide written informed consent prior to the performance of any screening-related procedures. Eligibility status will be determined and be provided to the physician that submitted the patient's tissue for testing. Medical history includes cancer history (including but not limited to, lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases, including tuberculosis, surgeries, use of alcohol and/or drugs abuse and reproductive status).

The Phase I, dose escalation part of this trial will be a limited evaluation of two planned BNT321 dose levels in combination with mFOLFIRINOX chemotherapy (24 weeks) followed by BNT321 monotherapy (24 weeks). Following determination of the combination recommended Phase II dose (RP2D), the Phase II (randomized treatment) part of this trial will be initiated as an open-label 2-arm evaluation of mFOLFIRINOX ± BNT321 (24 weeks) followed by BNT321 monotherapy (24 weeks) in the combination arm only to complete the adjuvant therapy course. Treatment cycles are every 2 weeks (14 days).

The primary endpoint for the Phase I part of this trial is characterization of the safety and RP2D of BNT321 in combination with mFOLFIRINOX. The primary endpoint for Phase II of this trial is to assess the efficacy of mFOLFIRINOX + BNT321 versus mFOLFIRINOX alone as adjuvant therapy in PDAC patients post R0 or R1 resection by DFS.

Safety monitoring assessments will be performed 28 days after the last dose of BNT321. Information on survival follow-up, new anticancer and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits from BNT321

treatment discontinuation and approximately every 12 weeks until 5 years (unless the patient withdraws consent, or the sponsor terminates the trial).

For a detailed summary of Phase I and Phase II design, see Section 4.1.1 and 4.1.2, respectively.

For a summary of the trial as a flow diagram, see the Schema in Section 1.2.

For the planned assessments and visits, see the Schedule of Activities (SoA) in Section 1.3.

Duration of the trial periods

For both Phase I and Phase II, there will be a screening period of 21 days.

Phase I will consist of ~48 weeks of therapy, with 24 weeks of mFOLFIRINOX + BNT321 combination therapy followed by 24 weeks of BNT321 monotherapy. Phase II will be a randomized 2-arm trial, with 48 weeks of treatment in the combination arm (mFOLFIRINOX + BNT321) and 24 weeks of therapy in the control arm (mFOLFIRINOX only).

For both Phase I and Phase II, there will be a safety follow-up of 28 days ± 14 days after the last dose of trial treatment. DFS status will be recorded every 3 months for 2 years and then every 6 months for the next 3 years. Overall survival status will be recorded up to 60 months.

The maximum trial duration for each phase is ~5 years after the last patient's first treatment in the trial.

Trial population

This trial will enroll patients aged >18 years or of an age deemed to be an adult per local authorities with recently resected PDAC considered appropriate for adjuvant treatment with mFOLFIRINOX. All enrolled patients must meet the trial eligibility criteria listed in Section 5.

Number of patients

A maximum of 320 patients will be included in this trial. Approximately 20 patients will be enrolled into the Phase I part with BNT321 in combination with mFOLFIRINOX. Approximately 300 patients will be randomized at 1:1 into the Phase II part with BNT321 in combination with mFOLFIRINOX or mFOLFIRINOX only.

Trial treatments

Name	mFOLFIRINOX	BNT321
Trial treatment type	Chemotherapy	Monoclonal antibody
Dosage form	NA	BNT321 is provided as a single-use glass vial containing 8.0 mL of sterile solution CCI [redacted]
Unit dose strength(s)	• Oxaliplatin: 85 mg/m^2 • Leucovorin: 400 mg/m^2 • Irinotecan: 150 mg/m^2 • 5-FU: 2400 mg/m^2 *	0.5 CCI mg/kg based on cohort

Name	mFOLFIRINOX	BNT321
Dosage regimen	mFOLFIRINOX will be administered on the first day of each 14-day cycle (i.e., C1D1, C2D1, C3D1, and so on for a total of 12 cycles) using the following dose and schedule for each agent: • Oxaliplatin: Day 1 • Leucovorin: Day 1 • Irinotecan: Day 1 (starting 30 minutes after leucovorin) • 5-FU: Day 1	BNT321 will be incorporated into the mFOLFIRINOX regimen starting from the second cycle and after the completion of the 5-FU infusion (e.g., initially on C2D3).
Diluent	mFOLFIRINOX is prepared and administered according to institutional standards, in compliance with the package insert for each drug	
Route of administration	• Oxaliplatin: IV over 2 hours • Leucovorin: IV over 2 hours • Irinotecan: IV over 90 minutes • 5-FU: Continuous IV infusion over 46 hours, following oxaliplatin, leucovorin, and irinotecan	IV infusion
Sourcing	See the Pharmacy Manual	See the Pharmacy Manual
Packaging and labeling	For details see the Pharmacy Manual	For details see the Pharmacy Manual

* Reduced 5-FU dose may be implemented for patients with DPD deficiency, per the discretion of the treating physician.
Abbreviations: 5-FU = 5-fluorouracil; CnDn = cycle number day number; DPD = dihydropyrimidine dehydrogenase; IV = intravenous; NA = not applicable.

Statistical analyses

The primary analysis in DFS will be performed once ~164 DFS events (in total) from the Phase II part have occurred in both arms combined. CCI [redacted]

1.2 Schema

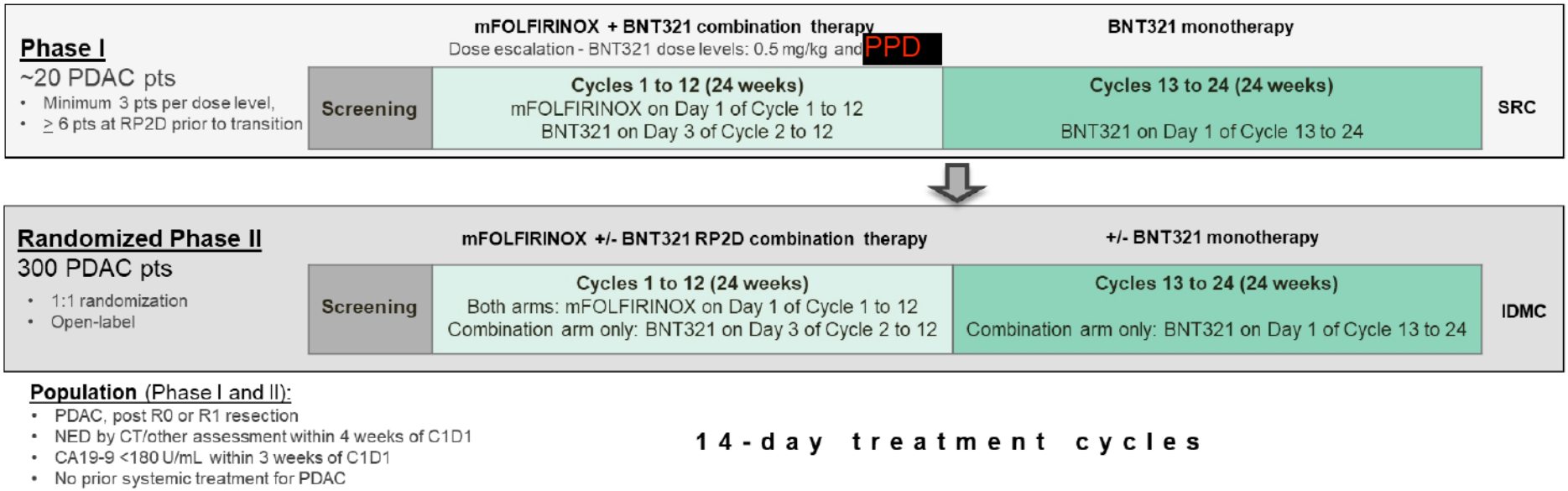

Figure 1: Trial design

The Phase I/II trial will test the safety, tolerability, and efficacy of BNT321 as an adjuvant with chemotherapy mFOLFIRINOX in PDAC patients.

Abbreviations: BNT321 = monoclonal antibody against CA19-9 (test item); C1D1 = Cycle 1 Day 1; CA19-9 = sialyl-Lewis A (sLe^a) antigen; CT = computed tomography; mFOLFIRINOX = (modified) oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil; IDMC = independent data monitoring committee; NED = no evidence of disease; PDAC = pancreatic ductal adenocarcinoma; pts = patients; RP2D = recommended Phase II dose; SRC = safety review committee.

1.3 Schedule of activities

The schedule of activities (SoA) and procedures for Phase I (mFOLFIRINOX + BNT321) is shown in Table 1 and for Phase II (mFOLFIRINOX ± BNT321) is shown in Table 2 and Table 4.

Assessments should be performed before trial treatment administration (on the applicable days) or any planned intervention, with the exception of post-dose blood sampling for exploratory PD, PK, immunogenicity assessments and any samples required for supplementary R&D. For the primary DFS endpoint, which includes disease assessment by computed tomography (CT)/magnetic resonance imaging (MRI) and serum CA19-9, analyses must be performed at screening (baseline post-operative scans <4 weeks and CA19-9 within 3 weeks of Cycle 1 Day 1 are required). After Cycle 1 Day 1 scans and CA19-9 must be performed every 3 months (12 weeks) for 2 years, and then every 6 months for 3 years thereafter (±7 days). Patients should be evaluated with the same imaging and assessment method (CT or MRI) throughout the trial.

Investigators must make every effort to adhere to the given visit schedule and to perform all assessments within the given time for each visit as specified in the SoA tables. This is especially true for the PK assessments according to the SoA in Table 3. Lost to follow-ups should be avoided and every effort should be taken by the trial site to follow-up on the whereabouts of the patients and their survival status.

Table 1: Schedule of activities and procedures – Phase I (mFOLFIRINOX + BNT321)

Treatment cycle (14 d)	SCR [2]	Cycle 1		Cycle 2			Cycle 3			Cycle 4-12			BNT321 monotherapy Cycles 13-24 [3]	EOT [4]	Safety FU [5]	Survival FU [6]
Days [1]		1	8	1	3	8	1	3	8	1	3	8	1			
Informed consent [7]	X															
Eligibility	X															
Medical history [8]	X															
TB screening [9]	X															
DPD deficiency screening [10]	X															
UGT1A1 mutation screening [11]	X															
Demographics	X															
Height	X															
Weight [12]	X	X		X			X			X			X	X		
Physical examination	X													X		
Symptom-directed exam [13]		X	[X]	X	[X]	[X]	X	[X]	[X]	X	[X]	[X]	X			
Vital signs [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [15]	X	X	X	X	X	X	X	X	X	X	X	X	X			
HRQoL [16]	X						X			[X]			[X]	X		X
Concomitant medications [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECGs [19]	X	X		X			X			[X]			X	X		
Hematology [20]	X	X	X	X		X	X		X	X		X	X	X	X	

Treatment cycle (14 d)	SCR [2]	Cycle 1		Cycle 2			Cycle 3			Cycle 4-12			BNT321 monotherapy Cycles 13-24 [3]	EOT [4]	Safety FU [5]	Survival FU [6]
Days [1]		**1**	**8**	**1**	**3**	**8**	**1**	**3**	**8**	**1**	**3**	**8**	**1**			
Chemistry [21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum amylase [22]		X		X	X		X	X		X	X		X	X		
Haptoglobin [22]		X		X	X		X	X		X	X		X	X		
Serum lipase [23]		X		X	X		X	X		X	X		X	X		
GGT [23]		X		X	X		X	X		X	X		X	X		
Urinalysis [24]	X															
Urine pregnancy test [25]	X	X		X			X			X			X	X		
CA19-9 [26]	X	X			X	X		X		[X]	X		X	X		X
Pharmacokinetics [27]					X	X		X	X	[X]	X		X			
Disease assessment [28]	X									X			X	X		X
Anti-drug antibody [29]		X					X			[X]			X	X		
ADCC, CDC, and cytokines [30]		X			X	X					X	X	X			
Tumor biopsy [31]	X													[X]		
ctDNA [32]		X								[X]			X	X		
BNT321 administration [33]					X			X		[X] [33]	X		X			
mFOLFIRINOX administration [34]		X		X			X			X						
Survival status [6]																X

X – Required, **[X]** – Optional, or not with every visit

1. Window for all procedures, except those performed on Day 3 of all cycles, is ±3 days of the scheduled day. Day 3 procedures are performed without window.
2. Screening visit performed within 21 days prior to Cycle 1 Day 1 and may be repeated within 7 days of C1D1 if requested by Medical Monitor (e.g., borderline eligibility or clinical instability).
3. BNT321 monotherapy will continue every two weeks on Day 1 of every cycle for an additional 12 cycles to complete the adjuvant therapy course.
4. End of treatment (EOT) visit will be performed on the day the decision is made to discontinue BNT321 administration or at the completion of 24 cycles of therapy.
5. Safety FU visit is performed 28 days (±14 days) after last dose of BNT321. EOT and Safety FU visits may be combined for patients who discontinue BNT321 outside of a clinic visit or who had no Grade 2 or higher toxicity at their last trial visit.
6. Survival FU visits will be performed beginning 12 weeks (±30 days) after safety FU until 5 years after C1D1. DFS status will be recorded every 3 months for 2 years and then every 6 months for the next 3 years. All patients will be contacted, or the medical records reviewed to report survival status, disease progression and to provide an update on CA19-9 and tumor imaging. Initiation of any additional therapy for pancreatic cancer will be documented.
7. Informed consent will be obtained prior to performing any trial-specific screening procedures.
8. Medical history should include but not limited to lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases, including tuberculosis, surgeries, use of alcohol and/or drugs abuse and reproductive status.
9. For patients whom the treating physician considers to be at increased risk for infection, in which case testing should be done according to institutional practice standards at screening.
10. DPD testing to be done at screening if required by local regulations.
11. UGT1A1 testing at screening if required by local regulations.
12. Obtained at screening, Day 1 of every cycle and EOT, may be reduced to every other cycle based on investigator's discretion.
13. Symptom-directed physical examinations will be performed on Day 1 of each cycle prior to treatment administration and at any visit where the patient indicates new symptoms that require evaluation or based on investigator's discretion.
14. Vital signs e.g., blood pressure, body temperature, heart rate, and respiratory rate will be recorded on each designated visit day and prior to and approximately every 30 minutes until at least 2 h after completion of BNT321 infusion. On mFOLFIRINOX treatment visits, vital signs will be performed prior to start of infusion. On non-treatment visits, vital signs will be performed once. Vital signs will also be performed at the Safety FU visit.
15. Performance status must be recorded as ECOG. Refer to the Appendix 1 for conversion between ECOG and KPS.
16. HRQoL will be performed at screening, Day 1 of every other treatment cycle starting from Cycle 3 to 24, at EOT, and at every disease assessment (see Footnote 28 for timing of disease assessments).
17. Recorded from 21 days prior to the first administration of mFOLFIRINOX to EOT or safety FU visits. Includes prescription medications, over-the-counter medications, and supplements.
18. Adverse events will be collected and reported from the signing of the trial-specific ICF until safety FU.
19. ECGs will be performed at screening and on Day 1 of every cycle for C1 through C3. On these days ECGs are obtained prior to treatment, at t_{max}, and at end of last mFOLFIRINOX infusion. Investigators may obtain ECGs at additional timepoints in Cycle 4 to 12 if indicated based on results in Cycle 1 to 3. ECGs will also be obtained prior to first BNT321 administration on Cycle 13, and at EOT and as clinically indicated during BNT321 monotherapy per assessment of the trial investigator. ECGs are performed as triplicate exams at all study timepoints per Section 8.3.3.

20. Complete blood count (CBC) with differential to include WBC, RBC, HGB, HCT, platelets, MCV, and MCH to be performed at screening and for every cycle on Day 1 and Day 8 until EOT and at safety FU visit.
21. Blood chemistry to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, and uric acid to be performed at screening, for Cycle 1 on Day 1 and Day 8 and for the next three cycles Day 1, 3 and 8 and thereafter once every week and at safety FU visit. During BNT321 monotherapy every cycle on Day 1 and Day 3 and as needed based on investigator's discretion.
22. Serum amylase and haptoglobin will be performed on C1D1 and thereafter on Day 1 and Day 3 of every cycle starting at Cycle 2 and at EOT.
23. Serum GGT and lipase will be performed on C1D1 and thereafter on Day 1 and Day 3 of every cycle starting at Cycle 2 and at EOT.
24. To include color, appearance, glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocyte esterase. If warranted by dipstick analysis, microscopic analysis to include RBC, WBC, casts, crystals, epithelial cells, and bacteria. Will be performed at screening and when clinically indicated.
25. For POCBPs only.
26. CA19-9 will be measured from blood collected at screening (post-operative measurement required within 3 weeks of C1D1), C1D1, every two weeks until EOT on days of BNT321 administration, at disease assessment time points detailed in Footnote 25 and during survival FU visit. For all collections on BNT321 administration days, blood will be collected both pre-infusion and post-infusion (end of infusion [EoI] +5 min [± 5 min]), for further details, refer to Table 3.
27. For a full pharmacokinetic profile and in-depth sampling, blood will be collected on C2D3 and C3D3, (pre-infusion, EoI +5 min [±5 min], EoI +30 min [±5 min], EoI +1 h [±5 min] and EoI +4 h [±30 min]). For Cycles 4 onwards, only C_{trough} (pre-infusion) and C_{max} (EoI +5 min [±5 min]) will be drawn on days of BNT321 administration. For further details, refer to Table 3.
28. Disease assessment will consist of imaging by CT/MRI scan and serum CA19-9 and will be performed at screening (baseline post-operative scans within 4 weeks of C1D1 and serum CA19-9 within 3 weeks of C1D1 are required), and then after C1D1 every 3 months (12 weeks) for 2 years, and then every 6 months for 3 years (±7 days). CT with contrast or MRI (as appropriate for patient, or multiparametric MRI following an inconclusive CT). Patients should be evaluated with the same imaging method (CT or MRI) throughout the trial.
29. Anti-drug antibodies will be measured from blood collected prior to dosing of mFOLFIRINOX on C1D1, C3D1, C6D1, C9D1, C12D1, and before dosing of BNT321 on C18D1, C24D1 and at EOT.
30. ADCC, CDC and cytokines will be measured from blood collected prior to dosing of mFOLFIRINOX and/or BNT321 on days of trial drug administration. Collected on the following days: C1D1, C2D3, C2D8, C4D3, C4D8, C13D1, C13D5, C22D1 and C22D5. For Cycle 4, collections should be adjusted to C4D1 and C4D5 if BNT321 administration is given on C4D1. Whole blood collected for PBMC isolation for ADCC assessment will only be collected if logistically manageable.
31. FFPE tumor tissue from surgical resection is required during screening. In the event of progression, if a biopsy is performed, a sample (optional) should be requested.
32. For ctDNA assessment, blood will be collected at C1D1, C6D1, C12D1, C18D1, C20D1, C24D1 and at time of progression. Additional information on sample submission is included in the laboratory manuals.
33. BNT321 will be administered following the completion of the 5-FU infusion (i.e., on Day 3 of each cycle, from Cycle 2). Patients in Phase I of the trial who have completed at least 8 weeks on trial (i.e., have completed the first four cycles), will have the option of receiving BNT321 earlier during each course of the combination mFOLFIRINOX + BNT321 treatment (e.g., on Day 1 of each cycle rather than Day 3, if tolerated and at discretion of the investigator). Day 1 administration of BNT321 may be utilized for the Phase II part of the trial, following review of Phase I safety data and alignment with the SRC. During the BNT321 monotherapy cycles, BNT321 will be given on Day 1 of every 14-day cycle as per Footnote 3.
34. mFOLFIRINOX will be administered as per Section 6.1.

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CnDn = cycle number day number; CA19-9 = sialyl-Lewis A (sLe^a) antigen; CDC = complement-dependent cytotoxicity; CT = computed tomography; ctDNA = circulating tumor DNA; d = days; DFS = disease-free survival; DPD = dihydropyrimidine dehydrogenase; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoI = end of infusion; EOT = end of treatment; 5-FU = 5-flourouracil; FFPE = formalin-fixed paraffin-embedded tissue; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; HGB = hemoglobin; HCT = hematocrit; HRQoL = health-related quality of life; IHC = immunohistochemistry; KPS = Karnofsky performance status; min = minutes; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PDAC = pancreatic adenocarcinoma; PK = pharmacokinetics; POCBP = patient of childbearing potential; RBC = red blood cell; SCR = screening; SRC = safety review committee; TB = tuberculosis; t_{max} = time required to reach C_{max}; UGT1A1 = UDP glucuronosyltransferase family 1 member A1; WBC = white blood cell.

Table 2: Schedule of activities and procedures – Randomized Phase II; combination arm (mFOLFIRINOX + BNT321)

Treatment cycle (14 d)	SCR [2]	Cycle 1	Cycle 2			Cycle 3		Cycle 4-12			BNT321 monotherapy Cycle 13-24 [3]	EOT [4]	Safety FU [5]	Survival FU [6]
Days [1]		1	1	3	8	1	3	1	3	8	1			
Informed consent [7]	X													
Eligibility	X													
Medical history [8]	X													
Demographics	X													
TB screening [9]	X													
DPD deficiency screening [10]	X													
UGT1A1 mutation screening [11]	X													
Height	X													
Weight [12]	X	X	X			X		X			X	X		
Physical examination	X											X		
Symptom-directed exam [13]		X	X	[X]	[X]	X	[X]	X	[X]	[X]	X			
Vital signs [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [15]	X	X	X			X		X			X	X		
HRQoL [16]	X					X		[X]			[X]	X		X
Concomitant medications [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [18]		X	X	X	X	X	X	X	X	X	X	X	X	
ECGs [19]	X	X	X			X		[X]				X		
Hematology [20]	X	X	X			X		X			X	X	X	
Chemistry [21]	X	X	X			X		X			X	X	X	

Treatment cycle (14 d)	SCR [2]	Cycle 1	Cycle 2			Cycle 3		Cycle 4-12			BNT321 monotherapy Cycle 13-24 [3]	EOT [4]	Safety FU [5]	Survival FU [6]
Days [1]		**1**	**1**	**3**	**8**	**1**	**3**	**1**	**3**	**8**	**1**			
Serum amylase [22]		X	X			X		X			X	X		
Serum lipase [22]		X	X			X		X			X	X		
Haptoglobin [22]		X	X			X		X			X	X		
GGT [23]	X	X	X			X		X			X	X		
Urinalysis [24]	X													
Urine pregnancy test [25]	X	X	X			X		X			X	X		
CA19-9 [26]	X	X		X	X		X	[X]**	X**		X**	X		X
Pharmacokinetics [27]				X	X		X	[X]**	X**		X**			
Disease assessment [28]	X							X			X	X		X
Anti-drug antibody [29]		X				X		[X]				X		
ADCC, CDC, and cytokines [30]		X		X	X				X	X	X			
Tumor biopsy [31]	X											[X]		
ctDNA [32]		X						[X]			X	X		
Randomization [33]	X [33]													
BNT321 administration [34]				X			X		X		X			
mFOLFIRINOX administration [35]		X	X			X		X						
Survival status [6]														X

X – Required, **[X]** – Optional, or not with every visit
** - Every fourth cycle (e.g., Cycle 4, Cycle 8, Cycle 12 etc.)

1. Window for all procedures, except those performed on Day 3 of all cycles, is ±3 days of the scheduled day. Day 3 procedures are performed without window.
2. Screening visit performed within 21 days prior to Cycle 1 Day 1 and may be repeated within 7 days of C1D1 if requested by Medical Monitor (e.g., borderline eligibility or clinical instability).
3. BNT321 monotherapy will continue every two weeks on Day 1 of every cycle for an additional 12 cycles to complete the adjuvant therapy course.
4. End of treatment (EOT) visit will be performed on the day the decision is made to discontinue BNT321 administration or at the completion of 24 cycles of therapy.
5. Safety FU visit is performed 28 days (±14 days) after last dose of BNT321. EOT and safety FU visits may be combined for patients who discontinue BNT321 outside of a clinic visit or who had no Grade 2 or higher toxicity at their last trial visit.
6. Survival FU visits will be performed beginning 12 weeks (±30 days) after safety FU until 5 years after C1D1. DFS status will be recorded every 3 months for 2 years and then every 6 months for the next 3 years. All patients will be contacted, or the medical records reviewed to report survival status, disease progression and to provide an update on CA 19-9 and tumor imaging. Initiation of any additional therapy for pancreatic cancer will be documented.
7. Informed consent will be obtained prior to performing any trial-specific screening procedures.
8. Medical history should include but not limited to lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases, including tuberculosis, surgeries, use of alcohol and/or drugs abuse and reproductive status.
9. For patients whom the treating physician considers to be at increased risk for infection, in which case testing should be done according to institutional practice standards at screening.
10. DPD testing to be done at screening if required by local regulations.
11. UGT1A1 testing at screening if required by local regulations.
12. Obtained at screening, Day 1 of every cycle and EOT, may be reduced to every other cycle based on investigator's discretion.
13. Symptom-directed physical examinations will be performed on Day 1 of each cycle prior to treatment administration and at any visit where the patient indicates new symptoms that require evaluation or based on investigator's discretion.
14. Vital signs e.g., blood pressure, body temperature, heart rate, and respiratory rate will be recorded on each designated visit days and prior to and approximately every 30 minutes until at least 2 h after completion of BNT321 infusion. On mFOLFIRINOX treatment visits, vital signs will be performed prior to start of infusion. On non-treatment visits, vital signs will be performed once. Vital signs will also be performed at the safety FU visit.
15. Performance status must be recorded as ECOG and will be performed at screening, Day 1 of every cycle, at EOT, and as needed according to investigator's discretion based on new symptoms and/or medical concerns. Refer to the Appendix 1 for conversion between ECOG and KPS.
16. HRQoL will be performed at screening, Day 1 of every other treatment cycle starting from Cycle 3 to 24, at EOT, and at every disease assessment (see Footnote 28 for timing of disease assessments).
17. Recorded from 21 days prior to the first administration of BNT321 to EOT or safety FU visits. Includes prescription medications, over-the-counter medications, and supplements.
18. Adverse events will be collected and reported from the signing of the trial-specific ICF until safety FU.
19. ECGs will be performed at screening and on Day 1 of every cycle for C1 through C3. On these days ECGs are obtained prior to treatment, at t_{max}, and at end of last mFOLFIRINOX infusion. Investigators may obtain ECGs at additional timepoints in Cycle 4 to 12 if indicated based on results in Cycle 1 to 3. ECGs will also be obtained

prior to first BNT321 administration on Cycle 13, and at EOT and as clinically indicated during BNT321 monotherapy per assessment of the trial investigator. ECGs are performed as triplicate exams at all study timepoints per Section 8.3.3.

20. Complete blood count (CBC) with differential to include WBC, RBC, HGB, HCT, platelets, MCV, and MCH to be performed at screening, Day 1 of every cycle, EOT, at safety FU visit, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
21. Blood chemistry to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, and uric acid to be performed at screening, Day 1 of every cycle,EOT, at safety FU visit, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
22. Serum amylase, -lipase and haptoglobin will be performed on Day 1 of every cycle and EOT, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
23. GGT will be performed at screening and on Day 1 of every cycle and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
24. To include color, appearance, glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocyte esterase. If warranted by dipstick analysis, microscopic analysis to include RBC, WBC, casts, crystals, epithelial cells, and bacteria. Will be performed at screening, and when clinically indicated.
25. For POCBPs only.
26. CA19-9 will be measured from blood collected at screening (post-operative measurement required within 3 weeks of C1D1), C1D1, during PK sampling, on days of BNT321 administration and at disease assessment time points detailed in Footnote 25. During BNT321 monotherapy every 3 months (12 weeks), every 2 years (±7 days), and then every 6 months for 3 years. For all collections on BNT321 administration days, blood will be collected both pre-infusion and post-infusion (end of infusion [EoI] +5 min [± 5 min]). For further details, refer to Table 3.
27. For a full pharmacokinetic profile and in-depth sampling, blood will be collected on C2D3 and C3D3, (pre-infusion, EoI +5 min [± 5 min], EoI +1 h [±15 min] and EoI +4 h [±30 min]). For Cycles 4 onwards, only C_{trough} (pre-infusion) and C_{max} (EoI +5 min [±5 min]) will be drawn on day of BNT321 administration. All other timepoints will include only one blood draw timepoint per day. For further details, refer to Table 3.
28. Disease assessment will consist of imaging by CT/MRI scan and serum CA19-9 and will be performed at screening (baseline post-operative imaging within 4 weeks of C1D1 and serum CA19-9 within 3 weeks of C1D1 are required), and then after C1D1 every 3 months (12 weeks) for 2 years and then every 6 months for 3 years (±7 days). CT with contrast or MRI (as appropriate for patient, or multiparametric MRI following an inconclusive CT). Patients should be evaluated with the same imaging method (CT or MRI) throughout the trial.
29. Anti-drug antibodies will be measured from blood collected prior to dosing of mFOLFIRINOX on C1D1, C3D1, C6D1, and at EOT.
30. ADCC, CDC and cytokines will be measured from blood collected prior to dosing of mFOLFIRINOX and/or BNT321 on days of trial drug administration. Collected on the following days: C1D1, C2D3, C2D8, C4D3, C4D8, C16D1 and C16D5. For Cycle 4 collections, should be adjusted to C4D1 and C4D5 if BNT321 administration is given on C4D1. Whole blood collected for PBMC isolation for ADCC assessment will only be collected if logistically manageable.
31. FFPE tumor tissue from surgical resection is required during screening. In the event of progression, if a biopsy is performed, a sample (optional) should be requested.
32. For ctDNA assessment, blood will be collected at C1D1, C6D1, C18D1, and at time of progression. Additional information on sample submission is included in the laboratory manuals.
33. Randomization should be done between Day -3 and C1D1.

34. BNT321 in randomized Phase II part of this trial will be administered following the completion of the 5-FU infusion (i.e., on Day 3 of each cycle from Cycle 2 onwards and on Day 1 during the monotherapy part of the protocol, as per Footnote 3). Day 1 administration of BNT321 may be utilized throughout the Phase II part of the trial, following review of Phase I safety data and alignment with the SRC.
35. mFOLFIRINOX will be administered as per Section 6.1.

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CnDn = cycle number day number; CA19-9 = sialyl-Lewis A (sLe^a) antigen; CDC = complement-dependent cytotoxicity; CT = computed tomography; ctDNA = circulating tumor DNA; d = days; DFS = disease-free survival; DPD = dihydropyrimidine dehydrogenase; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EoI = end of infusion; EOT = end of treatment; 5FU = 5-flourouracil; FFPE = formalin-fixed paraffin-embedded tissue; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; HGB = hemoglobin; HCT = hematocrit; HRQoL = health-related quality of life; IHC = immunohistochemistry; KPS = Karnofsky performance status; min = minutes; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PDAC = pancreatic adenocarcinoma; PK = pharmacokinetics; POCBP = patient of childbearing potential; RBC = red blood cell; SCR = screening; SRC = safety review committee; TB = tuberculosis; t_{max} = time required to reach C_{max}; UGT1A1 = UDP glucuronosyltransferase family 1 member A1; WBC = white blood cell.

Table 3: Supplementary table for PK – Phase I and Randomized Phase II - combination arm (mFOLFIRINOX + BNT321)

Assessment for Phase I	SCR	Cycle 1	Cycle 2–3						Cycle 4–24	
		Day 1	Day of BNT321 administration					Day 8	Day of BNT321 administration	
			Predose	EoI +5 min [±5 min]	EoI +30 min [±5 min]	EoI +1 h [±5 min]	EoI +4 h [±30 min]		Predose	EoI +5 min [±5 min]
Blood sample for BNT321 pharmacokinetics			X	X	X	X	X	X	X	X
Blood sample for CA19-9	X	X	X	X				X*	X	X

Assessment for Randomized Phase II-combination arm only (mFOLFIRINOX + BNT321)	SCR	Cycle 1	Cycle 2–3						Cycle 4–24	
		Day 1	Day of BNT321 administration					Day 8	Day of BNT321 administration	
			Predose	EoI +5 min [±5 min]	EoI +30 min [±5 min]	EoI +1 h [±5 min]	EoI +4 h [±30 min]		Predose	EoI +5 min [±5 min]
Blood sample for BNT321 pharmacokinetics			X	X		X	X	X*	X**	X**
Blood sample for CA19-9	X	X	X	X				X*	X**	X**

EoI = end of infusion; min = minutes; h = hours; SCR = screening.
* = only on Cycle 2; ** = every fourth cycle (e.g Cycle 4, Cycle 8, Cycle 12 etc.)

Table 4: Schedule of activities and procedures – Randomized Phase II; control arm (mFOLFIRINOX)

Treatment cycle (14 d)	SCR [2]	Cycle 1	Cycle 2			Cycle 3		Cycle 4-12			EOT [3]	Safety FU [4]	Survival FU [5]
Days [1]		1	1	3	8	1	3	1	3	8			
Informed consent [6]	X												
Eligibility	X												
Medical history [7]	X												
TB screening [8]	X												
DPD deficiency screening [9]	X												
UGT1A1 mutation screening [10]	X												
Demographics	X												
Height	X												
Weight [11]	X	X	X			X		X			X		
Physical examination	X												
Symptom-directed exam [12]		X	X	[X]	[X]	X	[X]	X	[X]	[X]	X		
Vital signs [13]	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status [14]	X	X	X			X		X			X		
HRQoL [15]	X					X		[X]			X		X
Concomitant medications [16]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [17]		X	X	X	X	X	X	X	X	X	X	X	
ECGs [18]	X	X	X			X		[X]			X		
Hematology [19]	X	X	X			X		X			X	X	
Chemistry [20]	X	X	X			X		X			X	X	
Serum amylase [21]		X	X			X		X			X		

Treatment cycle (14 d)	SCR [2]	Cycle 1	Cycle 2			Cycle 3		Cycle 4-12			EOT [3]	Safety FU [4]	Survival FU [5]
Days [1]		1	1	3	8	1	3	1	3	8			
Serum lipase [21]		X	X			X		X			X		
Haptoglobin [21]		X	X			X		X			X		
GGT [22]	X	X	X			X		X			X		
Urinalysis [23]	X												
Urine pregnancy test [24]	X	X	X			X		X			X		
CA19-9 [25]	X	X		X	X		X	[X]**	X**		X		X
Disease assessment [26]	X							X			X		X
ADCC, CDC, and cytokines [27]		X		X	X				X	X			
Tumor biopsy [28]	X										[X]		
ctDNA [29]		X						[X]			X		[X]
Randomization [30]	X [30]												
mFOLFIRINOX administration [31]		X	X			X		X					
Survival status [5]													X

X – Required, **[X]** – Optional, or not with every visit

** - Every fourth cycle (e.g., Cycle 4, Cycle 8, Cycle 12 etc.)

1. Window for all procedures, except those performed on Day 3 of all cycles, is ±3 days of the scheduled day. Day 3 procedures are performed without window.
2. Screening visit performed within 21 days prior to Cycle 1 Day 1 and may be repeated within 7 days of C1D1 if requested by Medical Monitor (e.g., borderline eligibility or clinical instability).
3. End of treatment (EOT) visit will be performed at Week 25 or on the day the decision is made to discontinue mFOLFIRINOX.
4. Safety FU visit is performed 28 days (±14 days) after last dose of mFOLFIRINOX. EOT and safety FU visits may be combined for patients who discontinue mFOLFIRONOX outside of a clinic visit or who had no Grade 2 or higher toxicity at their last trial visit.

5. Survival FU visits will include Week 35 for ctDNA and Week 48 for disease assessment and ctDNA. Survival FU will begin 12 weeks (±30 days) after safety FU until 5 years after C1D1. DFS status will be recorded every 3 months for 2 years and then every 6 months for the next 3 years. All patients will be contacted, or the medical records reviewed to report survival status, disease progression and to provide an update on CA19-9 and tumor imaging. Initiation of any additional therapy for pancreatic cancer will be documented.
6. Informed consent will be obtained prior to performing any trial-specific screening procedures.
7. Medical history should include but not limited to lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and reproductive status.
8. For patients whom the treating physician considers to be at increased risk for infection, in which case testing should be done according to institutional practice standards at screening.
9. DPD testing to be done at screening if required by local regulations.
10. UGT1A1 testing at screening if required by local regulations.
11. Obtained at screening, Day 1 of every cycle, and EOT, may be reduced to every other cycle based on investigator's discretion.
12. Symptom-directed physical examinations will be performed on Day 1 of each cycle prior to treatment administration and at any visit where the patient indicates new symptoms that require evaluation or based on investigator's discretion.
13. Vital signs e.g., blood pressure, body temperature, heart rate, and respiratory rate will be performed prior to start of infusion. On non-treatment visits, vital signs will be performed once. Vital signs will also be performed at the safety FU visit.
14. Performance status must be recorded as ECOG and will be performed at screening and Day 1 of every cycle, at EOT, and as needed according to investigator's discretion based on new symptoms and/or medical concerns. Refer to the Appendix 1 for conversion between ECOG and KPS.
15. HRQoL will be performed at screening, Day 1 of every other treatment cycle starting from Cycle 3 to 12, at EOT and at every disease assessment (see Footnote 26 for timing of disease assessments).
16. Recorded from 21 days prior to the first administration of mFOLFIRINOX to EOT or safety FU visits. Includes prescription medications, over-the-counter medications, and supplements.
17. Adverse events will be collected and reported from the signing of the trial-specific ICF until safety FU.
18. ECGs will be performed at screening and on Day 1 of every cycle for C1 through C3. On these days ECGs are obtained prior to treatment, at t_{max}, and at end of last mFOLFIRINOX infusion. Investigators may obtain ECGs at additional timepoints in Cycle 4 to 12 if indicated based on results in Cycle 1 to 3. ECGs will also be obtained prior to first BNT321 administration on Cycle 13, and at EOT and as clinically indicated during BNT321 monotherapy per assessment of the trial investigator. ECGs are performed as triplicate exams at all study timepoints per Section 8.3.3.
19. Complete blood count (CBC) with differential to include WBC, RBC, HGB, HCT, platelets, MCV, and MCH to be performed at screening, Day 1 of every cycle, Week 25/EOT, at safety FU visit, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
20. Blood chemistry to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, and uric acid to be performed at screening, Day 1 of every cycle, Week 25/EOT, at safety FU visit, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
21. Serum amylase, lipase and haptoglobin will be performed on Day 1 of every cycle, Week 25/EOT, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.

22. GGT will be performed at screening and on Day 1 of every cycle, Week 25/EOT, and as needed according to investigator's discretion based on new symptoms and/or medical concerns.
23. To include color, appearance, glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocyte esterase. If warranted by dipstick analysis, microscopic analysis to include RBC, WBC, casts, crystals, epithelial cells, and bacteria. Will be performed at screening, and when clinically indicated.
24. For POCBPs only.
25. CA19-9 will be measured from blood collected at screening (post-operative measurement required within 3 weeks of C1D1), C1D1, at EOT and at disease assessment timepoints detailed in Footnote 23.
26. Disease assessment will consist of imaging by CT/MRI scan and serum CA19-9 and will be performed at screening (baseline post-operative imaging within 4 weeks of C1D1 and serum CA19-9 within 3 weeks of C1D1 are required), and then after C1D1 every 3 months (12 weeks) for 2 years, and then every 6 months for 3 years (±7 days). CT with contrast or MRI (as appropriate for patient, or multiparametric MRI following an inconclusive CT). Patients should be evaluated with the same imaging method (CT or MRI) throughout the trial.
27. ADCC, CDC and cytokines will be measured from blood collected prior to dosing of mFOLFIRINOX. Collected on the following days: C1D1, C2D3, C2D8, C4D3, and C4D8. Whole blood collected for PBMC isolation for ADCC assessment will only be collected if logistically manageable.
28. FFPE tumor tissue from surgical resection is required during screening. In the event of progression, if a biopsy is performed, a sample (optional) should be requested.
29. For ctDNA assessment, blood will be collected at C1D1, C6D1, Week 35, Week 48, EOT visit and at time of progression, if applicable. Additional information on sample submission is included in the laboratory manuals.
30. Randomization should be done between Day -3 and C1D1.
31. mFOLFIRINOX will be administered as per Section 6.1.

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CnDn = cycle number day number; CA19-9 = sialyl-Lewis A (sLe^a) antigen; CDC = complement-dependent cytotoxicity; CT = computed tomography; ctDNA = circulating tumor DNA; d = days; DFS = disease-free survival; DPD = dihydropyrimidine dehydrogenase; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; 5FU = 5-flourouracil; FFPE = formalin-fixed paraffin-embedded tissue; FU = follow-up; GGT = gamma-glutamyl transferase; h = hours; HGB = hemoglobin; HCT = hematocrit; HRQoL = health-related quality of life; IHC = immunohistochemistry; KPS = Karnofsky performance status; min = minutes; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; PDAC = pancreatic adenocarcinoma; PK = pharmacokinetics; POCBP = patient of childbearing potential; RBC = red blood cell; SCR = screening; TB = tuberculosis; t_{max} = time required to reach C_{max}; UGT1A1 = UDP glucuronosyltransferase family 1 member A1; WBC = white blood cell.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS/TERMS

Abbreviation/Term	Explanation
AE	Adverse event
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
AUC	Area under the curve
AST	Aspartate aminotransferase
ADCC	Antibody-dependent cell-mediated cytotoxicity
CA19-9	Sialyl-Lewis A (sLe^a) antigen
CnDn	Cycle number day number
CRO	Contract research organization
CT	Computed tomography
DCO	Data cut-off
DFS	Disease-free survival
DLT	Dose-limiting toxicity
eCRF	Case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture (system)
EOT	End of treatment
EoI	End of infusion
FFPE	Formalin-fixed paraffin-embedded tissue
FOLFIRINOX	Leucovorin, 5-fluorouracil (5-FU), irinotecan, and oxaliplatin
FU	Follow-up
GGT	Gamma-glutamyl transferase
HRQoL	Health-related quality of life
[redacted]	[redacted]
IB	Investigator's brochure
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IRR	Infusion-related reactions
ITT	Intent to treat
IWRS	Interactive web response system
KPS	Karnofsky performance status
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
mDFS	Median disease-free survival

Abbreviation/Term	Explanation
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute common terminology criteria for adverse events
OS	Overall survival
PDAC	Pancreatic ductal adenocarcinoma
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
POCBP	Patient of childbearing potential
RBC	Red blood cell
RCP	Royal College of Pathologists
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SoA	Schedule of activities
SoC	Standard-of-care
SOC	System organ class
SRC	Safety review committee
TB	Tuberculosis
TEAE	Treatment-emergent adverse events
UGT1A1	UDP glucuronosyltransferase family 1 member A1
WBC	White blood cell

2 INTRODUCTION

2.1 Trial rationale

For early stage, non-metastatic PDAC, complete surgical resection can result in cure for some patients. mFOLFIRINOX is currently adapted as an adjuvant therapy for resectable PDAC, however, relapse in this setting is common, with a 3-year disease-free survival (DFS) realized in less than 40% of patients (Conroy et al. 2018). Improved PDAC adjuvant treatment options are therefore a high priority for clinical development.

BNT321-02 is planned as a Phase I/II clinical trial to evaluate the safety, multicycle tolerability, and efficacy of mFOLFIRINOX ± BNT321 as a novel combination adjuvant therapy for patients with R0 or R1 resected PDAC. The Phase I part of this trial will determine the safety and BNT321 recommended Phase II dose (RP2D) together with chemotherapy for previously untreated patients who are eligible to receive 24 weeks of PDAC adjuvant therapy. A key secondary pharmacodynamic endpoint in Phase I is determining the extent of complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) effects in peripheral blood longitudinally over an extended adjuvant therapy course. The safety and feasibility of continuing BNT321 monotherapy for 24 weeks beyond the initial 24 weeks of combination treatment will also be determined.

The BNT321-02 randomized Phase II part of this trial is a dedicated evaluation of the potential for mFOLFIRINOX + BNT321 combination therapy to provide meaningful clinical benefit over standard adjuvant mFOLFIRINOX. The Phase II part is designed to detect a substantial increase in median disease-free survival (mDFS), specifically with a target 36 months mDFS which represents more than 12 months improvement over current chemotherapy. Overall survival (OS) is a secondary endpoint for the Phase II, and demonstrated improvements will provide additional evidence of clinical benefit and further support the performance of additional follow-on trials in PDAC. Additional evaluations are limited pharmacokinetic and pharmacodynamic (ADCC, CDC, circulating tumor DNA [ctDNA], and CA19-9) assessments, which may help further characterize the clinical benefit and allow for more tailored designs in follow-on BNT321 trials.

For a rationale for the trial design, see Section 4.2.

For the rationale for the dosing regimen, see Section 6.2.

2.2 Background

Pancreatic ductal adenocarcinoma is one of the most aggressive and difficult to treat human cancers. In 2015, there were an estimated 46,960 new cases of PDAC diagnosed in the United States and 40,560 deaths from this disease. Despite the best available therapies, the 5-year OS rate remains a dismal 7.2%, a rate that has remained essentially unchanged since 1975. Currently, pancreatic cancer accounts for 3% of all newly diagnosed cancers in the United States, a figure that continues to rise, and is responsible for 7% of all cancer deaths. Additionally, ~90% of patients are initially diagnosed with an advanced/unresectable disease. Although stage at diagnosis is prognostic for survival,

even patients with localized disease and the best prognosis have poor outcomes, with a 5-year survival rate of only 27% (SEER Cancer Stat Facts).

Pancreatic cancer is considered resistant to most available chemotherapy and irradiation regimens. Response to immunotherapies has been poor, possibly related to the presence of thick stroma surrounding the tumor, which has, until recently, rendered immunotherapy ineffective (Brower 2014).

There have been modest improvements in treatment options for patients with metastatic PDAC. The FOLFIRINOX chemotherapy regimen demonstrated improvements in tumor response, progression-free survival (PFS) and OS benefit compared to single agent gemcitabine in the metastatic setting (Conroy et al. 2013). A modification of the FOLFIRINOX regimen (mFOLFIRINOX) is commonly used that may offer similar efficacy and a reduction in the need for dose reductions (de Jesus et al. 2018). Common side effects with either FOLFIRINOX or mFOLFIRINOX include neutropenia, febrile neutropenia, fatigue, vomiting, and diarrhea. In an effort to reduce the incidence of febrile neutropenia, FOLFIRINOX is commonly administered with prophylactic G-CSF. In addition, the combination of nab-paclitaxel (nanoparticle albumin-bound paclitaxel; Abraxane®) and gemcitabine demonstrated improvements in tumor response rate and PFS, with an OS benefit of ~2 months compared with gemcitabine alone. Based on these data, either the combination of nab-paclitaxel and gemcitabine or FOLFIRINOX are currently considered the standard-of-care (SoC) for first-line therapy in patients with locally advanced or metastatic pancreatic cancer with a good performance status (von Hoff et al. 2013; von Hoff et al. 2011).

FOLFIRINOX has subsequently been shown to improve the mDFS compared to gemcitabine alone in the PDAC adjuvant setting in the PRODIGE 24/CCTG PA 6 trial (Conroy et al. 2018). Patients in this trial who received adjuvant FOLFIRINOX experienced a mDFS of ~22 months. Unfortunately, relapse remains common even with adjuvant chemotherapy, with less than 40% of patients disease-free at 3 years (Conroy et al. 2018). New treatments that are feasible as adjuvant combination therapies and extend the DFS will represent a meaningful clinical improvement for this patient population.

2.2.1 Medical need

Complete resection of pancreatic cancer can result in cure for some patients with non-metastatic pancreatic cancer, however 5-year survival after surgical resection alone is only ~10%. As such, the use of adjuvant chemotherapy or chemo irradiation following complete surgical resection has been explored in an attempt to improve outcomes (Jones et al. 2014). In a large, randomized trial of mFOLFIRINOX versus gemcitabine in the adjuvant setting, adjuvant therapy with mFOLFIRINOX was shown to result in a meaningful improvement in DFS compared to gemcitabine alone. The mDFS was 21.6 months for the mFOLFIRINOX group versus 12.8 months for the gemcitabine group. The median OS was also significantly improved at 54.4 months in the mFOLFIRINOX group versus 35 months in the gemcitabine group. This improvement in survival was associated with an increase in Grade 3 or 4 adverse events (AEs) which were reported in 75.9% of the patients in the mFOLFIRINOX group and 52.9% of the gemcitabine group (Conroy et al. 2018).

Further improvements in DFS may be possible with the addition of BNT321 to the mFOLFIRINOX regimen without a significant increase in toxicity beyond that observed with mFOLFIRINOX alone.

2.2.2 Introduction to the investigational medicinal product

Sialyl-Lewis A (sLe^a) antigen CA19-9 is widely expressed on tumors of the gastrointestinal tract (Kishimoto et al. 1996; Passerini et al. 2012; Loy et al. 1993) and is often used as a tumor marker in pancreatic and colon cancer (Kannagi et al. 2007; Nakayama et al. 1995, Ballehaninna et al. 2012; Dong et al. 2014; Matsui et al. 2004). While sLe^a is expressed primarily as a glycolipid, the circulating CA19-9 antigen that is routinely used as a biomarker (Locker et al. 2006) appears to be a secreted, heavily glycosylated, high molecular weight mucin form of this antigen (Magnani et al. 1983; Ringel et al. 2003). Interestingly, sLe^a is predominantly expressed on cancer cells, while the natural counterpart, di-sialyl-Lewis A, is found on non-malignant epithelial cells (Kannagi et al. 2007). As a ligand for E-selectin, sLe^a facilitates tumor adhesion and extravasation, which are key events in tumor metastasis, and thus acts as a target marker of an aggressive tumor phenotype. sLe^a is also a known ligand for endothelial leukocyte adhesion molecules, and its expression is associated with increased metastatic potential in pancreatic adenocarcinoma (Kishimoto et al. 1996; Sato et al. 1997). sLe^a is a proven target for immune attack against cancer cells (Feizi 1985). Over 90% of pancreatic cancers are positive for CA19-9 expression, and its high expression rates are seen in bile duct carcinomas and transitional cell carcinomas (Passerini et al. 2012; Loy et al. 1993).

Serum CA19-9 levels have been found to be informative with respect to prognosis and treatment effect in patients with pancreatic cancer, with several studies correlating increasingly higher serum levels with poorer survival outcomes (Ballehaninna et al. 2012; Dong et al. 2014; Berger et al. 2004). In a Phase I/II clinical trial in advanced pancreatic cancer, decreases in CA19-9 levels correlated with tumor response, PFS, and OS (von Hoff et al. 2011). In a Phase II trial of 5-flurouracil-based chemo-radiotherapy in patients with locally advanced pancreatic cancer, a greater than 90% reduction in CA19-9 levels from baseline was associated with significantly improved median survival times, and in a multivariate analysis, a post therapy CA19-9 level of less than 85.5 U/mL was found to be an independent prognostic factor for survival (Yang et al. 2013). Because CA19-9 is highly expressed in pancreatic cancer, it was identified as a target for antibody-based biopharmaceuticals.

BNT321 (previously known as MVT-5873) is a fully human IgG1 lambda antibody discovered by MabVax in collaboration with investigators at Memorial Sloan Kettering Cancer Center (MSKCC). BNT321 was identified from blood lymphocytes following immunization with a sLe^a-KLH vaccine for the treatment of breast cancer (Ragupathi et al. 2009). This vaccine has been shown to induce high titers of both immunoglobulin G (IgG) and IgM antibodies against sLe^a in mice and humans without cross-reactivity to other similar blood group carbohydrate antigens (Ragupathi et al. 2009).

BNT321 binds specifically to the cancer associated sLe^a carbohydrate epitope and does not bind to Le^a, sLe^x, Le^y, or other related carbohydrates when evaluated by enzyme-

linked immunosorbent assay (ELISA) and surface plasmon resonance. In addition, an independent binding analysis on a glycan array with 465 distinct carbohydrates revealed that BNT321 had exquisite specificity for the carbohydrate epitope of the sLe^a antigen. Evaluation for specificity in tumors revealed BNT321 demonstrated cell surface binding in multiple CA19-9 expressing malignancies including pancreatic cancer cell lines (BxPC3 and Capan 2, both sLe^a positive), but not in CA19-9 negative melanoma cell line SKMEL28 (sLe^a negative) (BNT321 investigator's brochure [IB]).

BNT321 has demonstrated very potent CDC and ADCC, with assay EC_{50} values of 1.59 µg/mL and 0.269-0.439 µg/mL, respectively (additional details are given in Section 4.1.2, in the BNT321 IB, and in Sawada et al. 2011). Other preclinical assessments include mouse xenograft studies which indicated an inverse relationship between BNT321 serum concentrations and tumor volume, suggesting that the presence or expansion of the sLe^a target decreases the amount of circulating free drug and contributes to systemic clearance of BNT321. Indeed, analysis of BNT321 binding to tumor tissue by immunohistochemistry revealed an apparent dose-dependent uptake of BNT321, and an enhanced uptake by tumor tissue when BNT321 was administered in combination with chemotherapy. These studies support the clinical evaluation of BNT321, in combination with chemotherapy, in patients with pancreatic cancer (BNT321 IB).

Based on the above findings, BNT321 was selected for further development as a potential therapy for patients with CA19-9 expressing cancers.

2.3 Benefit/risk assessment

For BNT321 detailed information about the known and expected benefits and risks including expected AEs are also detailed in the BNT321 IB.

Additional information regarding the expected risks, including expected AEs for mFOLFIRINOX are provided in the product labels or summaries of product characteristics (SmPCs) for the individual agents of this regimen.

2.3.1 Benefit assessment

Modified FOLFIRINOX is established as a preferred treatment option for adjuvant therapy following potentially curative resection of pancreatic adenocarcinoma. A DFS of 21.6 months has been observed in a large Phase III PDAC adjuvant trial utilizing the mFOLFIRINOX regimen (Conroy et al. 2018). This same study demonstrated median OS of 54 months in mFOLFIRINOX treated patients. All patients participating in BNT321-02 will receive mFOLFIRINOX therapy according to SoC administration.

The efficacy of BNT321 as a single agent and in combination with mFOLFIRINOX as therapy for advanced CA19-9 expressing malignancies including PDAC has been evaluated in the Phase I trial MV-0715-CP-001.01. For BNT321 monotherapy in advanced line (2L/2L+) PDAC, stable disease greater than 90 days was observed in 12 of 53 evaluable patients (23%). Among 15 patients receiving mFOLFIRINOX + BNT321 combination therapy, the median number of treatment cycles (28 days) received was 3 (range 1-17 cycles) and seven patients remained on trial for more than 90 days. A confirmed partial response of greater than 10 months duration was observed for one

patient, and 7 additional patients (47%) have had RECIST 1.1 stable disease of greater than 12 weeks.

For the current trial, patients with resectable PDAC receiving adjuvant therapy with combination mFOLFIRINOX + BNT321 followed by BNT321 monotherapy may receive enhanced clinical benefit over SoC mFOLFIRINOX alone. As a potent, high affinity antibody for sialyl-Lewis A epitope of CA19-9, BNT321 has a mechanism of action distinct from the cytotoxic mFOLFIRINOX regimen. The combination regimen may provide for a significant extension of DFS following a potentially curative resection of pancreatic adenocarcinoma.

2.3.2 Risk assessment and mitigation strategy

BNT321-02 is conducted in two parts, a Phase I combination dose finding and safety evaluation, followed by a randomized Phase II of combination mFOLFIRINOX + BNT321 versus mFOLFIRINOX adjuvant SoC. Safety evaluation is the primary endpoint for the Phase I part of BNT321-02. A 3+3 dose escalation scheme will be used, along with additional parameters including regular safety data reviews will be performed by the safety review committee (SRC) and sponsor to evaluate potential safety concerns.

The sponsor will generate sufficient safety data in the Phase I part of the trial to identify the combination RP2D.

Considerations for risk assessment in the BNT321-02 trial include prior clinical safety data for mFOLFIRINOX administered in the PDAC adjuvant setting and mFOLFIRINOX + BNT321 administered in the PDAC metastatic setting in the MV-0715-CP-001.01 trial. The safety data for each of these are summarized below; additional details are available in the mFOLFIRINOX SmPCs/ product labels and the BNT321 IB.

mFOLFIRINOX adjuvant therapy

mFOLFIRINOX was established as an SoC option for adjuvant PDAC treatment following results of the PRODIGE 24-ACCORD Phase III trial in 2018 (Conroy et al. 2018). Among 493 patients enrolled, 247 received treatment in the mFOLIFIRINOX arm. The most prevalent safety events (all grades/Grade 3 or 4) in these patients included hematologic toxicities of decreased hemoglobin (84.7%/3.4%), neutropenia (66.5%/28.4%), thrombocytopenia (47%/1.3%), and lymphopenia (36.9%/1.3%). Febrile neutropenia was observed at a lower frequency (3%/3%). More prevalent non-hematologic toxicities include gastrointestinal events of diarrhea (84.4%/18.6%), nausea (78.9%/5.5%), emesis (45.6%/5.1%), anorexia (44.7%/2.5%), and mucositis (33.8%/2.5%). Prevalent non-gastrointestinal AEs include sensory peripheral neuropathy (61.2%/9.3%), paresthesia (57.4%/12.7%), and increases in liver function enzymes such as alanine aminotransferase (ALT) (64.0%/4.2%), aspartate aminotransferase (AST) (66.9%/3.8%), and alkaline phosphatase (73.6%/2.1%).

Based on frequently observed AEs in the above organ systems, detailed safety management parameters were used for PRODIGE 24-ACCORD and for subsequent mFOLFIRINOX adjuvant therapy. The BNT321-02 trial will implement dedicated safety monitoring for these identified safety risks, adopting dose withholding, dose reduction, and

dose discontinuation parameters similar to those utilized in PRODIGE 24-ACCORD for observed higher grade toxicities. Supportive care measures will be implemented for anticipated hematologic and gastrointestinal toxicities. Safety management is described in detail in Section 6 of this trial protocol.

mFOLFIRINOX + BNT321 combination therapy

The BioNTech Phase I trial MV-0715-CP-001.01 evaluated the safety, maximum tolerated dose (MTD) and recommended Phase II dose (RP2D) of mFOLFIRINOX + BNT321 chemotherapy. Patients eligible for this trial arm were those with PDAC or other CA19-9 expressing tumors receiving first or second line therapy for metastatic disease. As of April 2023, 15 patients received BNT321 in combination with mFOLFIRINOX over a BNT321 dose range of CCI [redacted]. More than 60 cycles (28-day cycles) of treatment have been administered for this combination.

The most prevalent (>25%) safety events (all grades/Grade ≥3) in these patients included nausea (86.7%/6.7%), diarrhea (80%/0%), fatigue (80%/0%), constipation (60%/0%), AST increase (53.3%/40%), ALT increase (46.7%/26.7%), abdominal pain (40%/0%), cough (33.3%/0%), peripheral sensory neuropathy (33.3%/0%), vomiting (26.7%/6.7%), stomatitis (26.7%/0%), dysesthesia (26.7%/0%), and dyspnea (26.7%/0%). Dose-limiting toxicities (DLTs) have been reported for three patients, including Grade 4 ALT + Grade 3 AST with Grade 2 total bilirubin elevation (one patient), Grade 3 ALT+ Grade 3 AST, and total bilirubin (one patient), and Grade 4 ALT + Grade 3 AST with Grade 1 alkaline phosphatase (one patient). Based on these findings, the BNT321 MTD and recommended combination dose with mFOLFIRINOX is CCI [redacted] for patients receiving this therapy in the metastatic setting.

Additional details are available in the BNT321 IB.

Based on frequently observed AEs in the above organ systems, detailed safety management parameters will be implemented throughout the BNT321-02 trial. These include the dose withholding, dose reduction, and dose discontinuation parameters planned for mFOLFIRINOX (above). Additionally, BNT321 safety monitoring and dose adjustments and/or dose withholding are implemented for observed changes in liver function tests and infusion-related reactions (IRRs). These are described in Table 5 below and in Sections 6.3 and 10.6.

Table 5: Risk assessment for BNT321 and mFOLFIRINOX

Potential risk of clinical significance	Summary of data/ Rationale for risk	Mitigation strategy
BNT321		
Changes in liver function: ALT, AST, and total bilirubin	Incidence in previous studies: of the most commonly occurring (≥25%) LFT events: • MV-0715-CP-001.01: For Phase I monotherapy cohorts were ALT increased (42.7%), AST increased (39%) and blood bilirubin increased (29.3%). • MV-0715-CP-001.01: For Phase I mFOLFIRINOX + BNT321 combination cohort were ALT increased (46.7%) and AST increased (53.3%).	Dedicated LFT monitoring throughout drug administration period. • Dose withholding, dose reductions, and dose discontinuation parameters see Section 6.3.1.1 and Section 10.6.
GI events: nausea, vomiting, diarrhea, constipation	Incidence of the most commonly occurring (≥25%) GI events: • MV-0715-CP-001.01: For Phase I monotherapy cohort was abdominal pain (30.5%), nausea (25.6%), • MV-0715-CP-001.01: For Phase I mFOLFIRINOX + BNT321 combination cohort were nausea (86.7%), diarrhea (80%), constipation (60%), abdominal pain (40%) and vomiting (26.7%).	Anti-emetic, anti-diarrheal, laxative, analgesic prophylactic, and supportive regimens according to institutional and SmPC guidelines.
IRR	Incidence of IRR: • MV-0715-CP-001.01: For Phase I monotherapy was 17.1% (mostly low [Grade 1] and reversible). • MV-0715-CP-001.01: For Phase I mFOLFIRINOX + BNT321 combination cohort was 20% (all Grade 2 and reversible).	• Corticosteroid pre and post medication regimen (Section 6.9.3). • Prolonged infusion for first two BNT321 administrations (Section 6.9.3). • Treatment recommendations by IRR grade including treatment interruption, standard IRR medications and additional prophylactic recommendations (Table 13 in Section 6.3.4).

Potential risk of clinical significance	Summary of data/ Rationale for risk	Mitigation strategy
mFOLFIRINOX*		
Changes in hematological function: WBC, neutrophils, RBC, and platelets	PRODIGE 24: Incidence of any grade hematological events in mFOLFIRINOX arm were neutropenia (66.5%), low hemoglobin level (84.7%), lymphopenia (36.9%), and thrombocytopenia (47%).	• Dedicated hematologic monitoring throughout drug administration period. • Dose adjustments (reductions, withholding, discontinuations) and supportive care interventions.(see Table 9 in Section 6.3.1.2).
GI events: diarrhea, nausea, vomiting, abdominal pain	PRODIGE 24: Incidence of any grade GI event were: diarrhea (84.4%), nausea (78.9%), vomiting (45.6%) and abdominal pain (46.8%).	• Anti-emetic, anti-diarrheal, laxative, analgesic prophylactic, and supportive regimens. • Dose adjustments, modifications, withholding and discontinuation guidelines and prophylactic and supportive care recommendations (see Section 6.3.1.2).
Mucositis	PRODIGE 24: Incidence of any grade mucositis was 33.8%.	• Dedicated ROS and AE assessment and reporting throughout drug administration period. • Dose adjustments, modifications, withholding and discontinuation guidelines and prophylactic and supportive care recommendations (see Section 6.3.1.2).
Cardiac toxicity	PRODIGE 24: Incidence not reported.	• Dedicated vital signs, ROS and AE assessment and reporting throughout drug administration period. • ECG monitoring, scheduled and as indicated at investigator's discretion based on clinical signs and symptoms. • Dose adjustments, modifications, withholding, and discontinuation guidelines (see Section 6.3.1.2).

Potential risk of clinical significance	Summary of data/ Rationale for risk	Mitigation strategy
Sensory peripheral neuropathy	PRODIGE 24: Incidence of any grade was 61.2%.	• Dedicated ROS and AE assessment and reporting throughout drug administration period. • Dose adjustments, modifications, withholding and discontinuation guidelines and prophylactic and supportive care recommendations (see Section 6.3.1.2 and Table 12).
Changes in liver function: ALT, AST, alkaline phosphatase	PRODIGE 24: Incidence of any grade ALT (64%), AST (66.9%), and increased alkaline phosphatase (73.6%).	• Dedicated LFT monitoring throughout drug administration period. • Dose withholding, dose reductions, and dose discontinuation parameters (see Section 6.3.1.2 and Section 10.6).

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; RBC = red blood cell; ROS = review of system; SmPC = summary of product characteristics; WBC = white blood cell.

*Source: Conroy et al. 2018, PRODIGE 24-ACCORD.

2.3.3 Overall benefit/risk conclusion

Taking into account the measures taken to minimize risk to patients participating in this trial, the potential risks identified for administration of mFOLFIRINOX + BNT321 are justified by the anticipated benefits including potential for clinically significant increase in DFS that may be afforded to patients with resected pancreatic cancer. Additional information is provided in the respective SmPCs for mFOLFIRINOX chemotherapy and in the BNT321 IB.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
PRIMARY	
Phase I	
To assess the safety and identify the RP2D of BNT321 in combination with mFOLFIRINOX as adjuvant therapy in patients with R0 or R1 resected PDAC.	The proportion (%) of patients who received at least one dose IMP reporting: • Incidence and occurrence of TEAEs including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of DLTs within a cohort during the DLT evaluation period.

OBJECTIVES	ENDPOINTS
Phase II	
To assess the efficacy of mFOLFIRINOX + BNT321 versus mFOLFIRINOX alone as adjuvant therapy in PDAC patients post R0 or R1 resection by mDFS.	In patients who are randomized into the trial: DFS defined as the time from randomization to occurrence of any of the following: • Locoregional recurrence or distant metastasis as determined by an independent central radiology assessment. • Occurrence of second primary (same or other) cancer as determined by an independent central radiology assessment. • Death from any cause.
SECONDARY	
Phase I and II	
To further assess the efficacy of mFOLFIRINOX + BNT321 or mFOLFIRINOX as adjuvant therapy in PDAC patients post R0 or R1 resection by OS.	In patients who are enrolled/randomized into the trial: • OS is defined as the time from first dose of trial treatment to death from any cause.
To further assess the efficacy of mFOLFIRINOX + BNT321 or mFOLFIRINOX as adjuvant therapy in PDAC patients post R0 or R1 resection by RFS and DFS rates.	In patients who are enrolled/randomized into the trial: RFS is defined as the time from randomization to occurrence of any of the following events, whichever occurs first: • Locoregional recurrence or distant metastasis as determined by the investigator. • Death from any cause.
To characterize the PK of BNT321 when co-administered with mFOLFIRINOX.	In patients who are dosed with at least one dose of IMP and who have evaluable PK data: • PK parameters derived from serum concentration of IMP, including mean AUC, mean C_{max}, and median t_{max} in Cycles 2 and 3 followed by sparse sampling through EOT.
To characterize immunogenicity of BNT321 when co-administered with mFOLFIRINOX.	In patients who are dosed with at least one dose of IMP: • Percentage of patients with detectable ADA formation in Cycles 1 and 3, followed by sparse sampling through EOT.
To describe the PD parameters of BNT321 co-administered with mFOLFIRINOX, including ADCC and CDC.	In all patients who are dosed with at least one dose of IMP: • Percentage of patients with detectable and durable (measurable throughout time on trial) ADCC and/or CDC activity in Cycles 2 and 4, followed by sparse sampling through EOT.

OBJECTIVES	ENDPOINTS
To assess self-reported HRQoL of patients receiving mFOLFIRINOX + BNT321 versus mFOLFIRINOX.	In all patients who are dosed with at least one dose of IMP: • Change from baseline at end of Cycle 12 for patient-reported HRQoL using EORTC QLQ-C30. • Change from baseline at end of Cycle 12 for patient-reported HRQoL using EORTC QLQ-Pan26 questionnaires. • Change from baseline at end of Cycle 12 in combined item scores from EORTC QLQ-C30 and EORTC QLQ-Pan26.
Phase II	
To evaluate the safety and tolerability of mFOLFIRINOX with and without BNT321 as adjuvant therapy in patients with R0 or R1 resected PDAC.	In patients receiving at least one dose of IMP: • Occurrence of TEAEs within a patient including Grade ≥3, serious, fatal TEAE by relationship. • Occurrence of dose reduction and discontinuation of IMP within a patient due to TEAE. • Occurrence of abnormal laboratory parameters within a patient.
EXPLORATORY	
Phase I and II	
To explore the CA19-9 peripheral and tumor expression level correlates with clinical outcome and PK.	CA19-9 levels measured from patient peripheral blood and tumor will be correlated with each other, with antibody clearance rates (PK), and with clinical activity (if data allowing).
To explore the immune correlates with clinical outcome (ADCC, CDC, and cytokines).	• ADCC and CDC measurements will be correlated with clinical activity (if data allowing). • Peripheral blood cytokine profiles will be measured to understand effects of treatment on peripheral immune milieu and will be correlated with clinical activity (if data allowing).
To explore the relationship between ctDNA and DFS to understand if freedom from relapse can be measured using liquid biopsy and/or predicted ahead of a clinical disease recurrence.	ctDNA will be measured longitudinally through targeted sequencing of peripheral blood to quantify specific gene mutations associated with the tumor (if data allowing).
To explore the relationship of clinical outcome with baseline* status of tumor resection classification R0 or R1, and resection nodal status pN0 or pN1.	Tumor resection classified for each patient as R0 (no tumor <1 mm from margin) or R1 (tumor within 1 mm from margin), RCP**. Tumor nodal status classified for each patient as pN0 (no nodal disease) or pN1 (nodal involvement in resection).
To determine mFOLFIRINOX dose intensity when administered with and without BNT321.	• The mFOLFIRINOX relative dose intensity (RDI), defined for each patient as the fraction of (cumulative chemotherapy dose received/ treatment duration) planned dose intensity. • Number of patients receiving RDI ≥70%.

* Baseline is defined as last value prior to initiation of trial treatment.

** RCP classification. Tumors designated R0 CRM+ (R0 narrow) according to CRM concept will be stratified as R1 tumor in this trial.

Abbreviations: AE = adverse event; ADA = anti-drug antibody; ADCC = antibody-dependent cell-mediated cytotoxicity; AUC = area under the curve; CDC = complement-dependent cytotoxicity; C_{max} = maximum serum concentration that the drug achieved after administration; ctDNA = circulating tumor deoxyribonucleic acid; CTCAE = US National Cancer Institute Common Terminology Criteria for Adverse Events; CRM = circumferential resection margin; DLT = dose-limiting toxicity; EOT = end of treatment; ECG = electrocardiogram; EORTC = European organisation for research and treatment of cancer; HRQoL = health-related quality of life; ICF = informed consent form; IMP = investigational medicinal product; mDFS = median disease-free survival; NA = not applicable; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; PD = pharmacodynamic; PK = pharmacokinetics; RCP = Royal College of Pathologists; RFS = relapse-free survival; RDI = relative dose intensity; RP2D = recommended Phase II dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time required to reach C_{max}.

4 TRIAL DESIGN

4.1 Overall design

This trial is designed as a Phase I/randomized Phase II open-label trial of mFOLFIRINOX ± BNT321 for adjuvant therapy in PDAC patients post R0 or R1 resection.

Screening will occur ≤21 days prior to Cycle 1 Day 1. Patients will provide written informed consent prior to the performance of any screening-related procedures. Eligibility status will be determined and be provided to the physician that submitted the patient's tissue for testing. Medical history includes cancer history (including but not limited to, lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases, including tuberculosis, surgeries, use of alcohol and/or drugs abuse and reproductive status).

The Phase I, dose escalation part of this trial will be a limited evaluation of two planned BNT321 dose levels in combination with mFOLFIRINOX chemotherapy (24 weeks) followed by BNT321 monotherapy (24 weeks). Following determination of the combination recommended Phase II dose (RP2D), the Phase II (randomized treatment) part of this trial will be initiated as an open-label 2-arm evaluation of mFOLFIRINOX ± BNT321 (24 weeks) followed by BNT321 monotherapy (24 weeks) in the combination arm only to complete the adjuvant therapy course. Treatment cycles are every 2 weeks (14 days).

The primary endpoint for the Phase I part of this trial is characterization of the safety and RP2D of BNT321 in combination with mFOLFIRINOX. The primary endpoint for Phase II of this trial is to assess the efficacy of mFOLFIRINOX + BNT321 versus mFOLFIRINOX alone as adjuvant therapy in PDAC patients post R0 or R1 resection by DFS.

Safety monitoring assessments will be performed 28 days after the last dose of BNT321. Information on survival follow-up, new anticancer and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits from BNT321 treatment discontinuation and approximately every 12 weeks until 5 years (unless the patient withdraws consent, or the sponsor terminates the trial).

The duration of the trial periods is given in Section 4.1.4.

The planned number of patients is given in Section 4.1.5.

For standard definitions, e.g., for trial completer and end of trial, see Section 10.7.

The expected duration of patient participation is 5 years.

4.1.1 Dose escalation (Phase I)

The Phase I part of the trial will be a limited dose finding evaluation, whereby a minimal number of BNT321 dose levels will be tested for safety and tolerability in combination with mFOLFIRINOX chemotherapy. Dose escalation will be conducted using a 3+3 design, with up to six additional patients treated at the Phase I defined combination MTD. Two BNT321 dose levels are initially planned, 0.5 mg/kg CCI (Table 6). Following evaluation of safety profile for dose level 2, additional BNT321 dose levels may be evaluated following safety data review, discussion and approval by the SRC, and health authority review and approval.

Table 6: BNT321 dose increments

Dose level	Dose*	Dose increment
1	0.5 mg/kg	Starting dose
2	CCI	CCI

*Can be reduced or increased as a function of the observed biologic activity and based on other data generated during the trial for dose finding. Intermediate dose levels may be investigated after data review, discussion, and approval by the SRC. Dose levels higher than CCI may be explored following review of data and approved protocol amendment.

4.1.2 Randomized mFOLFIRINOX ± BNT321 (Phase II)

Following completion of the dose escalation Phase I and identification of the recommended Phase II dose (RP2D), the trial will proceed to a randomized Phase II part. The Phase II part will be a 2-arm, randomization of mFOLFIRINOX ± BNT321, with up to 300 patients enrolled to enable a robust statistical evaluation of the trial's Phase II primary endpoint, i.e., mDFS. See Section 9 for a detailed statistical design.

Additional evaluations for Phase II will include determination of combination regimen safety and tolerability, determination of OS, pharmacokinetic (PK), and pharmacodynamic (PD) analyses including ADA, CDC, ADCC assessments, cytokine and ctDNA assessments.

The timing of these assessments is provided in the Phase II part SoA Table 2 and Table 4 in Section 1.3.

4.1.3 Adaptive trial design elements

The following adaptive design elements define conditions under which changes to the trial design may be implemented based on the SRC recommendation. Further changes not specified here will only be introduced via a protocol amendment.

- Addition or removal of PK sampling time points depending on emerging data on BNT321, can be performed at the sponsor's discretion and alignment with site investigator.
- Addition of safety assessment time points depending on emerging data on BNT321 can be performed based on SRC recommendation.
- Assessment time points for measurement of correlative and PD assays may be added or reduced at the sponsor's discretion and alignment with site investigator.
- For further understanding of the safety, tolerability, and PK of BNT321, up to six additional patients may be enrolled at preceding dose levels or to intermediate dose levels, while proceeding with further dose escalation or even thereafter.
- Intermediate dose levels may be implemented based on SRC recommendation.

4.1.4 Duration of the trial periods

For both Phase I and Phase II, there will be a screening period of 21 days.

Phase I will consist of ~48 weeks of therapy, with 24 weeks of mFOLFIRINOX + BNT321 combination therapy followed by 24 weeks of BNT321 monotherapy. Phase II will be a randomized 2-arm trial, with 48 weeks of treatment in the combination arm (mFOLFIRINOX + BNT321) and 24 weeks of therapy in the control arm (mFOLFIRINOX only).

For both Phase I and Phase II, there will be a safety follow-up of 2 days ± 14 days after the last dose of trial treatment. DFS status will be recorded every 3 months for 2 years and then every 6 months for the next 3 years. Overall survival status will be recorded up to 60 months.

The maximum trial duration for each phase is ~5 years after the last patient's first treatment in the trial.

4.1.5 Planned number of patients

The sample size for the Phase I part of the trial is driven by the classical 3+3 trial design and will range from three to six DLT-evaluable patients per cohort depending on the occurrence of DLTs through the DLT evaluation period (treatment cycles of the first two consecutive BNT321 doses). If one patient in the initial three patients experiences a DLT, the cohort will be expanded to six patients. Non-DLT-evaluable patients will be replaced.

A cohort will be closed to further accrual and the next higher dose cohort opened for accrual when 0 of 3, or ≤ 1 of 6 patients have demonstrated DLT in the current cohort. If two or more patients demonstrate DLT, then that cohort will be closed to further accrual and will be considered to have exceeded the MTD.

Once the MTD is reached, up to six additional patients with pancreatic cancer may be enrolled at the MTD level in Phase I, to obtain additional data on safety, PK. The BNT321 dose recommended for Phase II part of this trial will be selected after evaluation of available safety, PK and PD data generated in Phase I, with SRC discussion and agreement.

A maximum of 320 patients will be enrolled to the trial treatment with ~20 patients in Phase I and 300 patients in Phase II such that ~164 DFS events are recorded for the randomized Phase II part of the trial. See Section 9.3 for additional details regarding sample size for the randomized Phase II part of this trial.

4.2 Rationale for the trial design

4.2.1 Trial design rationale for Phase I: Dose escalation

The Phase I part of this trial will employ limited BNT321 dose finding in combination with mFOLFIRINOX regimen chemotherapy as adjuvant therapy in patients with R0 or R1 resected PDAC. A 3+3 dose escalation design is preferred over other limited escalation schemes, given that there is already substantial BNT321 Phase I data available as a guide for a combination starting dose and dose range. The planned BNT321 dose levels of 0.5 CCI mg/kg to be administered once every two weeks (Q2W) are selected based on the initial safety and tolerability observations from the ongoing BioNTech Phase I trial MV-0715-CP-001.01. In this trial, over 60 cycles of mFOLFIRINOX + BNT321 therapy have been administered in the PDAC metastatic disease setting, with CCI determined as combination MTD on a Q2W schedule. This dose was associated with RECIST partial response and prolonged stable disease. For the current trial it is considered that patients with limited stage disease and no prior systemic treatments for cancer may have improved tolerability relative to treatment administered in the metastatic setting. Therefore, a major objective of the first part of this trial is an independent evaluation of combination tolerability and RP2D selection specific to the PDAC adjuvant population. This may include the potential for RP2D evaluation at doses higher than the metastatic disease MTD. Specifically, following evaluation of the CCI dose level cohort, additional BNT321 doses may be considered following comprehensive review of safety data and approval of the trial SRC and Clinical Trial Information System (CTIS) amendment and approval

The Phase I part of this trial is designed to provide key PD data for BNT321 prior to its entry into pivotal Phase II trial conduct. Potent ADCC and CDC effects for BNT321 have been demonstrated in association with BNT321 preclinical activity (Gupta et al. 2020). A key translational objective is to demonstrate durable ADCC and CDC effects in circulating patient PBMCs and serum over an extended antibody treatment course at safety-tolerable dosing at or below the BNT321 RP2D. Demonstrating these PD parameters is an important mechanistic validation of the independent therapeutic effects anticipated for BNT321 against clinically nondetectable disease following primary PDAC resection.

Another key element of the BNT321-02 Phase I design is an extended monotherapy antibody treatment course beyond the initial 24 weeks in mFOLFIRINOX combination. The trial design is for single agent BNT321 administered on every 2 week schedule for an additional 24 weeks to complete a 48 week total adjuvant treatment course. The large majority of PDAC disease relapse occurs beyond the initial 6 months post-operative period when mFOLFIRINOX is administered. Extending the total treatment duration may further enhance the overall efficacy of adjuvant therapy in these patients. The approach of extended antibody monotherapy after an initial cytotoxic regimen has been successfully adopted in other adjuvant regimens, for example breast cancer adjuvant Trastuzumab

(Slamon et al. 2011). Extended BNT321 monotherapy will be adopted for the Phase II design following safety and tolerability confirmation from Phase I.

4.2.2 Trial design rationale for Phase II: Randomized mFOLFIRINOX ± BNT321

The randomized Phase II part of this trial is designed as a dedicated evaluation of the potential for BNT321 combination therapy with mFOLFIRINOX to provide meaningful clinical benefit to patients with R0 or R1 surgically resectable PDAC. mFOLFIRINOX, the selected regimen for combination and the comparator arm for BNT321-02, is considered a superior option to gemcitabine + nab-paclitaxel for PDAC adjuvant therapy based on results of Phase III PRODIGE 24 and APACT studies (Conroy et al. 2018 and Tempero et al. 2022 respectively). The BNT321-02 Phase II design employs several parameters from the pivotal Phase III PRODIGE 24 study.

DFS is selected as the primary endpoint for the randomized Phase II part of this trial. This is an established, clinically meaningful outcome previously used as primary endpoint in the PRODIGE 24 and APACT Phase III trials. A substantial improvement in mDFS is sought in trial BNT321-02, specifically a greater than 12 months increase with the introduction of Q2W BNT321 to the 24-week mFOLFIRINOX chemotherapy standard (target 36 vs 21.6 months DFS, hazard ratio [HR] 0.60).

In addition to primary endpoint mDFS, additional outcome measures evaluated as secondary endpoints include 12 months DFS and OS at 24 months. The mFOLFIRINOX 12 months DFS rate of 69.0% observed in PRODIGE 24 is a high efficacy benchmark, but a significant DFS improvement at this timepoint in BNT321-02 would represent a major efficacy advance and may be a consideration for accelerated registration. Overall survival assessment at 24 months is in a feasible timeframe relative to the trial mDFS primary endpoint and may provide additional supportive efficacy data in this first BNT321 adjuvant trial.

The randomized Phase II part of this trial will be conducted in an open-label fashion, consistent with design of other major adjuvant studies (Tempero et al. 2022). Another notable design consideration is inclusion of stratifications for surgical resection status (R0 versus R1) and nodal status at time of resection (pN0 versus pN1). Both of these resection characteristics are recognized as significant factors in clinical outcome in resected PDAC and so are justified for stratification in the BNT321-02 trial design, similar to an approach in previous PDAC adjuvant studies (Conroy et al. 2018).

4.2.3 Contraception and pregnancy testing

Currently, a risk of human teratogenicity/fetotoxicity can NOT be excluded by available data. Therefore, all trial patients biologically capable of having or fathering children must agree to use a highly effective method of contraception consistently and correctly as specified in the SoA (Section 1.3).

For definitions of POCBP, postmenopausal female and fertile men, as well as guidance on how to collect pregnancy information, see Section 10.5.

During BNT321 treatment, POCBPs and male patients with a partner who can become pregnant should use effective contraception during treatment and for at least 111 days (3 months and 3 weeks) after the last BNT321 dose.

During mFOLFIRINOX treatment POCBPs should use effective contraception during treatment and for at least 9 months after the last oxaliplatin dose. Male patients with partners who can become pregnant should use effective contraception during treatment and for 6 months after the last oxaliplatin dose.

In cases where oxaliplatin has been discontinued or not given, refer to Table 7 for contraception requirements for individual mFOLFIRINOX drugs per United States prescribing information (USPI) and EMA SmPCs.

Table 7: Contraception requirements for mFOLFIRINOX components

Drug	USPI (FDA)	SmPC (EMA)
5-fluorouracil (5-FU)	• POCBP should use effective contraception during treatment with 5-FU and for up to 3 months following cessation of therapy.	• POCBPs should be advised to avoid becoming pregnant and use an effective method of contraception during treatment with 5-FU and at least 6 months afterwards.
	• Male patients with female partners of reproductive age should use effective contraception during and for 3 months following cessation of therapy with 5-FU.	• Male patients treated with 5-FU are advised not to father a child during and for up to 3 months following cessation of treatment.
Leucovorin	None listed.	None listed.
Irinotecan	POCBPs should be advised to avoid becoming pregnant while receiving treatment with irinotecan.	• POCBPs should use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.
		• Male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan.

Abbreviations: EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; POCBP = patient of childbearing potential; SmPC = summary of product characteristics; USPI = United States Prescribing Information.

4.3 Definition of start of trial and end of trial

The trial start date is when the first potential trial patient has given informed consent, see Section 10.1.3.

The trial is considered completed when all patients:

- have had survival follow-up OR
- are lost to follow-up OR
- have withdrawn consent OR
- have died OR
- the sponsor discontinues the trial.

However, the maximum trial duration is 5 years after the last patient's first treatment in the trial.

A patient is considered to have completed the trial if they have discontinued BNT321 treatment and have completed safety and survival follow-up.

For guidance on the trial site start/closure and trial discontinuation, see Section 10.1.9.

For details about post-trial access to trial treatment, see Section 6.8.

5 TRIAL POPULATION

This trial will enroll patients aged >18 years or of an age deemed to be an adult per local authorities with recently resected PDAC considered appropriate for adjuvant treatment with mFOLFIRINOX. All enrolled patients must meet the trial eligibility criteria listed in Section 5.

The following eligibility criteria are designed to select patients for whom participation in the trial is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for enrollment.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Selection of trial population

Complete resection of pancreatic cancer can result in cure for some patients with non-metastatic pancreatic cancer, though historically 5-year survival after surgical resection alone is only ~10%. The use of adjuvant chemotherapy or chemo irradiation following complete surgical resection has been utilized to improve outcomes (Jones et al. 2014). Modified FOLFIRINOX emerged an adjuvant SoC following the PRODIGE 24 study (Conroy et al. 2018). While meaningful improvements in DFS and OS were achieved, PDAC patients post pN0/pN1 tumor resection remain a population at high risk for disease recurrence and death. Additional improvements in adjuvant SoC are needed for DFS and

further improvements in OS may be possible with the addition of novel therapies to mFOLFIRINOX.

5.2 Inclusion criteria

A patient who meets all of the following criteria at screening is eligible to enroll in the trial:

1. Has signed an informed consent form (ICF) before initiation of any trial-specific procedures.
2. Is >18 years or age deemed to be an adult per local authorities inclusive, at the time of giving written informed consent.
3. Willing and able to comply with scheduled visits, treatment schedule, laboratory tests, lifestyle restrictions, and other requirements of the trial (per investigator assessment, must be capable of understanding and following trial-related instructions).
4. Has an ECOG performance status of 0 to 1 (refer to Appendix 1 for conversion between ECOG and KPS).
5. Has histologically or cytologically confirmed PDAC.
6. Had macroscopically complete resection (R0 or R1 resection, RCP classification) performed between ≥21 and ≤84 days prior to C1D1. Submission of FFPE tumor tissue from resection or biopsy is required.
7. Has no radiologic (CT/MRI) evidence of metastatic disease, malignant ascites, or pleural effusion through an assessment obtained within 4 weeks of first trial medication (i.e., C1D1).
8. Full recovery from surgery and able to receive chemotherapy.
9. Has acceptable laboratory parameters including:
    a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    b. Hemoglobin ≥10.0 g/dL (may be accomplished with transfusion)
    c. Platelet count >100,000/mm^3
    d. AST and ALT ≤2.0 x ULN
    e. Total bilirubin ≤ULN
    f. Serum creatinine ≤1.5 x ULN or eGFR >50 mL/min
    g. Serum albumin >3.0 g/dL
10. Is willing to allow collection of pharmacokinetic samples.

11. Agree not to enroll in another trial of an IMP, starting after signing of the ICF and continuously until the last planned visit in this trial.

12. Patient of childbearing potential (POCBP) must have a negative urine beta human chorionic gonadotropin (βhCG) test at screening. Patients that are postmenopausal or permanently sterilized (verified by medical records; for definitions, see Section 10.5) will not be considered POCBP, and therefore are not required to undergo pregnancy testing.

13. POCBP who agree to practice a highly effective form of contraception (for guidance on highly effective forms of contraception, see Section 10.5) and to require their male partners to use condoms with a spermicidal agent, starting after signing of the ICF and continuously throughout trial and for a period of 111 days after the last dose of BNT321 and for 9 months after the last oxaliplatin dose. If the highly effective method of contraception is medically contraindicated, then only the use of condoms with a spermicidal agent is acceptable (Section 4.2.3).

14. Men who are sexually active with a POCBP and have not had a bilateral vasectomy or orchidectomy must agree to use condoms with a spermicidal agent and to require their female partners to practice a highly effective form of contraception (for guidance on highly effective forms of contraception, see Section 10.5) during the trial, starting after signing of the ICF and continuously until111 days after receiving the last dose of BNT321 and for 6 months after the last oxaliplatin dose (Section 4.2.3).

15. POCBP who agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting after signing of the ICF and continuously throughout trial and for a period of 3 months after the last dose of BNT321 and for 9 months after the last oxaliplatin dose.

16. Men who are willing to refrain from sperm donation, starting after signing of ICF and continuously until 111 days (one sperm cycle) after receiving the last dose of BNT321 and for 6 months after the last oxaliplatin dose.

5.3 Exclusion criteria

A patient who meets any of the following criteria at screening will be excluded from trial participation:

1. Is pregnant or breastfeeding or planning pregnancy or to father children during the trial or within 60 days after last IMP treatment.

2. A medical, psychological, or social condition which, in the opinion of the investigator, could compromise their wellbeing if they participate in the trial, or that could prevent, limit, or confound the protocol specified assessments or procedures, or that could impact adherence to protocol-described requirements.

3. Had major surgery within 3 weeks of first dose of the trial treatment, where participation in the trial could compromise the patient's wellbeing in the opinion of the investigator.
4. Has abnormal electrocardiograms (ECGs) that are clinically significant, such as Fridericia-corrected QT prolongation >>470 msec (for women) and >450 msec (for men), (average of three ECGs at least 5 minutes apart).
5. Has a history of anaphylactic reaction to human, or humanized, antibody.
6. Have other known active cancer(s) likely to require treatment in the next 2 years.
7. Had prior radiotherapy or systemic treatment for PDAC.
8. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT321.
9. Known hypersensitivity to any of the excipients of the experimental product BNT321.
10. Known history of seropositivity for human immunodeficiency virus (HIV) with CD4+ T-cell counts <350 cells/µL and with a history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections.
11. Known history/positive serology for Hepatitis B requiring active antiviral therapy (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy; patients with positive serology must have Hepatitis B virus viral load below the limit of quantification).
12. Active Hepatitis C virus infection (patients who have completed curative antiviral treatment with Hepatitis C virus viral load below the limit of quantification are allowed).
13. Use of any IMP or device within 21 days before administration of first dose of trial treatment or ongoing participation in the active treatment phase of another interventional clinical trial.
14. Is subject to exclusion periods from another investigational trial.
15. Are vulnerable individuals as per ICH E6 definition, i.e., individuals whose willingness to participate in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.
16. Serum CA19-9 >180 U/mL within 3 weeks of C1D1.
17. Incomplete macroscopic tumor removal (R2 resection).

18. Significant cardiovascular risk (past medical history of coronary stenting or myocardial infarction within 6 months, or NYHA Class III/IV, heart failure, or concurrent unstable angina) or risk factors for QT prolongation (sustained Grade 3 or higher hypokalemia, history of unstable arrhythmia orfamily history of long QT syndrome).
19. Pre-existing neuropathy.
20. Homozygous UGT1A1*28 mutation, if testing required by local regulations.
21. Inflammatory disease of the colon or rectum, or occlusion or sub-occlusion of the intestine or severe post-operative uncontrolled diarrhea.
22. Complete dihydropyrimidine dehydrogenase (DPD) deficiency, if testing required by local regulations.
23. Received a live vaccine within 3 weeks prior to the first dose of trial treatment.
24. Patients with a contraindication to receiving mFOLFIRINOX.
25. Patients with active or latent tuberculosis or history of Mycobacterium tuberculosis infection currently or within the last 2 years.
26. Individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

5.4 Lifestyle considerations

The sponsor foresees no particular lifestyle considerations for patients in this trial.

5.5 Screen failures

Screen failures are defined as trial patients who consent to participate in the clinical trial but are not subsequently entered in the trial or randomly assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, date of informed consent, screen failure details, eligibility criteria, and any SAE.

Screen failures may be rescreened two more times (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the ICF prior to any rescreening. Rescreened patients will be assigned a new patient number.

5.6 Criteria for temporarily delaying enrollment or randomization

Enrollment or randomization may be paused or delayed if the SRC or independent data monitoring committee (IDMC) recommends a pausing of trial treatment according to Section 7.1.2.

6 TRIAL TREATMENTS AND CONCOMITANT THERAPY

Trial treatment is defined as any investigational treatment(s), marketed product(s) used as auxiliary medicinal product (AxMP) intended to be administered to a patient according to the trial protocol.

An "IMP" is any medicinal product which is being tested or used as a reference in a clinical trial (the tested product and its reference products, including placebos).

An "AxMP" is a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an IMP (medicinal products used in the context of a clinical trial but not as investigational medicinal products).

Concomitant therapy is not considered trial treatment.

6.1 Trial treatments administered

Name	mFOLFIRINOX	BNT321
Trial treatment type	Chemotherapy	Monoclonal antibody
Dosage form	NA	BNT321 is provided as a single-use glass vial containing 8.0 mL of sterile solution at 10 mg/mL in a buffer at pH 6.0, containing 25 mM histidine, 150 mM sucrose, 55 mM sodium chloride, and 0.02% polysorbate 80.
Unit dose strength(s)	• Oxaliplatin: 85 mg/m^2 • Leucovorin: 400 mg/m^2 • Irinotecan: 150 mg/m^2 • 5-FU: 2400 mg/m^2 *	0.5 CCI mg/kg based on cohort
Dosage regimen	mFOLFIRINOX will be administered on the first day of each 14-day cycle (i.e., C1D1, C2D1, C3D1, and so on for a total of 12 cycles) using the following dose and schedule for each agent: • Oxaliplatin: Day 1 • Leucovorin: Day 1 • Irinotecan: Day 1 (starting 30 minutes after leucovorin) • 5-FU: Day 1	BNT321 will be incorporated into the mFOLFIRINOX regimen starting from the second cycle and after the completion of the 5-FU infusion (e.g., initially on C2D3).
Diluent	mFOLFIRINOX is prepared and administered according to institutional standards, in compliance with the package insert for each drug	Prior to infusion, BNT321 is diluted in normal saline to obtain a final concentration of less than 5 mg/mL

Name	mFOLFIRINOX	BNT321
Route of administration	• Oxaliplatin: IV over 2 hours • Leucovorin: IV over 2 hours • Irinotecan: IV over 90 minutes • 5-FU: Continuous IV infusion over 46 hours, following oxaliplatin, leucovorin, and irinotecan	IV infusion for 2 hours
Sourcing	See the Pharmacy Manual	See the Pharmacy Manual
Packaging and labeling	For details see the Pharmacy Manual	For details see the Pharmacy Manual

* Reduced 5-FU dose may be implemented for patients with DPD deficiency, per the discretion of the treating physician.
Abbreviations: 5-FU = 5-fluorouracil; CnDn = cycle number day number; DPD = dihydropyrimidine dehydrogenase; IV = intravenous; NA = not applicable.

6.2 Rationale for the trial treatment (dose, route, frequency)

Modified FOLFIRINOX + BNT321 combination therapy has been evaluated as first and second line treatment for advanced PDAC in the BioNTech trial MV-0715-CP-001.01. More than 60 cycles have been administered over a BNT321 dose range of CCI [redacted] IV on a Q2W schedule. The BNT321 combination MTD is CCI [redacted] Q2W in the metastatic setting and this is the highest prespecified dose cohort for the Phase I part of this trial adjuvant therapy. Additional BNT321 doses may be considered following comprehensive review of safety data and approval by an SRC that will be utilized for BNT321-02 Phase I. Extended course BNT321 monotherapy (Weeks 24 to 48) will be evaluated following the initial 12 cycles with combination chemotherapy. For Phase II patients randomized to BNT321 treatment, this 48-week regimen will be implemented following safety and RP2D determination in Phase I.

6.3 Dosing and administration

mFOLFIRINOX regimen

mFOLFIRINOX will be administered intravenously on the first day of the 14-day treatment cycle (i.e., on Day 1 of each cycle) using the following dose and schedule for each agent:

- Oxaliplatin, IV over 2 hours, 85 mg/m^2
- Leucovorin, IV over 2 hours, 400 mg/m^2
- Irinotecan, IV over 90 minutes, 150 mg/m^2 (starting 30 minutes after leucovorin)
- 5-FU, continuous IV infusion over 46 hours, 2400 mg/m^2, following oxaliplatin, leucovorin, and irinotecan

Modifications to the above dose and schedule for mFOLFIRINOX in response to toxicity considered secondary to mFOLFIRINOX will be made in accordance with Section 6.3.1.2 where specified, or otherwise with institutional SoC.

For BNT321 preparation, use of a patient's weight from the prior cycle is permitted. For patients who weigh more than 100 kg (220 pounds), the BNT321 administered dose should be calculated based on an adjusted weight of 100 kg.

The first dose of BNT321 for each patient will be administered as an IV infusion over at least 120 minutes. In patients who tolerate an initial infusion without difficulty, subsequent infusions may be reduced by 30 minutes to a minimum infusion duration of 60 minutes (i.e., a 120-minute infusion during the first infusion, a 90-minute infusion during the second infusion, a 60-minute infusion during the third and subsequent infusions). The BNT321 infusion duration should never be less than 60 minutes. Post-treatment monitoring period should be according to institutional guidelines.

Pre- and postmedications are defined in Section 6.9.3 and 6.9.2.

Patients with IRR should be treated according to Section 6.3.4.

Timing of BNT321 in relation to mFOLFIRINOX

BNT321 will be incorporated into the mFOLFIRINOX regimen from the second cycle onwards starting after the completion of the 5-FU infusion (i.e., initially on C2D3) and then every 2 weeks thereafter (i.e., Day 3 each cycle). In situations where the administration of mFOLFIRINOX is delayed or modified, any adjustment to the administration of BNT321 will be made in consultation with the Medical Monitor.

Patients in Phase I part of the trial, who have completed at least 8 weeks on trial (i.e., have completed the first four cycles), will have the option of receiving BNT321 earlier during each treatment course (e.g., on Day 1 of each cycle rather than Day 3). For all subsequent cycles, these patients are not required to come to the clinic on Day 3 of each cycle. Assessments called for on Day 3 will be moved to Day 1. In these patients, BNT321 should be administered after completion of irinotecan and prior to the start of the 5-FU infusion. Cycle Day 1 administration of BNT321 may be utilized for the Phase II part of the trial, following review of Phase I safety data and alignment with the SRC.

The Medical Monitor must be notified prior to implementing the modified assessment schedule for patients in Phase I, who have completed 8 weeks on trial and appear appropriate for consolidation of their treatment schedule.

6.3.1 Dose modifications

The SRC may request reduction of the planned dose and/or increase the interval between doses.

6.3.1.1 BNT321 dose delay or reduction (for BNT321-related events)

Prior to administration of all subsequent doses of BNT321, any clinically significant, BNT321 related, toxicity resulting from prior BNT321 administration must return to ≤ Grade 1 or baseline.

In the event that the administration of BNT321 was delayed for second incidence of Grade 2 or first incidence of Grade ≥3 BNT321-related toxicity, the patient may receive

subsequent administrations of BNT321 at a dose no more than 50% of the current dose. See Table 8 for specific dose modification guidelines for liver function tests (LFTs).

In the event that a clinically significant BNT321-related toxicity necessitates a delay of more than 14 consecutive days, the patient may be removed from trial treatment phase.

Re-escalation of BNT321 dose is not allowed for patients that previously have been dose reduced.

First occurrence of BNT321 related AE Grade ≥3 fulfilling DLT criteria:

- As a first measure, administration of BNT321 needs to be held.
- Investigator must contact the sponsor to discuss whether the patient should be withdrawn from BNT321 treatment or if the next dose should be delayed.
- Administration of BNT321 can be delayed for up to 14 days unless otherwise approved by the sponsor Medical Monitor. If the intensity of AEs resolves to Grade ≤1 within this period, retreatment may be considered under the following:
  - BNT321 should be administered at a dose of no more than 50% and after discussion with sponsor.

Second occurrence of an identical AE Grade ≥3 after re-exposure to BNT321:

- If retreatment leads to an identical AE with same intensity, the next administration of BNT321 should be stopped.
- Retreatment may only be considered on a case-by-case basis after review by the SRC.
- BNT321 must be permanently discontinued if the patient experiences an AE fulfilling the DLT criteria (after the DLT period has ended for the dose escalation) that fails to resolve to Grade ≤1 within 14 d after the planned dosing date, unless otherwise approved by the sponsor Medical Monitor.

Re-escalation of BNT321 dose is not allowed for patients that previously have been dose reduced.

The investigators are encouraged to contact sponsor in case of any safety concern that requires additional discussion or clarification.

Table 8: BNT321 dose modifications: elevated bilirubin and/or transaminases

	Cycle delay	BNT321 Dose reduction/modification
Grade 1 bilirubin, ALT, or AST	No delay	None
Grade 2 bilirubin alone	Delay treatment until recovery Grade ≤1 (14 days maximum)	1st episode: 50%-100% redose If no recovery to Grade ≤1 in this time frame discontinue BNT321 and DLT should be reported per Section 6.3.2. 2nd episode: reduce dose to 50% 3rd episode: discontinue
Bilirubin >2 x ULN and ALT or AST >3 x ULN	Evaluate for Hy's criteria see liver safety evaluation per Section 10.6	If meets Hy's law and deemed to be related to BNT321 discontinue and do not redose. If determined to be unrelated to BNT321 restart at 50–100% dose, following recovery to Grade ≤1.
Grade 2 bilirubin and Grade ≤2 ALT/AST (not meeting Hy's law criteria per Section 10.6)	Delay treatment until recovery Grade ≤1 (14 days maximum)	1st episode: 1st episode: 50%–100% redose If no recovery to Grade ≤1 in this time frame discontinue BNT321 and DLT should be reported per Section 6.3.2. 2nd episode: reduce dose to 50% 3rd episode: discontinue
Grade 2 bilirubin and Grade 3 AST or ALT (not meeting Hy's criteria per Section 10.6)	Delay treatment until recovery Grade ≤1 (14 days maximum)	1st episode: If recovery to Grade ≤1 within 14 days dose reduction by 50%. If no recovery to Grade ≤1 within this time frame discontinue BNT321 and report DLT per Section 6.3.2. 2nd episode: discontinue BNT321
Grade 2 ALT or AST with normal bilirubin	Delay treatment until recovery Grade ≤1 (14 days maximum)	1st episode: 50%-100% redose If no recovery to Grade ≤1 in this time frame discontinue BNT321 2nd episode: reduce dose to 50% 3rd episode: discontinue
Grade 3 ALT or AST with normal bilirubin	Delay treatment until recovery Grade ≤1 (14 days maximum)	1st episode: If recovery to Grade ≤1 within 14 days dose reduction by 50% If no recovery to Grade ≤1 within this time frame discontinue BNT321 and report DLT per Section 6.3.2. 2nd episode: discontinue BNT321
Grade 3 bilirubin	Delay treatment until recovery Grade ≤1 1 (14 days maximum)	1st episode: If recovery within 14 days dose reduction by 50%; If no recovery to Grade ≤1 within this time period discontinue BNT321 and report DLT per Section 6.3.2. 2nd episode: discontinue BNT321

	Cycle delay	BNT321 Dose reduction/modification
Any event of Grade 4 ALT, AST, or bilirubin	Discontinue treatment	Discontinue BNT321 and report any related event as DLT per Section 6.3.2.

Abbreviations: ALT = alanine aminotransferase, ALT = alanine aminotransferase, DLT = dose-limiting toxicity, ULN = upper limit of normal.

For total bilirubin elevation dose modifications for irinotecan may be also indicated see Section 6.3.1.2.

For AEs occurring in combination part of trial (mFOLFIRINOX + BNT321) which are considered clearly not related to BNT321 but related to the mFOLFIRINOX and require delay or discontinuation of the mFOLFIRINOX regimen, continuation of BNT321 administration as monotherapy is permitted after the AE has resolved to Grade ≤ 1 or baseline.

6.3.1.2 mFOLFIRINOX dose delay or reduction

In case a dose reduction is necessary, the reduced dosage will be maintained until the end of treatment.

In case of recurrent Grade 4 toxicity despite dose reduction, the investigator and the sponsor may discuss the possibility of stopping the treatment.

Table 9: Hematological toxicity based on Day 1 ANC and platelet count

	Cycle delay	Dose reduction		
		Irinotecan	Oxaliplatin	5-FU/leucovorin
Neutrophils <1.5 x 10^9/L	Delay treatment until neutrophils are ≥1.5 x 10^9/L and resume cycle with G-CSF*	1st episode: dose reduction to 120 mg/m² 2nd episode: maintain dose at 120 mg/m² 3rd episode: discuss treatment stop or maintain only LV/5-FU	1st episode: no dose reduction 2nd episode: reduce dose to 60 mg/m² 3rd episode: discuss treatment stop or maintain only LV/5-FU	1st episode: no dose reduction 2nd episode: no dose reduction
Platelets <100 x 10^9/L	Delay treatment until recovery (platelets ≥100 x 10^9/L)	1st episode: no reduction in dose 2nd episode: reduce dose to 120 mg/m² 3rd episode: discuss withholding irinotecan*	1st episode: reduce dose to 60 mg/m² 2nd episode: maintain dose at 60 mg/m² 3rd episode: discuss withholding oxaliplatin*	1st episode: no dose reduction 2nd episode: reduce the dose of IV continuous infusion by 25% 3rd episode: discuss withholding 5-FU

*Granulocyte colony stimulating factor and other hematopoietic growth factors may be used in the management of acute toxicity (such as febrile neutropenia) or prophylactically, when clinically indicated at the investigator's discretion. Blood cell transfusion (RBC or platelet) is allowed if clinically indicated. See Section 6.9.2 for more information.
Abbreviations: CBC = complete blood count; G-CSF = granulocyte colony stimulating factor; IV = intravenous; 5-FU = 5-fluorouracil; RBC = red blood cell.

Table 10: Hematological toxicity during the inter-cycle interval (nadir) with mFOLFIRINOX

Events	Dose reduction
Febrile neutropenia isolated Grade 4 neutropenia >7 days Infection with concomitant Grade 3 to 4 neutropenia	1st episode: reduce irinotecan dose to 120 mg/m^2 plus G-CSF 2nd episode: in addition, reduce oxaliplatin dose to 60 mg/m^2 3rd episode: discuss growth factor or further treatment reduction, maintain only LV/5-FU if necessary
Thrombocytopenia, Grade 3 to 4	1st episode: reduce the dose of oxaliplatin to 60 mg/m^2 2nd episode: in addition, reduce the irinotecan dose to 120 mg/m^2 and reduce 5-FU IV continuous by 25% 3rd episode: stop oxaliplatin and irinotecan, discuss withholding LV/5-FU

Abbreviations: G-CSF = granulocyte colony stimulating factor; IV = intravenous; LV/5-FU = continuous infusion of 5-fluorouracil and leucovorin.

Table 11: Gastrointestinal toxicities with mFOLFIRINOX

Events	Dose reduction
Isolated Grade 3 to 4 diarrhea OR diarrhea + fever AND/OR Grade 3 to 4 neutropenia	1st episode: reduce irinotecan to 120 mg/m^2 2nd episode: reduce oxaliplatin to 60 mg/m^2 and reduce 5-FU continuous by 25% 3rd episode: stop irinotecan
Recurrent diarrhea (>48 h) despite high doses of loperamide*	Irinotecan, oxaliplatin and 5-FU should be delayed by one week until Grade 1 or less, and redose at same level

*In no instance should loperamide be administered for more than 48 consecutive hours.
In case of occurrence of gastrointestinal ulceration, hemorrhagic or not, treatment with 5-fluorouracil should be stopped until disappearance of symptoms.
Abbreviation: 5-FU = 5-fluorouracil.

Supportive and prophylactic management per institutional guidelines and SmPCs for mFOLFIRINOX individual drugs.

Mucositis

These toxicities are caused by 5-FU. If Grade 3 to 4 toxicity occurs, 5-FU IV continuous infusion will be reduced by 25% for the remaining courses. Supportive care and prophylactic measures per institutional guidelines.

Cardiac toxicity

In case of angina pectoris with clinically significant ECG changes or myocardial infarction, 5-FU treatment shall be stopped. The reintroduction of 5-FU is not permitted.

Peripheral neuropathy

The dose of oxaliplatin can be adapted according to Table 12.

Table 12: Recommended dose modifications for oxaliplatin

Toxicity	≤7 days	>7 days and <14 days	Persisting between cycles
Asymptomatic or paresthesia/dysesthesia without functional alteration (Grade 1)	No modification	No modification	No modification
Moderate symptoms; limiting instrumental activities of daily living (Grade 2)	No modification	No modification	65 mg/m^2
Severe symptoms; limiting self-care activities of daily living (Grade 3)	65 mg/m^2	65 mg/m^2	Stop
Life-threatening consequences: urgent intervention indicated	N/A	N/A	Stop
Acute laryngopharyngeal dysesthesia	Prolong infusion duration to 6 hours. Add (if not previously done) 1 g of calcium gluconate and 1 g of magnesium sulfate over 15 min before the oxaliplatin infusion. Action to be repeated after the oxaliplatin infusion.		

If oxaliplatin is stopped because of neurotoxicity, irinotecan and 5-FU should be continued.

Elevated bilirubin

If bilirubin increase is >1.5 ULN, it is preferable to postpone mFOLFIRINOX chemotherapy because irinotecan has biliary elimination. The presence of a tumor relapse or obstruction of biliary anastomosis must be checked. Indication of chemotherapy will be retained, if these two diagnoses are eliminated. However, it is preferable to stop irinotecan if bilirubin elevation is persistent.

Other toxicities

Other Grade 2 toxicities, except anemia and alopecia, may justify a dose reduction of 25%. If it is medically indicated, for instance, reduction of irinotecan to 120 mg/m^2 and/or oxaliplatin to 60 mg/m^2 and/or 5-FU decreased by 25% depending on the type of toxicity.

6.3.2 Dose-limiting toxicity (DLT)

For all Phase I cohorts the DLT assessment period will encompass the treatment cycles of the first two consecutive BNT321 doses. Practically, this is 28 days within treatment Cycles 2 and 3.

To be considered a DLT, an AE must meet the following three criteria:

- Occurs during the DLT assessment period of BNT321.
- Is considered BNT321-related (i.e., definitely related or possibly related).
- Occurs in the presence of adequate supportive care (e.g., Grade 3 vomiting despite use of an appropriate anti-emetic regimen).

In addition, to be considered a DLT, an AE must meet at least one of the criteria listed below using CTCAE v5.0 criteria.

- Grade 4 hematologic toxicity (except for: Grade 4 thrombocytopenia without bleeding).
- Grade 3 or higher febrile neutropenia (i.e., ANC $<1.0 \times 10^9$ cells/L with a single temperature of >38.3°C [>100.9 F] or a sustained temperature of ≥38°C [≥100.4 F] for more than 1 h).
- Grade 3 thrombocytopenia associated with bleeding requiring platelet transfusion.
- Grade 3 microangiopathic hemolytic anemia.
- Grade 3 or higher non-hematologic toxicity (except for: Grade 3 peripheral neuropathy <14 days, Grade 3 fatigue for <7 days, Grade 3 AST or ALT for <14 days, Grade 3 total bilirubin for <72 hrs and not associated with Grade 3 or higher AST or ALT).
- Total bilirubin ≥2 x ULN for >14 consecutive days.
- Grade 2 total bilirubin in association with a Grade 3 or higher ALT or AST (also requires discontinuation of BNT321).
- Grade 2 or higher hemolysis.
- Delay for >14 consecutive days in administration of the second cycle of BNT321 secondary to liver toxicity (i.e., persistent elevations for this time period of serum transaminase and/or bilirubin).

Patients who will not be able to fulfill the criteria for the DLT assessment will be replaced (this only applies to patients who do not experience a DLT). Replaced patients can continue with BNT321 treatment and follow the same trial procedures except for DLT assessment until they meet the protocol-defined treatment discontinuation criteria.

The SRC will have the option of declaring other toxicities not listed above as DLT. These include sequalae (e.g., encephalopathy) considered related to AST or ALT elevations even if such elevations do not meet the Grade criteria stated above.

6.3.3 Retreatment of patients experiencing DLT

Patients experiencing DLT during the DLT assessment period will not receive additional trial treatment unless all the following conditions are met:

- The DLT has resolved to at least Grade 1 or returned to baseline with appropriate treatment (e.g., anti-emetics) or with a delay in trial treatment dosing.
- The DLT is not expected to recur based on an intervention such as prophylactic use of appropriate treatment (e.g., prophylactic anti-emetics), or dose reduction.
- Continued administration of trial treatment is considered to be in the patient's best interest based on the opinion of the investigator and the sponsor.

For the combination mFOLFIRINOX + BNT321, if a DLT is considered clearly related to a specific drug, the patient may continue with the remaining trial treatment if considered in the patient's best interest by the investigator and the sponsor.

6.3.4 Mitigation plans for BNT321 IRRs

IRRs are a general risk to be considered for any new compound administered IV irrelevant of its mechanism of action. An IRR is typically of immediate onset during or after the compound's administration. The risk of IRR cannot be excluded for BNT321.

All patients should be pre-medicated prior to BNT321 administration. Premedication to prevent IRR should be administered at the investigator's discretion according to local guidelines and recommendations of the SRC, see Section 6.9.3.

The following treatment guidelines are provided below for patients who experience an IRR associated with administration of BNT321 treatment (Table 13). The Medical Monitor should be contacted with any questions regarding these guidelines.

Table 13: Treatment guidelines for patients who experience a BNT321-related IRR

Grade	Definition	Treatment guideline
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Monitor for at least 2 hours after end of infusion; provide patient instructions and prophylactic medications at discharge as appropriate.
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment.	Infusion may be restarted once following a minimal 60-minute delay. A second infusion interruption requires discontinuation of BNT321 administration. Administration of medications (e.g., anti-histamines, steroids, NSAIDS and IV fluids etc.) as appropriate; monitor in clinic for at least 2 hours after completion of infusion; provide prophylactic medications as appropriate for subsequent BNT321 doses.

Grade	Definition	Treatment guideline
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae.	Administration of medications (e.g., anti-histamines, steroids, NSAIDS and IV fluids etc.) as appropriate; hospitalization for medical care and observation; discontinue BNT321 permanently.
4	Life-threatening consequences; urgent intervention indicated.	Hospitalization for urgent medical treatment; discontinue BNT321 permanently.

Abbreviations: IV = intravenous; NSAIDS = nonsteroidal anti-inflammatory drugs.

NOTE: For Grade 2 IRR prophylactic medications for subsequent BNT321 doses may include the institution of a prophylactic oral steroid regimen (20 mg dexamethasone 12 hours prior; 20 mg dexamethasone 6 hours prior; 6 mg dexamethasone twice daily for 3 days) at the investigator's discretion.

- All premedications must be reported on the Prior/Concomitant Medication electronic case report form (eCRF).
- IRR Grade ≥3 is an adverse event of special interest (AESI) (see Section 8.4.8).

6.3.5 Safety stopping rules

The following are safety stopping criteria for implementation of the Phase II part of the study only:

- Any death possibly related to the BNT321 within 30 days of receiving IMP.
- If during treatment, more than 33% of trial patients develop AEs meeting the DLT criteria, the trial cohort shall be paused pending a safety evaluation by the IDMC and sponsor.
- Any safety finding assessed as related to BNT321 that, in the opinion of the IDMC, contraindicates further dosing of trial patients.

These rules a priori will be followed by the SRC to take the temporary stopping decisions before final decision is implemented (e.g. permanent discontinuation, dose reduction of a treatment in the combination or adaptation of a monitoring plan)

Individual patients in all phases of the study will be discontinued from the study according to the safety stopping criteria detailed in Section 7.2.

6.4 Actions in case of overdose or errors in drug administration

For a definition of an overdose, see the subsection "AEs associated with an overdose or error in drug administration" in Section 10.4.1.3.3.

Overdose *per se* will not be reported as an AE but must be recorded on the relevant eCRF page.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose or an error in drug administration, the investigator should:

- Contact the sponsor's Medical Monitor immediately.
- Closely monitor the trial patient for any AE/SAE and laboratory abnormalities (at least 28 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor's Medical Monitor based on the clinical evaluation of the trial patient.

6.5 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all trial treatment received and any discrepancies are reported and resolved before use of the trial treatment.

Only patients enrolled in the trial may receive trial treatment and only authorized site personnel may supply or administer trial treatment. All trial treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site personnel.

The investigator, site, or the head of the site (where applicable) is responsible for trial treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Any non-compliance with the provided storage conditions should be reported to the sponsor upon discovery along with any actions taken. Once non-compliance is identified, the trial treatment must be quarantined and not used until the sponsor provides permission to use/discard/return the trial treatment.

Further guidance and information for handling, administration, and final disposition of trial drug are provided in the Pharmacy Manual.

6.5.1 BNT321

BNT321 for injection is stored at -15°C to -25°C and is provided as a single-use vial containing 8.0 mL of sterile solution at 10 mg/mL in a buffer at pH 6.0, containing 25 mM histidine, 150 mM sucrose, 55 mM sodium chloride, and 0.02% polysorbate 80. BNT321 for injection is packaged in clear USP Type I borosilicate glass vials with 20 mm West 4432/5- stoppers (grey colored coated closures) and blue 20 mm flip-off seals.

Prior to infusion, BNT321 is diluted in normal saline to obtain a final concentration of less than 5 mg/mL. The administration apparatus must include a 0.2-micron inline filter. BNT321 must be administered within 24 hours of preparation.

6.5.2 mFOLFIRINOX

mFOLFIRINOX will be prepared and administered according to institutional standards, in compliance with the package insert for each drug or as SmPC.

Pre- and postmedications will be administered in compliance with the package insert for each drug and according to institutional standards. Patients with IRR should be treated according with the package insert for each drug and according to institutional standards.

6.6 Patient assignment, randomization, and blinding

6.6.1 Assignment

For the Phase I part of this trial, patients will be enrolled sequentially to dose cohorts using a 3+3 dose escalation design.

For the Phase II part of this trial, patients will be enrolled to treatment arms through randomization, as described in Section 6.6.2.

6.6.2 Randomization

For Phase II, part 2, patients will be randomized in a 1:1 fashion to one of two treatment arms, mFOLFIRINOX + BNT321 or mFOLFIRINOX alone. Randomization will be conducted in the trial's interactive web response system (IWRS) up to 3 days before Cycle 1 Day 1. Randomization will include stratifications to ensure balanced enrollment between the two arms for the following characteristics: tumor resection status (R0 vs R1) and tumor nodal status at resection (pN0 vs pN1).

6.6.3 Blinding/Unblinding

BNT321-01 Phase II, part 2 is a randomized, open-label trial. Potential bias in assigning patients to treatment groups will be reduced by randomization. For the conduct of this part of the trial, trial site personnel will be unblinded regarding treatment allocation.

Radiologists that assess the CT scans will be blinded to the trial treatment.

6.7 Trial treatment compliance

Patients will receive trial treatment directly from the investigator or a designee under medical supervision. The date and time of each dose administered must be recorded in the source documents and in the eCRF. The dose of trial treatment and patient identification number will be confirmed at the time of dosing by a member of the trial site personnel other than the person administering the trial treatment. See Section 6.4 for guidance on the treatment of overdose or errors in drug administration.

6.8 Access to trial treatment after the end of the trial

The sponsor does not plan any extension studies or possibilities for continued access to trial treatment after completion of the trial.

6.9 Concomitant therapy

Prior treatments are any medications and non-drug therapies used by the patient up to 21 days before trial treatment initiation on Cycle 1 Day 1. Concomitant medications and therapies are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, or nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT321 administration and medications as a result of an AE).

6.9.1 Prohibited medication during the trial

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications and substances are prohibited during the trial:

- Any other investigational therapy.
- Antineoplastic systemic chemotherapy or biological therapy.
- Steroid treatment for any other purpose **except to** manage significant trial-related toxicity including to modulate symptoms of an IRR. Chronic systemic immunosuppressive corticosteroid doses (i.e., more than 10 mg/day prednisone or its equivalent) is prohibited. Steroid premedication may only be used prophylactically for chemotherapy-related toxicities when clinically indicated in the opinion of the investigator or per protocol Section 6.9.3.
- No dietary supplements are allowed during the trial period (except for multivitamins, vitamin D, calcium, and supplements in prevention of weight loss). The use of traditional/herbal medicines is not permitted.
- Strong CYP3A4 inducers, inhibitors, and UDP glucuronosyltransferase family 1 member A1 (UGT1A1) inhibitors should be discontinued for at least 2 weeks prior to initiation of mFOLFIRINOX therapy. The sponsor should be contacted if the primary investigator feels there are no therapeutic alternatives.
- Live or live attenuated vaccines should be avoided during irinotecan therapy and are exclusionary for the study if given within 3 weeks of the first dose of trial treatment.

If a patient receives any of these during the trial, the sponsor must be notified for determination of whether the patient may be permitted to continue on trial.

6.9.2 Permitted medication during the trial

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.9.1). Administration of concomitant medications must be reported in the appropriate section of the eCRF.

- Granulocyte colony stimulating factor and other hematopoietic growth factors may be used in the management of acute toxicity (such as febrile neutropenia) or prophylactically, when clinically indicated at the investigator's discretion.
- Blood cell transfusion (RBC or platelet) is allowed if clinically indicated and must be reported in the concomitant procedures section of the eCRF.
- Systemic (oral or IV) steroid therapy ≤10 mg prednisone daily or its equivalent for an underlying condition (refer to Section 6.5.1).
- Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency).
- Bisphosphonates (e.g., pamidronate, zoledronic acid, etc.) and denosumab.
- Paracetamol/acetaminophen, or acetylsalicylic acid/aspirin, at doses of less than 2 g/day, is permitted for use at any time during the trial.
- Multivitamins, vitamin D, calcium, and supplements in prevention of weight loss.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.3 BNT321 premedication

Pre and postmedications will be provided to mitigate potential reactions to BNT321. The recommended dose is 8 mg of dexamethasone IV at least 30 minutes prior to infusion and 4 mg dexamethasone twice daily for 2 days following BNT321 administration. The investigator may gradually reduce this regimen as appropriate in those patients without clinical evidence of IRRs.

The SRC or IDMC may modify the prophylactic regimen during the course of the trial as appropriate.

6.9.4 Vaccination against COVID-19

It is generally assumed that cancer patients may be at an increased risk of severe COVID-19 due to immunosuppression that may result from both anticancer treatment and the malignancy itself (Cook et al. 2020, Dai et al. 2020, Liang et al. 2020). As for the entire population, immunization with COVID-19 vaccine reduces the likelihood of SARS-CoV-2 infection as well as intensity of disease in patients with cancer. Additionally, decreasing the likelihood of SARS-CoV-2 infection by vaccination against COVID-19 may allow better adherence to anticancer therapeutic regimens and in doing so potentially increase treatment efficacy. Based on the available non-clinical and clinical data, the sponsor considers that the potential benefits of vaccination against COVID-19 in patients with PDAC treated with BNT321 outweigh the anticipated risks.

The following recommendations are proposed to mitigate potential risks:

- Patients with prior vaccination against COVID-19 will only be allowed to enter this trial with a washout period of at least 7 d since the last COVID-19 vaccine dose.

- Patients who are already enrolled in this trial and still receiving trial treatment will only be allowed vaccination COVID-19 if it is ensured that there are at least 7 d between individual doses of COVID-19 vaccine and trial treatment.
- In terms of the risk/benefit of COVID-19 vaccination, the final decision for individual patients should be taken by the investigator in accordance with individual country guidance on vaccination in patients with active cancer.
- Patients treated with BNT321 should not be immunized directly prior to and during the trial with live attenuated vaccines, as per prohibited concomitant medication and patients are excluded from the study if they have received a live vaccine within 3 weeks prior to the first dose of trial treatment (see Section 6.9.1).

6.9.5 Recording concomitant medication during the trial

All concomitant medication permitted or prohibited (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the trial patient receives should be reported to the investigator and recorded on the Prior/Concomitant Medications eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The trial Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The start and stop dates and name of the concomitant medication during the trial will be recorded in the eCRF for the period defined in the SoA (Section 1.3).

7 DISCONTINUATION OF TRIAL TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation or pausing (temporary halting) of trial treatment

7.1.1 Permanent discontinuation of trial treatment

Patients permanently discontinued from trial treatment will not be discontinued from the trial (i.e., will continue with trial visits, and complete disease assessments and Survival FU Visits).

Administration of BNT321 will be discontinued in the event of any of the following:

- Discontinuation of BNT321 for abnormal liver function should be considered by the investigator when a patient meets one of the conditions outlined in Section 6.3.1 or if the investigator believes that it is in best interest of the patient;
- Recurrence of disease;

- Continued treatment is not considered to be in the patient's best interest in the opinion of the investigator;
- Unacceptable AE(s) considered related to mFOLFIRINOX or BNT321, despite addition of appropriate therapy to manage toxicities (see Section 6.3);
- Pregnancy;
- Withdrawal of consent by the patient;
- Significant patient non-compliance as determined by the clinical investigator;
- Termination of trial by the sponsor.

See the SoA (Section 1.3) for data to be collected at the time of trial treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.2 Pausing of trial treatment (temporary halting)

Details for withholding of mFOLFIRINOX and BNT321 therapy are provided in Section 6.3.

A pause of trial treatment may be caused by a failure in the trial treatment supply chain such that there is no trial treatment available.

See the SoA (Section 1.3) for data to be collected at the time of pausing trial treatment discontinuation and for any further evaluations that need to be completed.

7.1.3 Rechallenge

Parameters for retreatment of mFOLFIRINOX and BNT321 following regression of observed toxicities are outlined in Section 6.3.

Patients are not permitted to re-enter the trial following termination of trial treatments and completion of the EOT visit.

7.2 Patient discontinuation/withdrawal from the trial

A patient who has consented during any phase of the trial, who requests to discontinue receipt of trial treatment, will remain in the trial, and the patient must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for further continuation in the trial.

A patient will be withdrawn from the trial at any time at their own request or discontinued from the trial at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

Reasons for patient discontinuation from the trial include the following:

- Lost to follow-up;
- Death;
- Withdrawal of content;
- Patient noncompliance;

- Investigator decision;
- Trial terminated (closure of all sites) by sponsor;
- Protocol deviation;
- Pregnancy.

See the SoA (Section 1.3) for data to be collected at the time of withdrawal/discontinuation from the trial and for any follow-up / further evaluations that need to be completed.

If discontinued from the trial, the patient will be permanently discontinued both from the trial and from the trial treatment at that time. In these cases, the sponsor will retain and continue to use any data collected before the permanent discontinuation.

If a patient withdraws from the trial, they may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as a protocol deviation as long as the patient's safety was preserved.

For guidance on premature termination or suspension of the whole trial, see Section 10.1.9.

Re-enrollment is not permitted following trial discontinuation.

7.3 Lost to follow-up

A patient will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, three telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, they will be considered to have withdrawn from the trial.

7.4 Replacement of permanently discontinued patients

Patients who are not considered evaluable for safety assessment during the dose escalation part of the trial may be replaced at the discretion of the sponsor.

In the Phase II part of the trial, patients who have been randomized but did not receive any treatment will be replaced.

8 TRIAL ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated informed consent before performing any trial-specific procedures.

All screening evaluations must be completed and reviewed to confirm that potential trial patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Protocol waivers or exemptions would be protocol deviations.

See the SoA (Section 1.3) for all planned time points for assessments.

Any safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.

Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct, but there may be protocol deviations. Every effort should be made to ensure that protocol-required activities are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the planned activity. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required activity cannot be performed, the investigator must document the reason for the missed activity and any corrective and preventive actions taken to ensure that required processes are adhered to as soon as possible. The sponsor must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the trial.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the informed consent may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1 Screening/baseline assessments and procedures

At screening, the following demographic data will be recorded for all patients:

- Age
- Sex
- Ethnic group
- Race

- Body weight, height, and derived body mass index

Adequate representation of demographic subgroups in this trial is necessary for understanding the safety and efficacy associated with novel cancer therapeutics. Medical history will be recorded for at the times given in the SoA (Section 1.3). It should include but not limited to lifetime history of cancer, tumor characteristics such as mutation status, cancer-related somatic genomic alterations and germline status, prior non-cancer significant medical conditions for the 2 years prior to trial entry, other clinically relevant diseases including tuberculosis, surgeries, use of alcohol and/or drugs abuse and reproductive status.

8.2 Efficacy assessments

Planned time points for efficacy assessments are provided in the SoA (Section 1.3). Response assessments will follow the procedures outlined in RECIST 1.1.

8.2.1 Tumor evaluations (CT/MRI)

Screening assessments must include computed tomography (CT) scans (with i.v. contrast unless contraindicated) of the chest and abdomen and pelvis. Magnetic resonance imaging (MRI) of the abdomen and pelvis may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). CT of the chest without contrast may be performed for patients for whom CT scans with contrast are contraindicated.

Patients should be evaluated with the same method of assessment and the same technique (CT or MRI) used at baseline screening, throughout the trial. At the investigator's discretion, imaging may be repeated at any time if disease recurrence or a new primary cancer is suspected.

On trial, imaging assessments will be performed on the following schedule: from C1D1 every 3 months (12 weeks) for 2 years, and then every 6 months for 3 years thereafter (±7 days).

Tumor assessments will be submitted for central review and assessed by radiologists blinded to the treatment assignment. The baseline screening assessments must be obtained post-operatively and must not be more than 4 weeks prior to first trial treatments. The baseline screening assessments must be available to confirm NED prior to enrollment of patients into both phases of this trial.

8.2.2 Tumor marker CA19-9

CA19-9 measurements will be taken to follow disease according to the SoA (Section 1.3).

8.2.3 Eastern Cooperative Oncology Group performance status

The ECOG PS should be assessed by the investigator or suitably qualified designee according to Table 14.

Table 14: Eastern Cooperative Oncology Group performance status grading

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

8.2.4 Survival follow-up

Following the safety follow-up visit, site staff will contact the patient every 3 months for 2 years and then every 6 months for the next 3 years or until the patient is lost to follow-up or dies. Survival follow-up will determine survival status and record if patients have taken any new anticancer treatments. This contact may be by telephone, E-Mail or other form of communication but must be documented in the source notes.

8.3 Safety assessments

Safety assessments will be performed routinely using vital signs, physical examinations, ECGs, performance status assessments, and clinical laboratory parameters.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical examinations, height, and body weights

Physical examinations will be performed (by inspection, palpation, and auscultation) by a physician or advanced practice provider (i.e., certified nurse practitioner or physician's assistant) at the trial site according to the SoA (Section 1.3).

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

An abbreviated physical examination (a limited, symptom-directed physical examination) will be performed at the other times noted in the SoA and as clinically indicated at other time points. New or worsened clinically significant abnormalities will be recorded on the AE page of the eCRF.

Height (in cm) and weight (in kg) will be assessed at screening. Weight will be assessed at additional time points as indicated in the SoA. Assessment of weight should be repeated at any time if there are apparent weight changes.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (see Sections 10.4.1 and 10.4.2) must be reported according to the processes in Sections 10.4.3 and 10.4.4.

8.3.2 Vital signs

Vital signs (oral body temperature (in °C), systolic/diastolic blood pressure, heart rate, and respiratory rate) will be assessed at the time points listed in Section 1.3).

The same position and methods for measuring the vital signs should be used for one trial patient throughout the trial.

Vital signs measurements should be preceded by at least 10 minutes of rest for the trial patient in a quiet setting without distractions (e.g., television, cell phones). Vital signs will be measured with trial patients in the seated position and before any blood draws.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

If vital signs measurements are abnormal, two further measurements must be done at intervals of 1 min and the average of the three measurements must be recorded on the eCRF.

Any untoward vital signs findings that are identified during the active collection period and meet the definition of an AE or SAE (see Sections 10.4.1 and 10.4.2) must be reported according to the processes in Sections 10.4.3 and 10.4.4.

8.3.3 Electrocardiograms

Planned time points for ECGs are provided in the SoA (Section 1.3).

If cardiac symptoms occur, during an AE the site should perform an unscheduled ECG to confirm/diagnose the event.

Triplicate/ 12-lead ECG will be recorded as outlined in the SoA using an ECG machine that automatically calculates the ventricular heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Triplicate ECG readings should include three individual ECG tracings obtained as closely as possible in succession, but no more than 2 min apart. The full set of triplicates should be completed in less than 4 min.

8.3.4 Clinical laboratory tests

Planned time points for biosampling for clinical laboratory tests are provided in the SoA (Section 1.3).

The below listed clinical laboratory parameters will be assessed. Blood sampling and urine collection for additional clinical laboratory tests (including the addition of parameters) may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

The planned clinical laboratory parameters include:

- Chemistry: to include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, and uric acid. Estimated glomerular filtration rate (eGFR) will be calculated.
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, MCV and MCH.
- Serum amylase, -lipase, GGT, and haptoglobin.
- Dipstick urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocyte esterase.
- Microscopic urinalysis: if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.
- Only in patients born female where the postmenopausal status needs to be confirmed: Follicle stimulating hormone (FSH) at signing of the ICF.
- Only for POCBP: urine ß-human chorionic gonadotropin (ßhCG).
- DPD and UGT1A1 genotype testing at screening if required by local regulations.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial as AEs in the AE section of the eCRF. The laboratory reports must be filed with the source documents. For a definition of clinically significant abnormal laboratory findings, see Section 10.4.1.3.2.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial or within 14 days after the last dose of trial treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the trial Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the site's local laboratory require a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

Any (serious) AEs resulting from laboratory tests values will be graded by the investigator.

8.3.5 Quality of life / patient-reported outcomes

Patient-reported outcome (PRO) instruments will be utilized to assess the treatment benefit, more fully characterize the safety profile of BNT321, and will enable the capture of each patient's direct experience with BNT321.

PRO data will be collected using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (QLQ-C30) combined with EORTC Quality of Life Questionnaire for pancreatic cancer (QLQ-Pan26). PRO instruments will be self-administered at the clinic at screening, Day 1 of every other treatment cycle starting from Cycle 3, at EOT, and at every disease assessment time point (see SoA Section 1.3) These instruments will be administered before the patient receives any information on their disease status, prior to the performance of non-PRO assessments, and prior to the administration of trial treatment.

8.3.5.1 Description of PRO assessment instruments

The EORTC QLQ-C30 is a validated and reliable self-reporting measure (Aaronson et al. 1993; Fitzsimmons et al. 1999) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health and quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales. The functioning and symptoms items are scored on a 4-point scale that ranges from “not at all” to “very much,” and the GHS and QoL items are scored on a 7-point scale that ranges from “very poor” to “excellent”.

The EORTC QLQ-PAN26 consists of 26 questions that assess nine pancreatic cancer-related and treatment-related symptoms (pain, eating-related items, cachexia, hepatic symptoms, side effects, altered bowel habits, ascites, indigestion, and flatulence) and five emotional domains specific to pancreatic cancer (body image, healthcare satisfaction, sexuality, fear of future health, an ability to plan for the future) (Mackay et al. 2022). The QLQ-PAN26 is scored on a 4-point scale that ranges from “not at all” to “very much”.

NOTE: This instrument has a current pending update which will be updated when available.

8.4 Adverse events and serious adverse events

Definitions of AEs and SAEs can be found in Section 10.4.

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs/SAEs will be collected from the signing of the ICF until the safety follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of trial treatment administration but after obtaining informed consent will be recorded on the respective Medical History/Current Medical Conditions section of the eCRF and not in the AE section.

8.4.2 Detecting and reporting AEs and SAEs

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs and SAEs. The investigator will record on the eCRF all observed directly, and all spontaneously reported AEs and SAEs reported by the patient.

Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences. Care will be taken not to introduce bias when detecting AEs and/or SAEs.

The recording, evaluating, and assessing of AEs and SAEs are provided in Section 10.4.

For grading the intensity of AEs and SAEs, Version 5 of the US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) will be used.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and they consider the event to be related (see Section 10.4) to the trial treatment or trial participation, the investigator must promptly notify the sponsor as described in Section 10.4.4.

The investigator may be requested by the sponsor to obtain specific follow-up information in an expedited fashion.

All SAEs (initial and follow-up reports) will be recorded and reported to the sponsor or designee within 24 h after the site becoming aware of the event, as indicated in Section 10.4.4.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4.2.2.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

If a patient dies during participation in the trial or during the follow-up period (see the SoA in Section 1.3), the investigator will provide the sponsor a copy of any postmortem findings including histopathology.

The investigator will submit any updated SAE data to the sponsor within 24 h of receipt of the information.

All ongoing AEs/SAEs will be followed until resolution, considered by the investigator to be stable or chronic (resolved with sequelae), the patient is lost to follow-up or the patient withdraws consent. If no final status is reached at the EOT visit, the investigator must confirm the unavailability of a final status.

8.4.4 Reporting requirements for SAEs including SUSARs

Prompt notification of an SAE via EDC and/or the provided SAE form by the investigator to the sponsor within 24 hours of the site awareness is essential so that the ethical responsibilities toward patients, the safety of the trial treatment under clinical investigation, and regulatory reporting obligations can be met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies involved in the conduct of trials with the same IMP about the safety of a trial treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators. The execution of reporting to the different entities may be delegated as detailed in the trial-specific Safety Management Plan.

All serious adverse reactions, the nature, intensity, or outcome of which is not consistent with the reference safety information are “unexpected serious adverse reaction”. The expectedness assessment for all related SAEs is based on the reference safety information included in Section 6.2 of the BNT321 IB.

All suspected adverse reactions related to an IMP (the tested drugs and comparators) that occur in this trial, and that are both unexpected and serious are qualify as suspected unexpected serious adverse reactions (SUSARs). SUSARs are subject to expedited reporting requirements according to applicable regulatory requirements and guidance (e.g., ICH E2A guidance).

For the IMPs, it is the sponsor’s or delegate’s responsibility to perform expedited SUSAR reporting submission to the applicable regulatory authorities, the IRBs/IECs within the timelines stipulated in the respective country regulations. Reporting to the investigators will follow country-specific regulatory requirements and applicable guidelines.

All AEs suspected to be related to the AxMP should be sent by the investigator to the national competent authority in the country where it occurred (according to the national legislation) or to the marketing authorization holder of the AxMP, but not to both, to avoid duplicate submissions (ENTR/CT-3, GVP Module VI EMA/873138/2011 Rev 2).

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) or SUSARs from the sponsor should review it and then file it together with the IB. If required by local requirements, the investigator will notify the relevant IRB/IEC.

8.4.5 Pregnancy counseling, testing, and collection of pregnancy information

For POCBP, pregnancy tests and counseling will be performed at the times given in the SoA (Section 1.3).

Any trial patient who becomes pregnant while participating in the trial will be immediately permanently discontinued from trial treatment.

For the details about the collection of pregnancy information, see Section 10.5.3.

8.4.6 Death events

Any death that occurs within the observation period will be reported as an SAE, if not covered by the exemptions to the SAE definition as defined in Sections 8.4.7, 10.4.2, and 10.4.2.2, which do also apply for fatal cases. Date and cause of death will be recorded. If available, a copy of an autopsy report should be submitted if available upon request.

In case of a fatal event, the event term should not be "death" but the underlying event which led to death (death = outcome). If there is more than 1 AE in a fatal case, only for the AE leading to death the outcome "fatal" should be selected. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be documented as event term.

In addition to reporting as SAE, the death page of the eCRF needs to be completed.

Deaths clearly related to the progression of the disease will not be documented as AEs nor reported as SAEs if fatal progression/death is a trial endpoint. These deaths must be collected on the death page of the eCRF.

8.4.7 Disease-related events and/or outcomes not qualifying as AEs or SAEs

The progression of underlying disease (e.g., new metastases, death) during trial participation is not considered as an AE if fatal progression/death is a trial endpoint.

Because disease progression is common for patients with cancer, it will not be reported according to the standard process for expedited reporting of an SAE even though the event may meet the definition of a SAE. These events will be recorded on the corresponding page in the patient's eCRF as for SAEs.

NOTE: Symptoms resulting from the progression of the underlying malignant disease fatal cases clearly related to the progression will not be documented as AEs and reported as SAEs. However, specific symptoms at time of progression that are considered relevant but that may be caused by other reason, and fatal cases due to another reason than the disease progression may not be discarded. The findings will have to be documented as AEs and reported as SAEs if applicable.

8.4.8 Adverse events of special interest

An AE of special interest (AESI), serious or non-serious, is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor are appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

- Grade ≥3 infusion-related reaction related to BNT321
- Grade ≥3 AST or ALT or Grade ≥2 bilirubin elevation lasting ≥7 days, related to BNT321

NOTE: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be

evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

AESIs including non-serious AESIs should be reported via the SAE Report Form according to the timelines and contact details given in Section 10.4.4 of this protocol. For non-serious AESIs, the seriousness criterion should not be reported/selected as these non-serious AESIs are to be reported according to the timelines of SAEs, but mostly do not have the seriousness of an SAE.

All AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3).

8.5 Pharmacokinetics

Planned time points for PK sampling to obtain plasma level BNT321 are provided in the SoA (Section 1.3, Table 3).

- The actual date and time (24-h clock time) of each sample should be recorded. Blood samples for PK analysis should be collected, handled, frozen and shipped as outlined in the Laboratory Manual.
- PK samples will be analyzed centrally by a specialty laboratory. Detailed instructions on collection of blood for BNT321 PK will be provided in the pharmacokinetic kit and Laboratory Manual.
- The sponsor may elect to adapt future collections of blood for PK levels based on previously generated PK data.

Leftover of samples collected for PK testing and of samples collected for immunogenicity testing can be used interchangeably if they were collected at the same timepoint and after the original purpose of the sample was fulfilled.

8.6 Genetics

No genetic analyses are planned for this trial.

8.7 Biomarker assessments

Sampling for biomarkers will be performed at the time points listed in Section 1.3.

Sample handling and storage – details on the collection, processing, shipment, and storage of samples will be provided in separate documents (e.g., sample handling sheets or laboratory manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the trial at a facility selected by the sponsor to enable further analyses.

The following biomarker assessments will be done centrally by a specialty laboratory:

- PBMCs will be isolated from collected blood to measure ADCC activity over the course of time on trial. This sample will only be collected if logistically manageable.

- Serum will be isolated from collected blood to measure CDC activity over the course of time on trial.
- Serum will be isolated from collected blood to measure cytokine/chemokine levels for pharmacodynamic assessment.
- Plasma will be isolated from collected blood to track and measure circulating tumor DNA (ctDNA) over the course of treatment as a surrogate for tumor burden. In addition, specific mutations may be monitored over time to understand potential resistance mechanisms.
- FFPE tumor tissue from resection or biopsy will be obtained during screening. In the event of progression, a biopsy collection should be requested as optional. IHC expression of CA19-9 and expression of other biomarkers may be evaluated for exploratory analysis of correlations between expression levels and indicators of response. Tumor samples may also be examined using RNAseq as an exploratory analysis of gene signatures correlating with response and/or by whole exome sequencing (WES) to inform ctDNA analysis.

Biomarker analyses may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there is not enough sample to allow adequate evaluation. If the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments in part or total is based on justification and intended utility of the data.

Medical history information – if any additional relevant information about the tumor, disease, or status of disease was collected during treatment prior to entry of the patient in the trial, these results may be taken into consideration during the biomarker analyses.

The results of biomarker investigations will be reported separately (e.g., in a biomarker evaluation report) instead of in the ICH E3 clinical trial report. All data generated using the biomarker samples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection, for sample shipment outside Germany, and a potential withdrawal of consent.

8.8 Immunogenicity assessments

Immunogenicity samples will be collected from all patients on the combination therapy arm (will not be collected for the control arm). Planned time points for immunogenicity sampling (anti-BNT321 antibodies) are provided in the SoA (Section 1.3). An extra sample will be taken for re-testing of future analysis if required. Samples will also be collected at the final visit from patients who discontinued trial treatment or were withdrawn from the trial.

Samples and any data derived using the collected samples will be processed in compliance with the applicable regulations and GCP.

Blood samples for immunogenicity analysis must be collected, handled, frozen and shipped as outlined in the laboratory manual.

Immunogenicity samples will be analyzed by a specialty laboratory. All collection and storage tubes will be provided in the laboratory sampling kits.

Leftover of samples collected for PK testing and of samples collected for immunogenicity testing can be used interchangeably if they were collected at the same timepoint and after the original purpose of the sample was fulfilled.

8.8.1 Exploratory research analyses

Blood samples will only be used for exploratory analyses if the patients have provided separate informed consent for these analyses.

In selected patients, further exploratory research analyses can be conducted using residual biological samples from subsets of patients in order to further characterize the mechanism of action of the antibody treatment, e.g., additional characterization of patient tumor, PBMCs, serum, and plasma.

Exploratory research analyses will be planned, conducted, and reported in accordance with the sponsor's standard operating procedures (SOP).

Biosamples for research analyses will be retained for use for up to 15 years (or shorter if required by local regulations) after the end of the trial. The tube with the biosample will be labeled with a number (optionally also with a bar code) and will not include information that could be used to identify the patient. Results of the analyses will be linked to the clinical information collected during the trial using this specific number. The analysis will only be carried out on the basis of the label data and biosamples. Research biosamples and all data generated using the biosamples, will be handled in accordance with applicable laws and regulations; this includes requirements applicable for data protection and a potential withdrawal of consent.

The patient may withdraw consent for future use of research samples at any time. To initiate the sample destruction process, the investigator must notify the sponsor of withdrawal of consent for the research samples and to request sample destruction. The sponsor will then initiate the process for sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed. If the patient withdraws consent for research samples, the sponsor may retain and continue to use any data from samples already analyzed before such a withdrawal of consent. Samples will be destroyed after they are no longer needed for the clinical trial.

8.9 Other assessments

No other assessments are planned.

8.10 Blood collection

According to trial SoAs the total blood volume drawn over any 2-week cycle in any group will be less than 115 mL. Additional blood samples may be taken, e.g., for safety assessments of AEs or SAEs.

As long as the absolute volume of blood drawn does not change per patient overall, the volume of individual blood draws may be adapted if required, e.g., due to unforeseen shortage of specific tubes. Leftover or back up clinical sample aliquots of a patient, which have the exact same collection times, intended to a particular assessment can be used for another assay than that stated on the label if both assessments are described in the SoA and, the patient has consented to all. This is only possible if a primary sample has been used first for its original purpose and it is confirmed that no re-testing is required. Samples can only be used interchangeably if the sample characteristics, collection, shipment, and storage conditions are the same.

8.11 Unscheduled visit(s)

Unscheduled visits can be performed at any time point when clinically indicated as per the treating provider. These assessments are symptom based and may include additional screening tests and procedures deemed medically necessary by the investigator. The data should be entered in the appropriate unscheduled visit eCRF pages.

8.12 Early termination visit(s)

If, for any reason, patients are permanently discontinued from the trial before completing all scheduled visits, patients will complete an Early Termination Visit. If possible, all assessments planned for the actual week or day of that visit as listed in respective SoA (Section 1.3) and which are not included in the EOT visit should also be performed.

9 STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this trial is described here and further detailed in the statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

There will be an SRC (for Phase I) and an IDMC (for Phase II). For relevant procedures relating to SRC and IDMC operation (e.g., charter, composition, and schedule of meetings etc.), see Section 10.1.5.

9.1 Statistical hypotheses

For the Phase I part of this trial, no formal hypotheses are tested.

For the Phase II part of this trial, the main primary endpoint (i.e., mDFS) will be assessed between the two randomized groups using the two-sided log-rank test, stratified by the randomization strata, at 5% significance level. Considering proportional hazards, i.e., $\lambda_{T(t)} = \theta \lambda_{C(t)}$, where λ (t) denotes the hazard at time t in combination group (T) and mFOLFIRINOX group I, respectively, and θ the unknown constant of proportionality of hazards, the following null and alternative hypothesis will be tested:

$$H0: \theta = 1 \text{ versus } H1: \theta \neq 1.$$

9.2 CCI

[redacted]

Table 15: CCI

[redacted]

9.3 Sample size determination

The sample size calculation is based on the primary endpoint of mDFS, ensuring that DFS will be adequately powered. The calculation of the required number of events is based on the following specifications:

- 1:1 randomization
- Hazard ratio (HR) = 0.60
- Significance level of α = 5% (two-sided)
- Power of 1-β = 90%

Based on these specifications [redacted] (Section 9.2) at least 164 aggregate events (i.e. 55% maturity) in both arms will be required to demonstrate efficacy assuming a true effect size of HR = 0.60 with a power of 90% using a two-sided statistical test at 5% significance level.

The calculation of the required number of patients is based on the following assumptions:

- Median DFS time from randomization of 21.6 months in the mFOLFIRINOX group and 36 months in the combination group (assume HR = 0.60)
- Accrual duration: ~24 months for Phase I and Phase II
- Follow-up duration: until DFS event
- Drop-out rate: 10% per year

Based on these assumptions at least 300 patients in both arms combined will be required to observe the required number of DFS events (164) ~34 months after last patient in (LPI) (randomized).

9.4 Analysis sets

The following analyses sets are defined:

Analysis set	Description
Screened Set	All patients who gave informed consent
Enrolled Set	All patients who are enrolled into the trial
Full Analysis Set (FAS)	All patients who are randomized into the trial
Modified Full Analysis Set (mFAS)	All patients who received IMP and have a baseline and at least one on-treatment / post-treatment tumor response assessment and satisfy major eligibility criteria
Safety Analysis Set (SAF)	All patients who received IMP (i.e., at least one dose of IMP)
DLT Evaluation Set	All patients who are enrolled in the dose escalation part of the trial (Phase I) and who meet at least one of the following criteria: • Experiences a DLT following at least one dose of BNT321

Analysis set	Description
	• Does not experience a DLT, has received at least 80% of the planned BNT321 dose, and is followed for the full DLT assessment period
Per Protocol Set (PP)	All patients who are randomized into the trial and absent of important protocol deviations (as identified throughout the conduct of the trial and before each data cut-off) which are considered to impact the analyses
PD Set	All patients with baseline and at least one valid on-treatment follow-up PD assessment
PK Set	All patients with baseline and at least one valid on-treatment follow-up PK assessment

Abbreviations: DLT = dose-limiting toxicity; IMP = investigational medicinal product; PD = pharmacodynamic; PK = pharmacokinetic.

All safety analyses will be based on the treatment actually taken by the patient ('as treated'). All other analyses will be based on the treatment the patient was assigned / randomized to ('as randomized'), unless stated otherwise.

9.5 Statistical analyses

Statistical analyses will be performed by BioNTech or a designated CRO. All statistical analyses will be carried out using SAS®, Version 9.4 or higher, and/or other statistical software as required.

The SAP will be finalized prior to first database lock for the primary analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. Any deviations from the planned analyses described in the final SAP will be described and justified in the clinical trial report. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.5.1 General considerations

In general, the statistical analyses will be performed for Phase I and Phase II parts separately. The Phase I part analysis will be performed by dose level cohort. The Phase II part will be performed by treatment group (i.e., mFOLFIRINOX + BNT321 and mFOLFIRINOX).

Continuous variables will be summarized by treatment group/cohort using the following descriptive statistics: number of patients (n), mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized by treatment group/cohort presenting absolute and relative frequencies (n and %) of patients in each category.

Time-to-event-endpoints will be analyzed using Kaplan-Meier methodology by treatment group/cohort and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and the EMA guidance "Guideline on the

evaluation of anticancer medicinal products in man". Censoring rules will be defined in the SAP.

The median survival time (including two-sided 95% confidence limits according to Brookmeyer and Crowley) and the first and third quartile will be presented for each treatment group/cohort. Survival rates and DFS rates (including two-sided 95% confidence interval based on the Greenwood 1926 formula) as well as the number and percentage of patients with events, censored and under risk will be displayed for selected time points (e.g., at 12, 24, 36 and 48 months).

The survival distributions for two treatment groups will be compared using the stratified log-rank test (stratified by the stratification factors surgical resection status and nodal status at time of resection), and the p-value will be provided. The associated HR and two-sided 95% confidence interval will be estimated by using stratified (i.e., R0 versus R1; pN0 versus pN1) Cox proportional hazard model with treatment as model covariate.

The time-to-event analysis will be illustrated using Kaplan-Meier plots by treatment group and additionally strata. Baseline is defined as last available value prior to randomization (Phase II)/first dose of IMP (Phase I).

Data up to and including the clinical cut-off date for the statistical analysis will be included in the statistical analysis. Handling of missing data will be described in the SAP.

9.5.2 Analysis of primary endpoints

Phase I

Analysis of the primary safety endpoints (i.e., TEAEs, SAEs and DLTs) will be performed using the Safety Analysis Set (for TEAEs and SAEs) and the DLT Evaluation Set (for DLTs), respectively.

Descriptive statistics with number and proportion (%) of patients reporting at least one TEAEs in the following categories will be summarized by:

- DLTs
- Any TEAE
- Treatment-related TEAE
- Grade of TEAE
- Related Grade ≥3 TEAE
- Serious TEAE
- Treatment-related serious TEAE
- TEAEs leading to permanent discontinuation of trial treatment
- Fatal TEAEs

None of the Phase I safety endpoints will be formally tested so that the type I error rate will be preserved for Phase II primary endpoint of mDFS.

Phase II

For the Phase II part of this trial, the primary analyses will be performed using the Full Analysis Set (FAS) at two-sided 5% type I error rate. The analysis will be repeated using the Per Protocol (PP) set as sensitivity analyses. The time to DFS will be analyzed using Kaplan-Meier methodology by treatment group and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" and the EMA guidance "Guideline on the evaluation of anticancer medicinal products in man". Censoring rules will be defined in the SAP.

The primary endpoint (mDFS) is defined as the time from randomization to occurrence of any of the following events, whichever occurs first:

- Locoregional recurrence or distant metastases as determined by an independent central radiology assessment.
- Occurrence of second primary (same or other) cancer as determined by an independent central radiology assessment.
- Death from any cause.

9.5.3 Analysis of secondary endpoints

The secondary endpoints are defined in Section 3.

The secondary efficacy analyses will be performed for both Phase I and Phase II parts. The full analysis set will be used and will be repeated using the PP set as sensitivity analyses.

Overall survival (OS)

OS is defined as the time from randomization to death from any cause.

The time to OS will be analyzed using Kaplan-Meier methodology by treatment group/cohort. Patients alive or patients lost to follow-up at date of analysis cut-off will be censored at the day of their last date known to be alive. Additional censoring rules will be defined in the SAP.

OS rate is defined as percentage of patients who are alive using the Kaplan-Meier methodology.

The OS rates in percentage will be presented by treatment and cohort at 12, 24, 36, and 48 months.

Disease-free survival (DFS)

DFS rates is defined as percentage of patients who are disease-free as defined in Section 9.5.2.

In addition to the primary analysis of time to DFS events the DFS rates in percentage will be presented by treatment and cohort at 12, 24, 36, and 48 months.

Relapse-free survival (RFS)

RFS is defined as the time from randomization to occurrence of any of the following events, whichever occurs first:

- Locoregional recurrence or distant metastases as determined by the investigator.
- Death from any cause.

The following are considered as events: locoregional recurrence, distant metastases, death from PDAC, death from other cancer, non-cancer death, treatment-related death. Occurrence of second primary (same or other) cancer as determined by the investigator are ignored. Patients still event-free or patients lost to follow-up at date of analysis cut-off will be censored at the day of their last date known to be event-free. Additional censoring rules may be defined in the SAP.

RFS will be analyzed using Kaplan-Meier methodology by treatment group.

Analysis of secondary efficacy endpoints

Pharmacokinetic (PK)

The PK analysis will be performed based on Pharmacokinetic Set (PK Set).

Individual and mean (± standard deviation) serum concentration of BNT321 when co-administered with mFOLFIRINOX will be tabulated and plotted over time. PK parameters will be estimated from the serum concentration data using a non-compartmental analysis method. PK parameters will include C_{max}, t_{max}, $t_{1/2}$, Vd, AUC, and CL. These parameters will be listed by individual patient and summarized using descriptive statistics (means, medians, ranges, standard deviations, and coefficient of variation as appropriate).

Immunogenicity

The immunogenicity analysis will be performed based on FAS.

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-BNT321 antibodies. The immunogenicity titre and neutralising ADA data will be listed for samples confirmed positive for the presence of anti-BNT321 antibodies.

The effect of immunogenicity as well as the effect of its neutralising properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

Pharmacodynamic (PD)

The PD analysis will be performed based on Pharmacodynamic Set (PD Set).

The percentage of lysis of target positive cells via patient-derived effector cells as a readout for ADCC activity, and/or patient-derived serum containing antibody and/or complement as a readout for CDC activity will be summarized by visit. Other PD parameters may be summarized if sufficient data is available.

Heath-related quality of life (EORTC QLQ-C30 and QLQ-Pan26)

The analysis of health-related quality of life analysis will be performed based on FAS. The EORTC QLQ-C30 and EORTC QLQ-Pan26 will be scored according to the EORTC Scoring Manual (Fayers et al. 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale according to the EORTC Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if at least 50% of the subscale items have been answered, then the subscale score can be calculated. The subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al. 2001). Otherwise, the subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

The main PRO measures identified in the secondary objectives are global health status/QoL, EORTC QLQ-C30 (includes physical functioning, fatigue, pain and appetite loss subscales). For EORTC QLQ-Pan26, one subscale (e.g. pancreatic pain) will be identified as part of the main analysis of the secondary endpoint. In addition, separate analysis may be conducted for each EORTC QLQ-Pan26 scale/symptom score.

The primary assessment of global health status/QoL, physical functioning, or symptom will focus on comparing mean change from baseline at end of Cycle 12 between treatment arms. Change from baseline at end of Cycle 12 will be analyzed using a mixed model repeated measurements analysis of post-baseline scores. The model will include treatment arm, visit, and treatment by visit interaction as explanatory variables, and the baseline score and baseline score by visit interaction as covariates. Adjusted mean change from baseline at end of Cycle 12 estimates per treatment arm and corresponding 95% CIs will be presented, along with an overall estimate of the treatment difference, 95% CI, and p-value. In addition, differences in LSMeans at end of Cycle 12 between treatments together with 95% CIs as well as standardized mean differences will be presented.

Summary tables of responses for each EORTC QLQ-C30 and EORTC QLQ-Pan26 scale/item score (global health status/QoL, 5 functions, fatigue, pain, appetite loss) for each assessment (improvement, deterioration, and no change) will be presented by treatment arm.

Finally, summaries of absolute and unadjusted change from baseline at end of Cycle 12 values of each

EORTC QLQ-C30 and EORTC QLQ-Pan26 scale/item score will be reported by assessment timepoint for each treatment arm. Graphical presentations may also be produced as appropriate.

Full details of the statistical analyses and appropriate sensitivity analyses will be described in full in the SAP.

9.5.4 Analysis of safety data

Safety data that will be summarized includes AEs, clinical laboratory parameters, vital signs, and ECGs. All safety analyses will be based on the Safety Analysis Set and will be summarized descriptively by treatment group Phase II/cohort Phase I unless otherwise stated.

Adverse events

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system to get a System Organ Class (SOC) and Preferred Term (PT) for each AE and graded for severity using NCI CTCAE v5.0.

A treatment-emergent AE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 28 days after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator.

Treatment-emergent AEs (as defined in Section 10.4.1) will be summarized overall and by treatment group Phase II/cohort Phase I.

The number and percentage of patients reporting at least one AE will be summarized by PT nested within SOC for each of the following AE types:

- Any AE
- Related AE
- Grade ≥3 AE
- Related Grade ≥3 AE
- Any SAE
- Related SAE
- SAE leading to death
- AEs leading to dose reduction
- AE leading to permanent discontinuation of treatment
- DLT (Phase I only)
- AESIs

Moreover, the number and percentage of patients with any AE will be summarized by worst NCI CTCAE grade by PT nested within SOC.

For Phase I only, DLTs will be presented in terms of listings presenting the reported term and MedDRA PT and SOC term, its time of onset, duration, and outcome, relationship, NCI CTCAE grade, and seriousness including dose exposure data.

Laboratory parameters

Clinical laboratory assessments to be summarized include hematology, blood chemistry, and urinalysis. The clinical laboratory parameters to be assessed are listed in Section 8.3.4 and at the time points specified in the SoA (Section 1.3).

Clinical laboratory parameters at each timepoint and change from baseline to each post-baseline timepoint will be summarized using descriptive summary statistics for each parameter by treatment group Phase II/cohort Phase I.

Clinical laboratory results will be classified according to the most recent version of NCI CTCAE. Shift tables from baseline to worst grade on-treatment will be provided for each laboratory parameter by treatment group Phase II/cohort Phase I.

Additionally, the occurrence of clinically significant abnormal laboratory results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by treatment group Phase II/cohort Phase I.

Laboratory results will be listed along with the normal ranges and NCI CTCAE grade. Laboratory values that are below or above the normal ranges will be flagged.

Vital signs

Vital sign parameters to be assessed are listed in Section 8.3.2 and at the time points specified in the SoA (Section 1.3).

Vital sign parameters at each timepoint and change from baseline to each post-baseline timepoint will be summarized using descriptive summary statistics for each parameter by treatment group Phase II/cohort Phase I.

Additionally, the occurrence of abnormal vital sign results within a patient will be analyzed using descriptive summary statistics for each parameter and visit by treatment group Phase II/cohort Phase I.

ECG

ECG parameters to be assessed are listed in Section 8.3.3 and at the time points specified in the SoA (Section 1.3).

ECGs will be judged by the investigator as clinically significant (yes/no). The number and percentage of patients with clinically significant ECG findings will be summarized by treatment group Phase II/cohort Phase I for each visit.

9.5.5 Analysis of exploratory endpoints

The exploratory endpoints are defined in Section 3 and will be further described in the SAP.

9.5.6 Other analyses

Dose intensity

mFOLFIRINOX dose intensity will be analyzed based on Safety Analysis Set. This will be expressed as the mFOLFIRINOX relative dose intensity (RDI), defined as follows:

Cumulative chemotherapy dose received / total planned doses

For each patient the % RDI will be determined. The number and percentage of patients with RDI ≥70% versus ≤70% will also be summarized categorically.

Treatment exposure

The following dose exposure variables will be derived and analyzed for mFOLFIRNOX and BNT321:

- Number of cycles
- Treatment Duration (weeks) defined as follows: (Date of last administration - Date of first administration + Planned Duration)/7, whereas the Planned Duration (days) is defined as the planned time between two consecutive administrations
- Cumulative Dose (µg) defined as sum of all administered doses
- Dose Intensity (DI) defined as Cumulative Dose (µg)/Treatment Duration (weeks)

Relative Dose Intensity (RDI) is defined as follows:

$$RDI_{(\%)} = \frac{\text{Actual Dose Intensity}\left(\frac{\mu g}{week}\right)}{\text{Planned Dose Intensity}\left(\frac{\mu g}{week}\right)} \times 100 = DI \times TI \times 100$$

Whereas

$$\text{(Actual) Dose Intensity}\left(\frac{\mu g}{week}\right) = \frac{\text{(Actual) Cumulative Dose (µg)}}{\text{(Actual) Treatment Duration (weeks)}}$$

$$\text{Planned Dose Intensity}\left(\frac{\mu g}{week}\right) = \frac{\text{Planned Cumulative Dose (µg)}}{\text{Planned Treatment Duration (weeks)}}$$

$$\text{Dose Index (DI)} = \frac{\text{Total Administered Dose (µg)}}{\text{Total Planned Dose (µg)}}$$

$$\text{Time Index (TI)} = \frac{\text{Planned Treatment Duration (weeks)}}{\text{Actual Treatment Duration (weeks)}}$$

Other analyses will be described in the SAP.

9.6 Analyses in support of SRC/IDMC

For details on the SRC/IDMC, see Section 10.1.5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, ethical, and trial oversight considerations

This trial will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP guidelines, and applicable laws and regulations.

10.1.1 Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents, will be submitted to the relevant regulatory authorities as required by applicable regulations. If required, approval for conducting the trial will be obtained from regulatory authorities in accordance with relevant regulatory requirements.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will be submitted for IRB/IEC approval and (if required) competent authority approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.

The principal investigator or delegate will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 (if applicable), and all other applicable local regulations.

- Informing the sponsor immediately about any urgent safety measures taken by the investigator to protect the trial patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

The principal investigator, any investigator(s), the sponsor, or personnel at other establishments, must cooperate with any inspection of the documents, facilities, records, and other resources deemed appropriate by the inspecting authorities to be related to the trial and that may be located at the trial site, at the sponsor, or at other establishments.

The sponsor must be notified as soon as possible about any upcoming regulatory authority inspection.

10.1.2 Financial disclosure

All investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3 Informed consent process

Informed consent must be obtained before any trial-specific screening procedure is performed.

Patients must be informed that their participation is voluntary.

The investigator or their representative will explain the nature of the trial to the patient or their legally authorized representative and answer all questions regarding the trial.

Patients or their legally authorized representative will be required to sign and date a statement of informed consent that meets the requirements of local regulations (e.g., US 21 CFR 50), ICH GCP guidelines, US Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be informed in a timely manner if new information becomes available that may impact their willingness to participate in the trial. If required, patients will be re-consented to updated written information and ICFs.

Patients who are rescreened must reconsent.

A copy of the ICF(s) must be provided to the patient or their legally authorized representative.

Patients or their legally authorized representative defined must be re-consented to the most current version of the ICF during their participation in the trial.

A separate ICF will be used in this trial for exploratory research.

10.1.4 Data protection

All data collection and processing during this trial will be performed in accordance with the applicable data protection requirements.

Patient personal data will be stored at the trial site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized trial personnel have access. The trial site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the trial site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

Patients will be assigned a unique identifier by the investigator according to the sponsor specifications on unique identifier assignment. The trial site will maintain a confidential list of patients who participated in the trial, linking each patient's unique identifier to their actual identity and medical record identification.

Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that their personal trial-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF.

The patient must be informed that their medical records may be examined by sponsor Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

If the patient withdraws from the trial and/or withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. When patient data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorized access, disclosure, dissemination, alteration, or loss of information and processed personal data, the sponsor has implemented and maintains the following measures:

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors.
- Ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial.
- Implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services.

- Implementing network, application, database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks.
- Logging of security events/incidents in information systems.
- Implementing procedures that cover reporting, analysis, monitoring, and resolution of security incidents.
- Ensuring that BioNTech SE information systems, computers and software involved in the performance of the services provided in the trial are backed up.
- A process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing.
- Implementing procedures and practices for securing destruction of paper documents containing personal data.
- Implementing business continuity procedures ensuring that the sponsor can continue to provide services through operational interruption.

All locations, personnel and information systems that are used to perform services for the clinical trial will be covered.

The sponsor will ensure the technical and organizational security measures described above are regularly reviewed and updated to take into account any evolution on technological developments. The sponsor may apply additional specific statutory requirements, where applicable in the national laws, and will implement the necessary security measures even if they are not expressly listed above.

Besides the already above-mentioned technical and organizational measures, the sponsor, by means of internal measures and imposed contractual clauses to the selected sub-contractors, ensures the confidentiality of records and personal data of patients.

The sponsor has put in place a functional process of reporting of any data breach occurring at the sponsor's or its sub-contractor's facilities and premises. In case of the occurrence of any data breach, the sponsor will immediately apply relevant measures to mitigate the risks to data patients as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data patients will be reported to the relevant supervisory data protection authority within 72 hours of the sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, patients will be informed by the sponsor (via clinical trial site).

10.1.5 Committees (SRC and IDMC)

For the Phase I part of this trial an SRC will be established to provide medical oversight of patient safety during the conduct of this trial, with a focus on guidance, management of emergent safety issues, and decision-making as outlined in the SRC Charter. This includes periodic in-depth review of safety data by trial patient, cohort, and cumulatively, in

order to confirm mechanism of action, identify potential off-target toxicities, and to understand the IMP's safety profile and feasibility for further clinical development. The SRC is also a forum for the discussion of other data which could impact the IMP benefit-risk assessment, thereby allowing the SRC to periodically assess the overall benefit-risk of the IMP.

The SRC will be constituted and act according to procedures described in the SRC Charter. The SRC will prepare written minutes of its meetings.

All SAEs considered related either by the investigator or the sponsor will trigger an ad hoc review by the SRC.

For the randomized Phase II part of this trial, an IDMC will be established prior to the inclusion of the first patient in this phase. The IDMC will review unblinded analyses of safety data and primary endpoint data provided by an unblinded independent statistician.

The IDMC will meet to review safety data at least twice a year throughout the trial.

CCI [redacted] Further details will be specified in a separate IDMC Charter.

10.1.6 Dissemination of clinical trial data

A final ICH E3 conform clinical study report (CSR) integrating all trial results will be prepared by the sponsor.

In all cases, trial results will be reported in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the trial or the country in which the trial was conducted.

Clinical trial data and documentation will be disseminated as required per applicable laws and regulations, e.g., the European Union (EU) Regulation No 536/2014, EU Regulation 1049/2001, and the US Final Rule, which implements Section 801 of the US Food and Drug Administration Amendments Act (FDAAA 801). Clinical documents under such laws includes protocols and protocol amendments, SAPs, and CSRs.

This trial will be registered, and trial results be publicly posted, on publicly accessible trial registries (e.g., ClinicalTrials.gov, EU Clinical Trials Register, etc.) as required per applicable laws and regulations.

If this clinical trial is used to support marketing authorization packages/submissions, the sponsor will comply with the EU Policy 0070, the proactive publication of clinical data on the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, ICH E3 CSRs, and appendixes containing the protocol and protocol amendments, sample eCRFs, and statistical methods. under Phase 2 of this policy, "clinical data" includes the publishing of individual patient data.

Even if not required by applicable laws and regulations, this trial will be registered, and trial results be publicly posted on ClinicalTrials.gov. In addition, expert summaries of the

outcomes for all primary and secondary outcome measures (irrespective of outcome) and lay summaries, will be posted on a publicly accessible website.

BioNTech may provide researchers secure access to participant level data, expert summaries, lay summaries, and CSRs for the purposes of "*bona fide* scientific research" that contributes to the scientific understanding of the disease, target, or compound class. In these cases, all trial patient level data will be anonymized in accordance with applicable privacy laws and regulations.

The results for all primary and secondary outcome measures, irrespective of outcome, will be submitted for publication in academic journals (for further details, see Section 10.1.10).

10.1.7 Data quality assurance

All patient data relating to the trial will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other parties (e.g., CRO).

Ongoing source data verification will be performed to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the investigator for 30 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

10.1.9 Early trial site closure and trial termination

A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

All trial sites will be closed upon trial completion.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended trial site closure.

The sponsor reserves the right to close a trial site early or to terminate the whole trial or to suspend the whole trial (a temporary halt; an unplanned interruption of the conduct of a trial by the sponsor with the intention to resume it) at any time for any reason.

Reasons for the sponsor to close a trial site early include (but are not limited to):

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of trial patients by the investigator

Reasons for the sponsor to prematurely terminate the whole trial include (but are not limited to):

- When there are safety concerns (e.g., if there is an SRC or IDMC recommendation)
- Discontinuation of further trial treatment development

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the trial of the reason, as specified by the applicable regulatory requirements.

10.1.9.1 Investigator tasks triggered by premature termination of the trial

If the trial is prematurely terminated for any reason, the investigator should promptly inform the trial patients, should assure appropriate therapy and follow-up for the patients, and, where required by the applicable regulatory requirement(s), should inform the regulatory authorities. In addition:

- If the investigator terminates a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator should promptly inform the sponsor and the IRB/IEC and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination.
- If the sponsor terminates a trial, the investigator should promptly inform the institution where applicable, and the investigator should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination.
- If the IRB/IEC terminates its approval/favorable opinion of a trial, the investigator should inform the institution where applicable, and the investigator should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination.

10.1.10 Publication policy

The results for all primary and secondary outcome measures, irrespective of outcome, will be submitted by the sponsor for publication in academic journals. The results of this trial may also be presented by the sponsor at scientific meetings.

The results of this trial may be published or presented at scientific meetings by the investigator. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any trial treatment-related information necessary for the appropriate scientific presentation or understanding of the trial results.

Unless agreed in advance otherwise, site- or subpopulation-specific analyses may only be published after the outcomes of the primary endpoint analyses have been published.

The sponsor will comply with applicable requirements for publication of trial results. In accordance with standard editorial and ethical practice, including those established by the International Committee of Medical Journal Editors (ICMJE). The sponsor will generally support publication of multi-site trials only in their entirety and not as individual site data. In this case, an investigator will be designated by mutual agreement to coordinate the publication.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.11 Protocol preparation and approval

This protocol has been prepared, reviewed, and approved in accordance with the sponsor's SOP. Documentation of this process is filed in the trial master file (TMF).

10.1.12 Investigators and trial administrative structure

10.1.12.1 Investigators and trial site personnel

There must be an investigator at each trial site.

If the trial is conducted by a team of individuals at the trial site, the investigator leading and responsible for the team is called the principal investigator.

The responsibilities of principal investigator(s) must be documented before any trial-related procedure is performed. All persons assigned responsibility as principal investigator must sign a declaration of their responsibilities. They must also sign a declaration that they have read and understand the content of the protocol, that all questions have been adequately answered, and that they are qualified by experience and training to act as investigator for this trial.

The principal investigator at each trial site is responsible for ensuring that this trial is conducted in accordance with the protocol, the principles of GCP, and applicable regulatory requirements.

If the trial is conducted at multiple trial sites, a coordinating investigator must be assigned who is responsible for the coordination of investigators at different trial sites. The responsibilities of the coordinating investigator must be documented before any trial-related procedure is performed.

Documentation of all involved investigators must be maintained according to ICH GCP and applicable regulatory requirements.

Curriculum vitae and/or other relevant documents confirming the current qualification of the investigators must be provided to the sponsor. This should include any previous training in the principles of GCP, experience obtained from work with clinical trials, and experience with medical care.

10.1.12.2 Trial site personnel assigned trial-related duties

The principal investigator may define appropriately qualified personnel at a trial site to perform significant trial-related procedures and/or to make trial-related decisions under their supervision. In this case, the principal investigator must maintain a signed list of the persons to whom they delegate significant trial-related duties/responsibilities; the delegated trial-related duties/responsibilities must be specified in the list.

When personnel or responsibility changes are made, the principal investigator must ensure that the relevant documentation is updated before any trial-related activities are performed.

Documentation of all involved trial site personnel performing significant trial-related procedures and/or making trial-related decisions must be maintained according to GCP and applicable regulatory requirements.

10.1.12.3 Contract research organizations

Documentation of all involved CRO must be maintained according to GCP and applicable regulatory requirements. This includes documentation of any delegation of responsibilities to CROs.

10.1.12.4 The sponsor and sponsor's personnel

The trial sponsor listed on the title page accepts the responsibilities of the sponsor according to GCP and applicable regulatory requirements.

The sponsor will designate appropriately qualified personnel to advise on trial-related topics. The trial site will be provided with contact details for these personnel before any trial-related procedure is performed.

A list of key sponsor personnel involved in the preparation of this protocol and the conduct of the trial, including their full names, titles, roles, and responsibilities, will be maintained.

10.1.13 Liabilities and insurance

The sponsor is responsible for taking out relevant clinical trial insurance in accordance with local law and regulations.

10.2 Data collection and management

The trial documentation must be adequate for the reconstruction of the trial.

10.2.1 Data management

The CRO will be responsible for data management of this trial, including quality checking of the data.

Data will be collected through the use of an electronic data capture (EDC) system. Trial sites will be responsible for data timely entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the trial sites, which the trial sites will resolve electronically in the EDC system.

The CRO will produce a Trial Data Validation Specification document that describes the quality checking to be performed on the data. eCRFs and correction history will be maintained in the EDC system's audit trail.

System backups for data stored by the CRO and sponsor and records retention for the trial data will be in accordance with regulatory requirements.

At the end of the trial, the investigator will receive trial patient data for their trial site in a readable format that must be kept with the trial records. Acknowledgment of receipt of the patient data will be obtained.

10.2.2 Case report forms

CRFs will be completed through use of a validated EDC system. Trial site personnel will receive training and have access to eCRF completion guidance. The CRFs should be handled in accordance with instructions and be submitted electronically to the sponsor via the system.

The eCRFs are set up in accordance with the protocol, reviewed, and tested via user acceptance testing before they are released to production. Different user groups will be given different access for their specific roles.

All eCRFs should be completed in a timely manner by designated, trained trial site personnel. eCRFs should be reviewed, verified, and then electronically signed and dated by the investigator or a designee.

10.2.3 Patient-reported outcomes

The following PROs will be collected from all patients who entered screening and who are subsequently enrolled either into the combination arm or control arm: EORTC QLQ-C30 and EORTC QLQ-Pan26. After enrollment or randomization, PROs will be collected as outlined in the SoAs in Section 1.3. PROs will be provided to the trial site as printed copies as part of the ISF or electronically. At the given time points each patient must complete all PROs by him/herself. PROs completed by the patient are considered as source documents. The investigator or designee must transfer the PRO data to the eCRF if provided on paper.

10.2.4 Investigator's Site File and the Trial Master File

The principal investigator is responsible for the filing of all essential documents in an ISF. The sponsor is responsible for the timely filing of all essential documents in the TMF. As applicable, these files must be available for monitoring visits and during audits or regulatory inspections.

After trial completion, the principal investigator must ensure that all source data/documentation related to the trial is recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. The principal investigator must take measures to prevent accidental or premature destruction of these documents.

The principal investigator must keep the ISF, the source data/documentation arising from the trial according to the prescribed record retention period in the country and/or according to the hospital policy, but at least until informed by the sponsor that the trial-related records are no longer required.

10.3 Clinical laboratory tests

Blood and urine will be collected for clinical laboratory tests at the times given in the SoA (Section 1.3). The parameters that will be analyzed are listed in Section 8.3.4.

10.4 AEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.4.1 Definition of AEs and TEAEs

- An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP).
  NOTE: AEs with an onset date more than 60 days after the last administration of IMP will be considered as treatment-emergent only if assessed as related to IMP by the investigator.

10.4.1.1 Events meeting the AE definition:

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions or worsening of pre-existing conditions detected or diagnosed after signing the ICF.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE.
- AE leading to medical/surgical procedure needs to be captured as an AE.

10.4.1.2 Events not meeting the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. However, specific symptoms resulting from the progression and fatal cases due to the progression must be documented as AEs and reported as SAEs if applicable.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur or continue (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- DREs and/or disease-related outcomes not qualifying as AEs or SAEs are further specified in Section 8.4.7.

10.4.1.3 Documentation of particular situations

10.4.1.3.1 AEs that are secondary to other events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be documented as an independent AE in source data and eCRF. For example:

If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be documented as AE.

If vomiting results in severe dehydration, both events should be documented as AEs separately.

10.4.1.3.2 Abnormal laboratory results and vital signs values

Not every laboratory or vital signs abnormality needs to be documented as AE. For clinically significant laboratory/vital signs abnormalities the following definitions and documentation rules apply:

- If a laboratory/vital signs abnormality is a sign of a disease or syndrome, the laboratory/vital signs abnormality is clinically significant and only the diagnosis of the causing disease or syndrome needs to be documented as AE.
- If a laboratory/vital signs abnormality results in specific symptoms but no diagnosis of a disease or syndrome can be made, the laboratory/vital signs abnormality is clinically significant and only the symptoms need to be documented as AEs.
- If a laboratory/vital signs abnormality is not a sign of a disease or syndrome and does not result in specific symptoms but leads to a change in trial treatment or in a medical intervention, the laboratory/vital signs abnormality is clinically significant and must be documented as AE.

10.4.1.3.3 AEs associated with an overdose or error in drug administration

An overdose is the accidental or intentional use of a drug in an amount (per administration or cumulatively) higher than the dose being studied (for the trial treatment) or higher than the maximum recommended dose according to the authorized product information (for approved concomitant medications). An overdose or incorrect administration of a drug is not itself an AE, but it may result in an AE.

All AEs associated with an overdose or incorrect administration should be documented as AE in source data and eCRF and reported as SAE if applicable.

10.4.1.4 Suspected adverse reaction

Suspected adverse reactions are untoward and unintended responses to an IMP related to any dose administered.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

10.4.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization:
  - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity:

  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or birth defect.
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.2.1 Use of the terms "severe" and "serious"

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v5.0; see Section 10.4.2.2 for guidance on the assessment of intensity; the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be assessed independently for each AE recorded on the eCRF.

SAEs must be reported by the investigator to the sponsor immediately (i.e., within 24 h after learning of the event; see Section 10.4.4 for reporting instructions).

10.4.2.2 SAE exemptions

In general, SAEs are defined according to ICH Topic E2A (CPMP/ICH/377/95), EU Directive 2001/20/EC and ENTR/CT-3 (see Section 10.4.2). In the present trial, some events are excluded from the SAE definition. The following events do not need to be reported as SAEs:

- AEs and SAEs occurring after the end of the observation period must only be reported by the investigator to the sponsor if a relationship to trial treatment or trial procedure is suspected.
- Hospitalizations for respite care will not be considered as reportable SAE.

- Hospitalizations solely for coordination of care, including hospice arrangements, will not be considered as reportable SAE.
- Hospitalizations that were necessary solely because of patient requirement for care outside of normal outpatient clinic operating hours will not be considered as reportable SAE.
- Planned hospitalizations required by the protocol (e.g., for trial treatment administration or insertion of access device for trial treatment administration) will not be considered as reportable SAE.
- Hospitalizations for procedures or interventions of a pre-existing condition of the patient (elective surgery = planned, non-emergency surgical procedure) will not be considered as a reportable SAE (unless the intervention/procedure is not caused by an acute worsening of the pre-existing condition during the time trial participation):
    - if it was planned and documented in patient record before the trial-specific patient informed consent was signed (ICF for trial participation, see Section 10.1.3, or
    - if it was scheduled during the trial when elective surgery became necessary, and the patient has not experienced an AE.

NOTE: nevertheless, this kind of hospitalization should be avoided during trial treatment.

- The progression of the underlying malignant disease (e.g., new metastases, death) during trial participation is not considered as AE if progression/death is a trial endpoint. However, specific symptoms resulting from the progression and fatal cases due to the progression must be documented as AEs and reported as SAEs if applicable.
- Routine treatment or monitoring of the underlying disease not associated with any deterioration in the patient's condition.

10.4.3 Recording and follow-up of AEs and/or SAEs

AE and SAE recording

The investigator needs to assess and document any AE regardless of association with the use of the trial treatment during the period of observation (see Section 8.4.1).

- Data pertaining to AEs will be collected during each trial visit either. Based on the patient's spontaneous description or investigator's inquiry or discovered in the course of examinations done during the visit, clinical significance of any sign or symptom needs to be evaluated by the investigator.

- Clinically significant findings need to be documented as AEs in the source data and eCRF. Findings that are evaluated and documented in the source data as not clinically significant (e.g., an abnormal laboratory value without any clinical manifestation), should not be documented as AE.
- The investigator will then record all relevant AE information in the eCRF and perform an assessment on:
  - Intensity (see the section Assessment of intensity)
  - Seriousness
  - Outcome including onset and end dates
  - Causal relationship of the AE to the trial treatment/trial procedure
  - Any trial treatment action and/or any other action taken
- All assessments as well as AE term (diagnosis/description), start date and time of onset, end date and time need to be documented in the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor.
- To avoid colloquial expressions, the AE should be reported in standard medical terminology. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

Assessment of intensity

The intensity of an AE (i.e., severity of organ toxicity) will be graded according to the NCI CTCAE v5.0. AEs that are not listed in this CTCAE version should be classified according to the investigator's discretion as close as possible to CTCAE v5.0, based on the comparison with the most severe case encountered in past training and clinical experience.

The investigator will assess the intensity of each (serious) AE reported during the trial and assign it to one of the following categories:

- Grade 1 - Mild
- Grade 2 - Moderate
- Grade 3 - Severe
- Grade 4 - Life-threatening consequences; urgent intervention indicated
- Grade 5 - Death related to AE

With regards the intensity of an (serious) AE, the following needs to be documented and eCRF:

- Initial intensity of the AE
- For each change of intensity:
  - New grade of intensity
  - Date of change (= start of new grade of intensity)
  - Time of change (only if relevant)
  - New action taken

A change of intensity only needs to be documented if there is a clearly definable change in grading of the AE (e.g., a laboratory result changes from severe to moderate).

An event is defined as “serious” when it meets at least one of the predefined seriousness criteria as described in the definition of an SAE, independent from its intensity.

Actions taken by the investigator

Actions taken by the investigator as a result of an AE must be documented.

Action(s) taken with trial treatment (IMPs) by the investigator:

- Dose not changed (= continuation of trial treatment administration according to the trial protocol)
- Dose reduced (i.e., reduction of the trial treatment dosage *)
- Drug interrupted (i.e., trial treatment withdrawn temporarily, interruption and resumption); i.e.:
  - Delayed administration of IMP within one treatment cycle
  - Delayed start of the next treatment cycle
  - Cancellation of IMP administration at a given visit
  - Interruption of IMP administration during a given visit
- Drug withdrawn (i.e., trial treatment permanently withdrawn)
- Unknown (e.g., in case the patient is lost to follow-up)
- Not applicable (e.g., in case treatment with trial treatment has not yet started or event starts after last trial treatment administration)

*If an increase of trial treatment dosage is intended according to the trial protocol and the dosage is kept in comparison to last administration of trial treatment, it needs to be documented as “Dose reduced.”

Other action(s) that may be taken by the investigator include:

- None
- Initiation of a concomitant therapy for the treatment of the AE
- Initiation of a non-drug therapy for the treatment of the AE

Investigator assessment of the outcome of an AE

The investigator has to assess the outcome of an AE (and not the patient's outcome) at the time of documentation based on the following criteria:

- Recovered/resolved* (= complete resolution of the AE)
- Recovering/resolving (= AEs which are improving but not yet resolved completely, e.g., decrease in an intensity grade)
- Not recovered/not resolved (= AEs which are ongoing without improving or still present when the patient deceases due to another cause)
- Recovered/resolved with sequelae* (= patient recuperated but retained pathological conditions resulting from the AE; the sequelae should be indicated)
- Fatal** (= death due to the AE)
- Unknown (e.g., in case the patient is lost to follow-up)

* Generally, an AE is defined as recovered/resolved if all symptoms have ceased, no medication for treatment of the event is taken anymore and no other measures (e.g., hospitalization) are ongoing.

If the patient has developed permanent or chronic symptoms or if the event requires long-term medication(s), the AE is defined as recovered/resolved with sequelae as soon as no changes of symptoms and/or medication(s) are expected anymore.

An AE that is documented as a worsening of a medical condition already known at baseline, is defined as recovered as soon as the medical condition has returned to baseline status.

** In case of a fatal event, the event term should not be "death" but the underlying event which led to death (death = outcome). If there is more than one AE in a fatal case, only the AE leading to death will be attributed with the outcome "fatal". All other AEs ongoing at the time of death will be attributed with the outcome "not recovered/not resolved". A copy of an autopsy report should be submitted if available.

Assessment of causality

The investigator is obligated to assess the relationship between each occurrence of each AE/SAE and trial treatment (i.e., against IMP and comparator product, respectively) / and/or trial procedure.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.

It is sufficient to document the causality in the source data and eCRF as:

- Related (= there is a reasonable possibility of a causal relationship) or
- Not related (= there is no reasonable possibility of a causal relationship)

The relationship or association of an AE or SAE to a trial treatment/trial procedure will be assessed by the investigator after having evaluated all accessible data and, if necessary, the investigator will re-evaluate the case as new information becomes available.

Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected adverse reactions but not events caused by the AxMP or the procedure of trial treatment administration.

In this trial, it cannot be excluded that during the course of the trial some procedures give rise to AEs which are related to the trial procedure and not to the trial treatment. Procedure-related AEs can occur on the site of injection of the trial treatment (e.g., redness, swelling, hematoma or itching) or during or after trial-specific procedure (e.g., discomfort after blood drawing). These events must be reported in the eCRF on Adverse Event pages as “related to trial procedure” with the causing procedure specified. The intensity of these AEs will be characterized according to the NCI CTCAE v5.0

Relationship to trial treatment

- The relationship or association of an AE or SAE to a trial treatment (either BNT321 or mFOLFIRINOX) will be made by the investigator after having evaluated all accessible data and, if necessary, he/she will re-evaluate the case as new information becomes available.
- Events caused by the procedure of trial treatment administration should be differentiated from events caused by the trial treatment itself. Only events suspected to be caused by the IMPs itself should be documented as suspected ARs but not events caused by the AxMP or the procedure of trial treatment administration.

Notes applicable for initial reporting of SAEs where the investigator has minimal information available

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.4.4 Reporting of SAEs

For the period of observation please refer to Section 8.4.1.

All AESIs (whether serious or not), SAEs, and DLTs which occur in a patient during the observation period, whether considered to be associated with trial medication or not, must

be reported by the investigator to the sponsor within 24 h following first knowledge of the event.

All AESIs and SAEs occurring after the end of the period of observation only have to be reported to the sponsor if the investigator suspects a relationship to trial medication or the trial procedure.

SAE, DLTs and AESIs Reporting to the sponsor using paper report forms

All AESIs (serious and non-serious)/SAEs and DLTs which occur in a patient during the observation. period, whether considered to be associated with trial treatment or not, must be reportedby the investigator to the sponsor within 24 h following knowledge of the event.

All AESIs (serious and non-serious)/SAEs and DLTs occurring after the end of the period of observation only have to be reported to the sponsor if the investigator suspects a relationship to trial treatment or the trial procedure.

The investigator must ensure the respective paper report form is completed and transmitted to the sponsor via one of the following reporting lines:

- Safety Report Fax No.: [redacted]
- Safety Report E-Mail address: [redacted]

Information for the final description and evaluation of a case report may not be available within the required time frames for reporting. Nevertheless, for regulatory purposes, initial reports should be submitted if the following minimal information is available:

- An identifiable patient (patient number)
- A suspected medicinal product
- An identifiable reporting source (investigator/trial site identification)
- An event or outcome that can be identified as serious

For SAEs, follow-up information should be sent to the sponsor (indicating that this is a “follow-up” report using the respective SAE Form or AESI Form or the Additional Information and Follow-Up Form) without delay as described above and accompanied by appropriate anonymous supporting documentation (e.g., discharge letters, medical reports or death certificates), until a final outcome and date are available. All confidential information (name, address, full day of birth) needs to be blackened before sending.

For SAEs, in addition to a medical record, the investigator should complete an Additional Information and Follow-Up Form, which contains the SAE term and patient number.

A copy of the submitted SAE/AESI report must be retained on file by the investigator. If explicitly required according to national legislation, the investigator must submit copies of the SAEs/AESIs to the IRB/IEC or authority and retain documentation of these submissions in the Site Trial File.

In case an investigator or any other trial team member has questions on safety reporting the sponsor may be contacted via:

- E-Mail: [redacted]

For medical questions, the trial Medical Monitor should be contacted.

10.5 Contraceptive guidance and collection of pregnancy information

The following definitions and guidance is based on the Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials issued in 2020 (CTFG 2020).

10.5.1 Definitions

Patients of childbearing potential

For the purpose of this document, a patient born female is considered of childbearing potential, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes or during cancer treatment), additional evaluation should be considered.

Patients born female in the following categories are not considered POCBP:

- Premenarchal
- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For trial patients with permanent infertility due to a medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

Postmenopausal female

For the purpose of this document, a postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Patients born female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Fertile men

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral vasectomy or orchidectomy.

10.5.2 Contraception guidance

The following guidance describe what is considered highly effective and acceptable methods of contraception.

The investigator or delegate should advise the trial patient how to achieve highly effective contraception.

The following birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly may be considered as highly effective:

- Combined estrogen and progestogen-based hormonal contraception associated with inhibition of ovulation [1], i.e., established use of (oral, intravaginal, or transdermal) hormonal methods of contraception.
- Progesterone-only based contraception associated with inhibition of ovulation [1], i.e., established use of (oral, injected, or implanted) hormonal methods of contraception. [2]
- Intrauterine device. [2]
- Intrauterine hormone-releasing system. [2]
- Bilateral tubal occlusion. [2]
- Bilateral vasectomy (for a male trial patient or male partner of a female trial patient). [2, 3]
- Sexual abstinence. [4]

1. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
2. Contraception methods that in the context of this guidance are considered to have low user dependency.
3. A vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the POCBP trial patient and that the vasectomized partner has received medical assessment of the surgical success.
4. In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the trial patient.

Unless practicing true sexual abstinence, the following birth control methods may be considered as acceptable methods (an “acceptable method” is not an “highly effective” method) that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with a spermicidal agent. [5]
- Cap diaphragm or sponge with a spermicidal agent. [5]

5. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

10.5.3 Collection of pregnancy information

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

Pregnancy information will only be collected after obtaining written informed consent from the pregnant trial patient (or if a male trial patient's partner becomes pregnant, written informed consent from the partner or from both depending on the national regulations).

The initial and follow-up information must be documented on the paper-based Pregnancy Reporting Form and submitted to the sponsor within 24 h of learning of a trial patient's pregnancy/partner's pregnancy and in the eCRF. The completed form needs to be sent to the Safety Report Fax number or E-Mail given in Section 10.4.4. Completed pregnancy forms must be signed by an investigator before faxing/mailing them to the sponsor. Blank reporting forms are provided to the investigator during the site initiation visit and are filed in the Investigator's Site File (ISF).

The investigator will collect follow-up information on the trial patient/trial patient's partner and the neonate, and the information will be forwarded to the sponsor. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth. In order to collect further follow-up information on the health status of the newborn and its development, both parents need to provide written consent. Information to be collected includes the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their presumed relation to the IMP. Generally, the follow-up will be of a duration determined in consultation with the pediatrician.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-trial pregnancy-related SAE considered reasonably related to the trial treatment by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former trial patients, the investigator may learn of an SAE through spontaneous reporting.

10.5.4 Management of contraception

At time points indicated in the SoA (Section 1.3), the investigator or designee will inform the trial patient of the need to use the prescribed contraception consistently and correctly, and will document the conversation. This will include advice about donation and cryopreservation of germ cells. In addition, the investigator or designee will instruct the trial patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the trial patient or partner.

The investigator or designee, in consultation with the trial patient, will confirm that the trial patient has selected an appropriate method of contraception for the individual trial patient and his or her partner(s) from the permitted list of contraception methods and will confirm that the trial patient has been instructed in its consistent and correct use.

POCBP will only be administered trial treatment after negative pregnancy test outcomes at the time points indicated in the SoA (Section 1.3).

10.6 Liver safety: Suggested actions and follow-up assessments

Patients with post-treatment transaminase elevations greater than three times ULN concurrent with total bilirubin >2 x ULN should be assessed for potential drug induced liver injury (DILI) per Hy's law criteria. Initial management includes withholding trial treatment according to specifications in Section 6.3.1.1 and 6.3.1.2. In such cases additional work up is warranted, including the following:

- Repeat transaminases and serum bilirubin tests two or three times weekly. Other laboratory tests to consider include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. The frequency of re-testing can decrease to once a week or less if abnormalities stabilize
- Obtain a more detailed history of symptoms and prior or concurrent diseases
- Obtain other history including review of family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals
- Assessment of history of concomitant drug use (including nonprescription medications, acetaminophen/paracetamol and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Other assessments may include testing for acute viral etiologies (hepatitis types A, B, C, D, and E; acute EBV or CMV infections), autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Evaluation for obstructive etiologies (ultrasound or other diagnostic imaging method)
- Consideration of gastroenterology or hepatology consultations

All cases meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has been found.

Such potential DILI cases are to be reported as AESI, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

In selected patients who demonstrate hepatic toxicity following administration of BNT321 (including, but not limited to elevations of serum AST, ALT, total and/or direct/indirect bilirubin, alkaline phosphatase), a liver biopsy may be performed. These biopsies will only be performed in situations where the biopsy can be obtained with reasonable safety for the patient, as well as when judged clinically reasonable by the investigator and sponsor/Medical Monitor. Liver biopsies are performed with the goal of better

understanding the mechanistic basis of AEs following administration of BNT321. Liver biopsies will be performed in accordance with institutional practices. Given that liver biopsy may be most informative if obtained at or near the time of greatest observed toxicity, tissue should be obtained coinciding with this period whenever possible.

10.7 Standard definitions

10.7.1 Definition of enrolled patient

After providing informed consent, patients are considered enrolled in this trial, i.e., are enrolled patients.

10.7.2 Definition of trial completer

A trial patient is considered to have completed the trial if they have completed safety and survival follow-ups as shown in the SoA (see Section 1.3).

10.8 Country-specific requirements

Not applicable.

10.9 Protocol amendments and version updates

10.9.1 Protocol amendment no. 01/Update from version 1.0 to 2.0

Overall amendment rationale:

Changes to the protocol version 1.0 were made in response to request for information (RFI) comments received via CTIS from Denmark.

A comparison of the new sponsor approved protocol version with the last approved version is filed together with the protocol in the trial master file (TMF).

Description of changes:

Minor editorial changes, such as the correction of typing errors, are not specifically listed.

See the table for a summary of the reasons for major changes compared to the previous version.

Section	Change	Reason for change
2-page lay summary	Removal from the protocol.	According to CTIS requirement to submit lay summary as a stand-alone document
1.3 Section - Schedule of activities (Table 1,	Update of schedule of activities: • Addition of urine pregnancy test during treatment on Day 1 for Cycle 1 to 3 and Cycle 4	Revised according CTFG guidelines per EU-CTA query

Section	Change	Reason for change
Table 2 and Table 4)	to 12, BNT321 monotherapy Cycle 13 to 24, and at EOT. • Addition of chemistry assessments at EOT. • Addition of safety examinations (chemistry, hematology and vital signs) at the safety FU visit. • Addition of TB, DPD deficiency, and UGT1A1 mutation assessments at screening. • Addition of ECG monitoring including examinations at screening prior to treatment, at t_{max}, and at the end of last mFOLFIRINOX infusion during Cycle 1 to 3. • Addition of wording to allow investigators to obtain ECGs in later cycles based on results from investigations in Cycle 1 to 3. • Modification of "disease dissemination" footnote to include an option for multiparametric MRI.	
4.1.1 and 4.1.2	Clarification that dose escalation beyond pre-specified dose level of CCI may be pursued in study Phase I part.	Revised per EU-CTA query
4.1.3	Update to the adaptive trial design elements: • Modification of safety assessment time points dependent on emerging data, confirming they can only be added and not removed. • Removal of the adaptive trial design element for dose escalation. • Clarification that all available data will be considered in the final decision for RP2D for BNT321-02 Phase II part conduct.	Revised per EU-CTA query
4.2.3	Modification of contraception and pregnancy testing.	Revised per EU-CTA query
5.2	Increase in the period, from 90 to 111 days, after last dose of BNT321 in criteria #13, #14 and #16.	Revised per EU-CTA query
5.3	Update of the exclusion criteria: • Modification for baseline QT intervals and several risk factors for QT prolongation (criterion #4). • Clarification added for criterion #20 and #22: if testing required by local regulations	Revised according to ICH Topic E14, 2005, and Article 34 Regulation (EU) No. 536/2014 in conjunction with Sec 40a S. 1 No. 2 of the German Medicinal Products Act (Arzneimittelgesetz –

Section	Change	Reason for change
	• Addition of new exclusion criteria: "Received a live vaccine within 3 weeks prior to the first dose of trial treatment" (criterion #23). • Addition of new exclusion criteria: "Patients with a contraindication to receiving mFOLFIRINOX" (criterion #24). • Addition of new exclusion criteria: "Patients with active or latent tuberculosis or history of Mycobacterium tuberculosis infection currently or within the last 2 years" (criterion #25). • Addition of new exclusion criteria: "Individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities" (criterion #26).	AMG), guidelines per EU-CTA query
6.3.2	Modification of dose-limiting toxicity: • Inclusion of Grade 3 or higher febrile neutropenia (i.e., ANC <1.0 × 10^9 cells/L with a single temperature of >38.3°C [>100.9 F] or a sustained temperature of ≥38°C [≥100.4 F] for more than 1 h) and Grade 3 thrombocytopenia associated with bleeding requiring platelet transfusion. • Specification of the exemptions for Grade 3 peripheral neuropathy of less than 14 days and Grade 3 fatigue of less than 7 days duration.	Revised per EU-CTA query
6.3.5	Addition of safety stopping rules for Phase II including the following: • Any death possibly related to the BNT321 within 30 days of receiving IMP. • If during treatment, more than 33% of trial patients develop AEs meeting the DLT criteria, the trial cohort shall be paused pending a safety evaluation by the IDMC and sponsor. • Any safety finding assessed as related to BNT321 that, in the opinion of the IDMC, contraindicates further dosing of trial patients.	Revised according to GCP ICH E16, section 6.4, guidelines per EU-CTA query
6.9.1	Modification of prohibited medication during trial list to reflect updates made in Section 5.3.	Revised per EU-CTA query
6.9.4	Modification of vaccination against COVID-19 to reflect updates made in Section 5.3.	Revised per EU-CTA query
7.1.1	Addition of "pregnancy" to the list of reasons for patient discontinuation.	Revised per EU-CTA query

Section	Change	Reason for change
7.2	Addition of “patient noncompliance” and “pregnancy” to the list of reasons for patient discontinuation.	Revised per EU-CTA query
8.1	Modification of screening/baseline assessments and procedures to reflect updates made in Section 5.3.	Revised per EU-CTA query
8.3.3	Modification of electrocardiograms to reflect updates made in Section 1.3.	Revised per EU-CTA query
8.3.4	Modification of clinical laboratory tests to reflect updates made in Section 1.3.	Revised per EU-CTA query

11 REFERENCES

Investigator’s brochure BNT321, Version 7.0, Human Monoclonal Antibody for the Treatment of Metastatic Pancreatic Cancer and CA19-9 Positive Malignancies. Dated 01 JUN 2023.

Clinical trial protocol: MV-0715-CP-001.01 Version 13.0, Phase 1 Safety and Tolerability Study of Human Monoclonal Antibody 5B1 (MVT-5873) with Expansion in Subjects with Pancreatic Cancer or Other CA19-9 Positive Malignancies. Dated 29 SEP 2022.

Guidance

CTFG 2020. Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials. Version 1.1, issued 21 SEP 2020.

EMA (2017). Guideline on the evaluation of anticancer medicinal products in man.

FDA (2018). Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Literature

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376. doi:10.1093/jnci/85.5.365

Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol. 2012;3(2):105-119. doi: 10.3978/j.issn.2078-6891.2011.021.

Berger AC, Meszoely IM, Ross EA, et al. Undetectable preoperative levels of serum CA 19-9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. Ann Surg Oncol. 2004;11(7):644-649. doi:10.1245/ASO.2004.11.025.

Brower V. New approaches tackle rising pancreatic cancer rates. J Natl Cancer Inst. 2014;106(12):dju417. Published 2014 Dec 22. doi:10.1093/jnci/dju417.

Conroy T, Gavoille C, Samalin E, et al. The role of the FOLFIRINOX regimen for advanced pancreatic cancer. Curr Oncol Rep. 2013;15(2):182-189. doi:10.1007/s11912-012-0290-41.

Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018;379(25):2395-2406. doi:10.1056/NEJMoa1809775.

Cook G, John Ashcroft A, Pratt G, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. Br J Haematol. 2020;190(2):e83-e86.

Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020;10(6):783-791.

de Jesus VHF, Camandaroba MPG, Donadio MDS, et al. Retrospective comparison of the efficacy and the toxicity of standard and modified FOLFIRINOX regimens in patients with metastatic pancreatic adenocarcinoma. J Gastrointest Oncol. 2018;9(4):694-707. doi:10.21037/jgo.2018.04.02.

Dong Q, Yang XH, Zhang Y, et al. Elevated serum CA19-9 level is a promising predictor for poor prognosis in patients with resectable pancreatic ductal adenocarcinoma: a pilot study. World J Surg Oncol. 2014;12:171. Published 2014 Jun 2. doi:10.1186/1477-7819-12-171.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.

Feizi T. Demonstration by monoclonal antibodies that carbohydrate structures of glycoproteins and glycolipids are onco-developmental antigens. Nature. 1985;314(6006):53-57. doi:10.1038/314053a0.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer. 1999;35(6):939-941. doi:10.1016/s0959-8049(99)00047-7

Gupta S, McDonald JD, Ayabe RI, et al. Targeting CA 19-9 with a humanized monoclonal antibody at the time of surgery may decrease recurrence rates for patients undergoing resections for pancreatic cancer, cholangiocarcinoma and metastatic colorectal cancer. J Gastrointest Oncol. 2020;11(2):231-235. doi:10.21037/jgo.2020.02.01.

Jones OP, Melling JD, Ghaneh P. Adjuvant therapy in pancreatic cancer. World J Gastroenterol. 2014;20(40):14733-14746. doi:10.3748/wjg.v20.i40.14733.

Kannagi R. Carbohydrate antigen sialyl Lewis a--its pathophysiological significance and induction mechanism in cancer progression. Chang Gung Med J. 2007;30(3):189-209.

Kishimoto T, Ishikura H, Kimura C, et al. Phenotypes correlating to metastatic properties of pancreas adenocarcinoma in vivo: the importance of surface sialyl Lewis(a) antigen. Int J Cancer. 1996;69(4):290-294. doi:10.1002/(SICI)1097-0215(19960822)69:4<290:AID-IJC9>3.0.CO;2-S.

Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-337.

Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313-5327. doi:10.1200/JCO.2006.08.2644.

Loy TS, Sharp SC, Andershock CJ, Craig SB. Distribution of CA 19-9 in adenocarcinomas and transitional cell carcinomas. An immunohistochemical study of 527 cases. Am J Clin Pathol. 1993;99(6):726-728. doi:10.1093/ajcp/99.6.726.

Mackay TM, Dijksterhuis WPM, Latenstein AEJ, et al. The impact of cancer treatment on quality of life in patients with pancreatic and periampullary cancer: a propensity score matched analysis. HPB (Oxford). 2022;24(4):443-451. doi:10.1016/j.hpb.2021.09.003

Magnani JL, Steplewski Z, Koprowski H, Ginsburg V. Identification of the gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. Cancer Res. 1983;43(11):5489-5492.

Matsui T, Kojima H, Suzuki H, et al. Sialyl Lewisa expression as a predictor of the prognosis of colon carcinoma patients in a prospective randomized clinical trial. Jpn J Clin Oncol. 2004;34(10):588-593. doi:10.1093/jjco/hyh110.

Nakayama T, Watanabe M, Katsumata T, et al. Expression of sialyl Lewis(a) as a new prognostic factor for patients with advanced colorectal carcinoma. Cancer. 1995;75(8):2051-2056. doi:10.1002/1097-0142(19950415)75:8<2051::aid-cncr2820750804>3.0.co;2-4.

Passerini R, Cassatella MC, Boveri S, et al. The pitfalls of CA19-9: routine testing and comparison of two automated immunoassays in a reference oncology center. Am J Clin Pathol. 2012;138(2):281-287. doi:10.1309/AJCPOPNPLLCYR07H.

PRODIGE 24-ACCORD: Trial comparing adjuvant chemotherapy with gemcitabine versus mFOLFIRINOX to treat resected pancreatic adenocarcinoma. ClinicalTrials.gov identifier: NCT01526135.

Ragupathi G, Damani P, Srivastava G, et al. Synthesis of sialyl Lewis(a) (sLe (a), CA19-9) and construction of an immunogenic sLe(a) vaccine. Cancer Immunol Immunother. 2009;58(9):1397-1405. doi:10.1007/s00262-008-0654-7.

Ringel J, Löhr M. The MUC gene family: their role in diagnosis and early detection of pancreatic cancer. Mol Cancer. 2003;2:9. Published 2003 Jan 7. doi:10.1186/1476-4598-2-9.

Sato M, Narita T, Kimura N, et al. The association of sialyl Lewis(a) antigen with the metastatic potential of human colon cancer cells. Anticancer Res. 1997;17(5A):3505-3511.

Sawada R, Sun SM, Wu X, et al. Human monoclonal antibodies to sialyl-Lewis (CA19.9) with potent CDC, ADCC, and antitumor activity. Clin Cancer Res. 2011;17(5):1024-1032. doi:10.1158/1078-0432.CCR-10-2640.

SEER Cancer Stat Facts: Pancreas Cancer. Natl Cancer Institute, Bethesda, MD.

Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-1283. doi:10.1056/NEJMoa0910383.

Tempero MA, Pelzer U, O'Reilly EM, et al. Adjuvant nab-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial [published online ahead of print, 2022 Dec 15]. J Clin Oncol. 2022;JCO2201134. doi:10.1200/JCO.22.01134.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691-1703. doi:10. 1056 /NEJMoa1304369.

Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol. 2011;29(34):4548-4554. doi:10.1200/JCO.2011.36.5742.

Yang GY, Malik NK, Chandrasekhar R, et al. Change in CA 19-9 levels after chemoradiotherapy predicts survival in patients with locally advanced unresectable pancreatic cancer. J Gastrointest Oncol. 2013;4(4):361-369. doi:10.3978/j.issn.2078-6891.2013.045.

APPENDIX 1 ECOG KARNOFSKY CONVERSION

Table 16: Conversions for ECOG and Karnofsky performance status grades

Karnofsky status	Karnofsky grade	ECOG grade	ECOG status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death non-imminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	0	5	Dead

Signature page

Document Title: BNT321-02-CTP-v2.0-2024-01-22-final

Document Name: BNT321-02-CTP-v2.0-2024-01-22-final

Document Version: 2.0, LATEST, Approved

Date GMT	Reason	Signed By
2024-01-19 21:38:9	Signing as Reviewer	PPD
2024-01-20 16:32:45	Clinical Development Approval	PPD
2024-01-22 11:9:12	Biostatistics Approval	PPD