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Supplementary appendix 2

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SUPPLEMENTARY APPENDIX

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METHODS

Inclusion Criteria

General Inclusion Criteria

(1) Aged 18 years or older.

(2) Able to understand and provide informed consent for participation in the study.

(3) Eastern Cooperative Oncology Group performance status of 0 or 1.

Disease-Specific Inclusion Criteria

(4) Histopathologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma that has not been previously treated in the metastatic setting.

(5) Initial diagnosis of metastatic disease (according to the eighth edition of the American Joint Committee on Cancer staging manual) must have occurred ≤6 weeks prior to screening.

(6) Patient has one or more metastatic lesions measurable by computed tomography/magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

Haematologic, Biochemical, and Organ Function Inclusion Criteria

(7) During the screening period, adequate biological parameters as evidenced by: (a) an absolute neutrophil count of ≥2000/mm^3 without the use of haemopoietic growth factors within the 7 days prior to randomisation; (b) a platelet count of ≥100,000/mm^3; (c) a haemoglobin level of ≥9 g/dL obtained ≤14 days prior to randomisation.

(8) Adequate hepatic function as evidenced by: (a) a serum total bilirubin level of ≤1·5 × upper limit of normal (ULN) (biliary drainage is allowed for biliary obstruction); (b) aspartate aminotransferase and alanine aminotransferase levels of ≤2·5 × ULN (≤5 × ULN was acceptable if liver metastases were present).

(9) Adequate renal function as evidenced by a creatinine clearance of >30 mL/min. Actual body weight should be used for calculating creatinine clearance using the Cockcroft–Gault equation (except for patients with a body mass index of >30 kg/m^2, for which adjusted body weight should be used instead):

$$Creatinine\ clearance\ \left(\frac{mg}{mL}\right) = \frac{(140 - Age\ [years]) \times (Weight\ [kg])}{72 \times Serum\ creatinine\ \left(\frac{mg}{mL}\right)} \times Sex$$

where Sex = 1 for men and 0.85 for women.

(10) Electrocardiogram without any clinically significant findings at screening, as per investigator's assessment.

(11) Adequate coagulation studies (obtained ≤14 days prior to randomisation) as demonstrated by prothrombin time and partial thromboplastin time within normal limits (≤1·5 × ULN). Patients on warfarin or other vitamin K antagonists should be discussed with the sponsor.

(12) No clinically significant abnormalities in urinalysis results (obtained within the 7 days prior to randomisation), as per investigator's assessment.

(13) Patients infected with human immunodeficiency virus (HIV) are eligible if they meet all the following criteria: (a) CD4 count is ≥350 cells/uL, viral load is undetectable, and not taking prohibited cytochrome (CYP)-interacting medications; (b) probable long-term survival with HIV if cancer were not present; (c) stable on a highly active antiretroviral therapy (HAART) regimen for ≥4 weeks and willing to adhere to their HAART regimen with minimal overlapping toxicity and drug–drug interactions with the experimental agents in this study; (d) HIV is not multi-drug resistant; (e) taking medication and/or receiving antiretroviral therapy that does not interact or have overlapping toxicities with the study medication.

Exclusion Criteria

General Exclusion Criteria

(1) Any medical or social condition deemed by the investigator to be likely to interfere with a patient's ability to give informed consent, cooperate, and participate in the study or be likely to interfere with the interpretation of the results.

(2) Pregnancy or breastfeeding; women of childbearing potential must test negative for pregnancy at the time of enrolment based on a serum pregnancy test. Women of childbearing potential are defined as fertile, after menarche, and until becoming postmenopausal unless permanently sterile. Postmenopausal women are defined as those that have an absence of menstruation for 12 months. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Female patients of reproductive potential must agree to use a highly effective method of birth control during the study and for 7 months after receiving the last dose of the study drug. Men must agree to use condoms during the study and for 6 months after receiving the last dose of the study drug.

(3) Unwilling or unable to comply with study procedures and/or study visits, including long-term follow-up for survival.

Disease-Specific Exclusion Criteria

(4) Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy,chemotherapy, or investigational therapy; palliative radiotherapy and placement of a biliary stent/tube are permitted.

(5) Prior treatment of pancreatic adenocarcinoma with chemotherapy in the adjuvant setting, except those in which at least 12 months have elapsed since completion of the last dose and no persistent treatment-related toxicities are present.

(6) Patient has only localised advanced disease.

(7) Documented serum albumin <3 g/dL within the 7 days prior to randomisation.

(8) Known history of central nervous system metastases. But patients on a stable or decreasing dose of steroids and deemed clinically stable as per the investigator's assessment are eligible.

(9) Clinically significant gastrointestinal disorders including hepatic disorders, bleeding, inflammation, occlusion, diarrhoea >grade 1, malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, or partial bowel obstruction.

(10) History of any second malignancy in the last 2 years; patients with prior history of *in-situ* cancer or basal or squamous cell skin cancer are eligible. Patients are also eligible if they: (a) have a history of other malignancies and have been continuously disease free for at least 2 years prior to screening; (b) have a concurrent malignancy that is clinically stable and does not require tumour-directed treatment.

Haematologic, Biochemical, and Organ Function Exclusion Criteria

(11) Known hypersensitivity to any of the components of: (a) liposomal irinotecan injection, other liposomal products, or any components of 5-fluorouracil, leucovorin, or oxaliplatin; (b) nab-paclitaxel or gemcitabine.

(12) Concurrent illnesses that would be a relative contraindication to trial participation such as active cardiac or liver disease, including: (a) severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) <6 months before screening; (b) high cardiovascular risk, including recent coronary stenting or myocardial infarction in the year prior to screening; (c) New York Heart Association Class III or IV congestive heart failure, ventricular arrhythmias, or uncontrolled blood pressure; (d) known historical or active infection with hepatitis B, or active infection with hepatitis C (note that patients with hepatitis C who have been clinically cured, defined as persistent absence of hepatitis C RNA detected by polymerase chain reaction test in serum 12 weeks after completing antiviral treatment, are eligible).

(13) Active infection or an unexplained fever of >38·5°C during screening visits or on the first scheduled day of dosing that in the investigator's opinion may compromise the patient's participation in the trial or affect the study outcome.

(14) Major surgery, other than diagnostic surgery, within the 4 weeks prior to randomisation.

(15) Use of strong inhibitors or inducers of CYP3A, CYP2C8, and UGT1A1.

(16) There is presence of any contraindications outlined in the contraindications or warnings and precautions sections of: (a) the investigator's brochure for liposomal irinotecan injection, or in the prescribing information for 5-fluorouracil, leucovorin, or oxaliplatin; (b) the product prescribing information for nab-paclitaxel or gemcitabine.

(17) Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.

(19) Patients who, in the opinion of the investigator, have symptoms or signs suggestive of clinically unacceptable deterioration of the primary disease at the time of screening.

(20) History of systemic connective tissue disorders (e.g. lupus, scleroderma, arteritis nodosa).

(21) History of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies, or peripheral artery disease (e.g. claudication, Leo Buerger's disease).

(23) Patients who have received a live vaccine within the 4 weeks prior to randomisation.

(24) Known low or absent dihydropyrimidine dehydrogenase (DPD) activity. If required by local regulations, testing for DPD deficiency must be performed using a validated method that is recommended by local health authorities.

Study Design and Treatment

Discontinuation and Withdrawal

Criteria for permanent discontinuation of study treatment for patients receiving liposomal irinotecan in combination with 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX) or nab-paclitaxel plus gemcitabine included:

- radiologically determined progressive disease, as per RECIST version 1.1
- clinical deterioration sufficient to prevent further radiological assessment
- unacceptable toxicity, defined as a study drug related adverse event, prior to disease progression, which:
  - in the opinion of the investigator, precludes ANY further treatment with the study drug
  - requires treatment with the study drug to be withheld for more than 14 days, unless the patient is receiving benefit overall from the study treatment in the opinion of the investigator
  - would result in a fourth dose reduction in NALIRIFOX or a third dose reduction in nab-paclitaxel plus gemcitabine
  - requires discontinuation of liposomal irinotecan injection, 5-fluorouracil or leucovorin, or nab-paclitaxel or gemcitabine.
- development of an intercurrent medical condition or need for concomitant therapy that precludes any further treatment with study drug
- withdrawal of consent for further treatment and survival follow-up
- discretion of the treating physician
- pregnancy.

A patient who permanently discontinued study treatment and had not withdrawn from the study was required to continue with all ongoing protocol requirements.

Reasons for withdrawal from the study included the following:

- significant noncompliance with the protocol, as per investigator assessment
- patient was lost to follow-up
- withdrawal of consent for further participation in the study
- death
- study termination by the sponsor.

Outcomes

Primary efficacy analysis.

- Overall survival (OS), defined as the number of months from randomisation to the date of death (any cause). Patients who did not have a date of death recorded at the time of the final analysis were censored at the last known time that the patient was alive.

Secondary efficacy analysis.

- Progression-free survival (PFS), defined as the number of months from randomisation to the first documented objective disease progression using RECIST version 1·1 or death due to any cause, whichever occurred first. Determination of PFS was as per investigator assessment.
- Overall response rate, defined as the proportion of patients who achieved partial response or complete response according to RECIST version 1·1 guidelines.

Exploratory objectives analysis.

- Patient-reported outcomes (PRO) exploratory endpoints were as follows:
  - time-to-deterioration or worsening of patients' physical functioning, disease-related symptoms and treatment-related symptoms of interest using the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQ-C30), the specific pancreatic cancer module (QLQ-PAN26) questionnaire, and the PRO of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)
  - time-to-deterioration or worsening of remaining quality of life (QoL) subscales of the EORTC-QLQ-C30 and QLQ-PAN26

  - % of subjects with stable, improved, or worsened QoL scores as assessed by the QLQ-C30, QLQ-PAN26, and PRO-CTCAE
  - health-related QoL score at each visit as assessed by the QLQ-C30, QLQ-PAN26, PRO-CTCAE, and 5-level 5-dimension EuroQol questionnaire (EQ-5D-5L).
- Pharmacokinetics, and the relationship between pharmacokinetic exposure and efficacy and safety, of the NALIRIFOX regimen.
- Time-to-treatment-failure, defined as the number of months from randomisation to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death.
- Duration of response, defined as the time of initial response (complete response or partial response) until documented tumour progression using RECIST version 1.1 guidelines or death. For patients who did not have documented tumour progression or death, duration of response was censored at the time of the last evaluable tumour assessment.
- Time-to-response, defined as time-from-randomisation to the first objective tumour response. Time-to-response was computed only for patients who achieved complete response or partial response.
- Genotyping — the possible association between genotypes included UGT1A1*28 and other UGT1A genotypes; SN-38 concentration (only for those treated with NALIRIFOX) and safety was described.
- Biomarkers — the biomarker CA 19-9 was measured and concentrations were compared between treatment arms.
- Biobanking — biobanked samples may be used for future analysis.
- Gene mutation and genomic alteration status associated with pancreatic adenocarcinoma of the patients was determined prior to screening if available. Several genes are associated with an increased risk of developing pancreatic ductal adenocarcinoma. Those of key interest include germline mutations and genomic alterations: BRCA1, BRCA2, PALB2, ATM, CDKN2A, MLH1, MSH2, MSH6, TP53, and EPCAM;[1] and somatic mutations and genomic alterations: KRAS, TP53, CDKN2A, SMAD4, RNF43, ARID1A, TGFβR2, GNAS, RREB1, and PBRM1.[2] Gene mutations and genomic alteration may be used for exploration of potential predictive biomarkers and correlation with clinical outcome.

Safety analysis.

- Safety analyses (adverse events, serious adverse events, laboratory analyses, dose modifications, and discontinuations) were performed using the safety population, defined as all patients receiving any study drug. Treatment assignment will be according to actual treatment received.
  - Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or later.
  - Severity was graded according to the CTCAE version 5·0.
  - Treatment-emergent adverse events were defined as any adverse events reported from the date of first study drug exposure to 30 days after the last date of study drug exposure.

Statistical analysis

Sample size and power considerations

- The sample size required to demonstrate an improvement in OS with NALIRIFOX compared with nab-paclitaxel plus gemcitabine was calculated assuming that:
  - expected median OS with nab-paclitaxtel plus gemcitabine would be 9 months
  - expected median OS with NALIRIFOX would be 12 months
  - a hazard ratio of 0·75 would be detected with a one-sided test
  - overall two-sided type I error rate would be 0·05 with a power of 90%
  - patients would be randomised 1:1.
- Approximately 750 patients were randomised in a 1:1 ratio to the two treatment arms. Accounting for the planned interim analysis, follow-up until at least 543 OS events were observed across the two treatment arms provided at least 90% power to detect a true hazard ratio of ≤0·75 (modified OS: 9 vs 12 months), using a stratified log-rank test with an overall two-sided significance level of 0·05.
- Assuming enrolment over 16 months increasing to approximately 62 patients per month, with 5% of patients lost to follow-up across both treatment arms, the timing of the interim and final analyses was expected to be at 24 months and 36·5 months, respectively, after the first patient was treated.

Primary efficacy analysis

- There were two planned analyses of OS: interim analysis and final analysis. The interim analysis was planned when at least 272 OS events had been observed in the intention-to-treat population. If that analysis did not indicate

futility or efficacy, then the final analysis was planned at 543 OS events when all planned patients had been enrolled.

- The overall type I error was controlled at a two-sided significance level of 0.05 (equivalent to one-sided level of 0.025). To control type I and type II errors, the Hwang-Shih-DeCani (HSD) α and (non-binding) β spending function with γ parameter equal to -4 for type I error type and γ equal to -1 for type II error was utilized with respective alpha allocations of 0.006 and 0.048 for the interim and final analyses, respectively. The futility stopping boundary is specified as no binding.

Secondary efficacy analysis

- Secondary efficacy endpoints were to be tested no more than once. If the primary endpoint of OS was declared significant at the interim analysis, secondary efficacy endpoints were to be tested at the interim, or otherwise, at the final analysis if OS was found to be statistically significant at that analysis.
- Hypothesis testing of secondary efficacy endpoints was conducted in a stagewise hierarchical manner incorporating α spending for each endpoint using HSD_{α} of -4, similar to that specified for the primary efficacy analysis.
- The nominal level for the comparison depended on whether the analysis was carried out at the OS interim or at the planned OS final analysis.
- The first endpoint in the hierarchy of secondary endpoints was PFS. If OS and PFS were both significant, then objective response rate would be tested. Any parameter not formally tested for significance (as per the hierarchy) was to be regarded as descriptive and exploratory.

TABLES

Table S1 (online only). Number of patients recruited and randomised at each participating site.

Country	Site Name	Principal Investigator	Patients recruited, n	Patients randomised, n
Australia	Monash Medical Centre	Andrew Strickland	3	3
	Bankstown-Lidcombe Hospital	Ray Asghari	1	1
	Sir Charles Gairdner Hospital	Siobhan Ng	2	1
	Fiona Stanley Hospital	Christopher Lomma	9	8
	St John of God Subiaco Hospital	Andrew Dean	11	10[a]
	Queen Elizabeth Hospital	Vy Broadbridge	2	2
Austria	Ordensklinikum Linz GmbH Barmherzige Schwestern	Andreas Petzer	4	4
	Medizinische Universitaet Wien	Gerald Prager	7	5
	Uniklinikum Salzburg – Universitaetsklinik fuer Nuklearmedizin und Endokrinologie	Richard Greil	10	6
	Medizinische Universitaet Graz	Armin Gerger	3	2
Belgium	Hospital Centre Jolimont	Alexandre Dermine	6	5
	Universitaire Ziekenhuizen Leuven	Eric Van Cutsem	1	1
	University Hospital Gent	Karen Geboes	3	2
	ASBL Grand Hôpital de Charleroi (GHdC) – Site Notre Dame	Isabelle Sinapi	3	2
	Onze-Lieve-Vrouwziekenhuis	Koen Hendrickx	7	7
	University Hospital Mont-Godinne	Lionel d'Hondt	4	2
Brazil	Instituto Nacional de Câncer (INCA)	Bruno dos Santos Vilhena Pereira	1	1
	CIP – Centro Integrado de Pesquisas do Hospital de Base de São José do Rio Preto	Káthia Cristina Abdalla	5	3
	Hospital de Caridade de Ijuí	Fábio Franke	4	1
	ICESP – Instituto do Câncer do Estado de São Paulo	Luiz Antonio Senna Leite	1	1
	Fundação Pio XII – Hospital de Câncer de Barretos	Arinilda Campos Bragagnoli	13	8
	Clinica Neoplasias Litoral	Giuliano Borges	3	3
	Hospital Alemão Oswaldo Cruz	Cheng Tzu Yen	10	6
	Irmandade da Santa Casa de Misericórdia de Porto Alegre	Katsuki Arima Tiscoski	4	3

	IOP – Instituto de Oncologia do Paraná	Luciano Semensato Biela	1	1
	Hospital Bruno Born	Rafael Seewald	4	4
	CRIO – Centro Regional Integrado de Oncologia	Eduardo Henrique Cronemberger	5	2
	CEPON – Centro de Pesquisas Oncológicas	Yeni Verônica Nerón	6	2
	CePclin – Centro de Pesquisas Clínicas de Natal	Juliana Florinda de Mendonça Rego	3	3
	Centro de Pesquisa – Instituto COI	Fernando Meton de Alencar Câmara Vieira	3	2
Canada	Alberta Health Services Cross Cancer Institute	Michael Sawyer	3	1
	Centre Hospitalier Universitaire de Sherbrooke	Frédéric Lemay	5	3
	Queen Elizabeth II Health Sciences Centre	Ravi Ramjeesingh	2	2
	McGill University Faculty of Medicine – Royal Victoria Hospital	Jamil Asselah	8	6
Czechia	Fakultní Nemocnice Hradec Králové	Stanislav John	12	10
	Fakultní Thomayerova Nemocnice	Eugen Kubala	9	7
	Masarykův Onkologický Ústav	Igor Kiss	18	13
	Department of Oncology, University Hospital Olomouc	Bohuslav Melichar	10	8
France	Centre Hospitalier Universitaire de Poitiers	Camille Evrard	3	3
	CHRU de Tours – Hôpital Trousseau	Thierry Lecomte	8	8
	Centre Oscar Lambret	Diane Pannier	7	6
	Hôpital Privé Jean Mermoz	Pascal Artru	6	5
	AP-HP Hôpital Saint Louis	Thomas Aparicio	2	2
	Strasbourg Oncologie Liberale	Louis Marie Dourthe	2	1
	Hôpital Édouard Herriot – Hospices Civils de Lyon	Thomas Walter	4	2
	CHU Bordeaux – Hôpital Haut-Lévêque	Eric Terrebonne	8	7
	Centre Antoine Lacassagne	Angélique Saint	6	5
	Centre Léon Bérard	Christelle De La Fouchardière	14	11
Germany	Asklepios Klinik Altona	Dirk Arnold	6	4
	Klinikum Mannheim	Nadine Schulte	4	3
	Universitaetsklinikum Ulm	Thomas Seufferlein	2	1
	Krankenhaus Nordwest GmbH	Thorsten Götze	10	10
	Universitaetsklinikum Tuebingen	Michael Bitzer	3	1
	Martin-Luther-Universitaet Halle-Wittenberg	Petra Büchner-Steudel	2	2

	SLK-Kliniken Heilbronn GmbH	Uwe Martens	10	8
	Krankenhaus St. Franziskus – Kliniken Maria Hilf GmbH	Ullrich Graeven	3	3
	Facharztzentrum Eppendorf	Eray Gökkurt	10	9
	St. Josef-Hospital	Anke Reinacher-Schick	3	2
	Studiengesellschaft BSF	Norbert Steudel	1	1
Greece	University General Hospital of Ioannina	Davide Mauri	2	1
	National and Kapodistrian University of Athens	Christos Papadimitriou	2	1
	Agios Savvas Anticancer Hospital	Alexandros Ardavanis	1	1
	Eugenideion Therapeutirion Hospital	Michalis Karamouzis	1	1
Hungary	Jász-Nagykun-Szolnok Megyei Hetényi Géza Kórház-Rendelőintézet	Tibor Csőszi	7	5
	Semmelweis Egyetem Belgyógyászati és Hematológiai Klinika	Júlia Lohinszky	1	1
	Országos Onkológiai Intézet	Erika Hitre	4	1
	Debreceni Egyetem Klinikai Központ	Péter Árkosy	6	3
	Somogy Megyei Kaposi Mór Oktató Kórház	Lukács Gábor	4	3
	Dél-pesti Centrumkórház - Szent László Kórház Telephely	Bodoky György	9	5
Israel	Rambam Health Care Campus	Maria Passhak	6	4
	Soroka Medical Center	Alexander Gluzman	1	1
Italy	AUSL di Piacenza-Ospedale Guglielmo Da Saliceto	Luigi Cavanna	3	2
	Azienda Ospedaliero-Universitaria di Modena	Fabio Gelsomino	2	1
	Istituto Europeo di Oncologia	Nicola Fazio	4	4
	Azienda Ospedaliero-Universitaria Pisana	Enrico Vasile	2	1
	Azienda Ospedaliera-Universitaria Integrata Verona-Ospedale Borgo Roma	Davide Melisi	49	39
	IRCCS Azienda Ospedaliero-Universitaria di Bologna-Policlinico di Sant'Orsola-Malpighi	Giovanni Brandi	5	4
	IRCCS Istituto Romagnolo per lo Studio dei Tumori Dino Amadori - IRST S.r.l.	Giovanni Luca Frassineti	6	2
	Azienda Ospedaliero Universitaria-Ospedali Riuniti di Ancona	Rossana Berardi	2	2
South Korea	CHA Bundang Medical Center	Hong Jae Chon	1	1
	National Cancer Center	Woo Jin Lee	12	9
	Inje University Haeundae Paik Hospital	Il Hwan Kim	7	6
	Korea University Guro Hospital	Sang Cheul Oh	5	4

	Seoul St. Mary's Hospital, The Catholic University of Korea	Myung-Ah Lee	2	1
	Asan Medical Center	Baek-Yeol Ryoo	2	1
Portugal	Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE	António Moreira Pinto	1	1
	Hospital de Braga	Ana Daniela Marques	2	1
	Unidade Local de Saúde Matosinhos, EPE – Hospital Pedro Hispano	Alexandra Mesquita Magalhaes	3	2
	Champalimaud Foundation	Nuno Couto	5	5
	Centro Hospitalar Universitário de Lisboa Norte, EPE – Hospital de Santa Maria	Catarina Abreu	2	1
Russia	Federal State Budgetary Institution – The Russian Scientific Center of Radiology and Surgical Technologies named after Academician A.M. Granov	Luiza Korytova	5	4
	EviMed LLC	Oleg Gladkov	6	5
	Kursk Oncological Research and Clinical named after G.E. Ostroverkhov	Igor Lifirenko	12	9
	Clinica Druzhkovyh LLC	Ekaterina Amirova	2	1
	Main Military Clinical Hospital named after N.N. Burdenko	Alexey Smolin	4	2
	Volga District Medical Centre	Anna Alyasova	4	4
Spain	Hospital General Universitario de Elche	Javier Gallego Plazas	13	11
	Hospital Universitario Marqués de Valdecilla	Fernando Rivera Herrero	14	11
	Complejo Hospitalario Universitario de Granada – Hospital Universitario Virgen de las Nieves	Joaquina Martínez Galán	1	1
	Hospital de la Santa Creu i Sant Pau	Raúl Terés Lleida	9	6
	Centro Integral Oncológico Clara Campal	Antonio Cubillo Gracián	15	11
	Hospital Universitario Vall d'Hebron	Teresa Macarulla Mercadé	12	11
	Corporació Sanitària Parc Tauli – Hospital de Sabadell	Ismael Macías Declara	10	9
	Hospital Regional Universitario de Málaga	Inmaculada Alés Diaz	8	3
	Hospital Universitario de Badajoz	Marta González Cordero	9	5
	Hospital General Universitario Gregorio Marañón	Andres Muñoz Martín	5	3
	Hospital Fundación Jiménez Díaz	Cristina Caramés Sánchez	7	6
	Hospital Clínic de Barcelona	Tamara Saurí Nadal	4	2
	Hospital Universitario La Paz	Jaime Feliú Batlle	11	10
	Hospital Universitario Miguel Servet	Roberto Pazo Cid	34	21
	Institut Català d'Oncologia – L'Hospitalet	Berta Laquente	7	7
	Complejo Hospitalario de Navarra	Ruth Vera	7	7

	Hospital Germans Trias i Pujol	Laura Layos Romero	8	8
	Hospital Universitario 12 de Octubre	Rocío García Carbonero	8	5
	Hospital Quirónsalud Barcelona	José Luis Cuadra	6	6
United Kingdom	Cancer Research UK – The Christie NHS Foundation Trust – Department of Medical Oncology	Richard Hubner	1	1
	Nottingham City Hospital	Arvind Arora	2	1
	Royal Marsden NHS Foundation Trust	Ian Chau	3	3
	Guy's and St. Thomas' NHS Foundation Trust	Paul Ross	5	5
	Imperial College Healthcare NHS Trust	Harpreet Wasan	2	2
	Institute of Cancer Research	Ian Chau	1	1
United States	University of California Los Angeles (UCLA)	Zev Wainberg	10	9
	Sarah Cannon and HCA Research Institute	David Spigel	6	6
	Carle Foundation Hospital	Suparna Mantha	2	2
	Maine Medical Center	Matthew Dugan	1	1
	HealthPartners Institute	Daniel Anderson	6	5
	Oncology Hematology West P.C. dba Nebraska Cancer Specialists	Nagendra Natarajan	7	4
	Cancer and Hematology Centers of Western Michigan	Sreenivasa Chandana	16	13
	University of Rochester	Aram Hezel	8	5
	Beth Israel Deaconess Medical Center	Mary Peters	6	4
	Willis-Knighton Cancer Center	Anil Veluvolu	3	3
	Mount Sinai Medical Center of Florida, Inc.	Mike Cusnir	4	1
	Clinical Research Alliance, Inc	Morton Coleman	2	1
	Kaiser Permanente – Northwest	Sandeep Mashru	4	3
	University of California, Irvine Medical Center	Farshid Dayyani	9	5
	Henry Ford Health System	Gazala Khan	13	10
	University of Alabama at Birmingham	Grant Williams	7	4
	Pikeville Medical Center	Mohamad Khasawneh	2	1
	Froedtert Hospital and the Medical College of Wisconsin	Mandana Kamgar	3	2
	University of Kentucky, Markey Cancer Center	Reema Patel	4	3
	The Center for Cancer and Blood Disorders	Henry Xiong	4	3

	The Ohio State University Comprehensive Cancer Center - Arthur G. James Cancer Hospital and Richard J. Solovev Research Institute (OSUCCC – James)	Anne Noonan	3	2
	David H. Koch Center for Cancer Care at Memorial Sloan Kettering Cancer Center	Alice Zervoudakis	12	7
	Houston Methodist Research Institute	Maen Abdelrahim	5	2
	University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center	Roby Thomas	6	3
	University of Oklahoma Health Sciences Center	Hassan Hatoum	10	6
	Virginia Cancer Specialists	Keeran Sampat	4	4
	Mayo Clinic Scottsdale	Tanios Bekaii-Saab	3	2
	City of Hope National Medical Center	Vincent Chung	9	4
	Sutter Health Sacramento	Deepti Behl	1	1
	Ochsner Medical Center	Suma Satti	1	1
	Siouxland Hematology-Oncology Associates, LLP	Donald Wender	2	1
	Frontier Cancer Center	Patrick Cobb	2	1
	Florida Cancer Specialists Panhandle	Pareshkumar Patel	7	4
	Florida Cancer Specialists St. Petersburg	Maen Hussein	25	13
	Florida Cancer Specialists Fort Myers	Anjan Patel	15	7
	Torrance Memorial Physician Network Cancer Care	Hugo Hool	4	3
	Comprehensive Cancer Centers of Nevada	Brian Vicuna	6	6
	St. Jude Hospital Yorba Linda dba St. Joseph Heritage Healthcare	David Park	6	2
	Illinois CancerCare, P.C.	Srinivas Jujjavarapu	1	1
	Texas Oncology-Baylor Charles A. Sammons Cancer Center	Scott Paulson	6	3
	Utah Cancer Specialists	S. DiSean Kendall	5	4
	Fort Wayne Medical Oncology and Hematology	Sunil Babu	5	3[b]
	MD Anderson Cancer Center	Shubham Pant	3	2
	Florida Cancer Specialists East	Todd Gersten	6	6
	Chattanooga Oncology & Hematology Associates – Tennessee Oncology	Mark Womack, IV	10	9
	Research Medical Center	Mohammad Mozayen	1	1
	Banner Health MD Anderson Cancer Center	Madappa Kundranda	3	1
	Baylor College of Medicine	Tannaz Armaghany	2	2
	Comprehensive Blood & Cancer Center	Pradip Rustagi	2	1

	Miami Cancer Institute	Antonio Ucar	6	2
	Rocky Mountain Cancer Center	Allen Cohn	9	7
	Compass Oncology – Rose Quarter Cancer Center	Spencer Shao	6	6
	Blue Ridge Cancer Care	Mark Kochenderfer	8	4
	Texas Oncology, Austin	Vivian Cline	3	2
	Texas Oncology, Northeast Texas (Tyler)	Donald Richards	5	3
	Oncology Associates of Oregon	Marc Uemura	1	1
	Texas Oncology, Wichita Falls	Brian K. Ulrich	3	1
	Maryland Oncology Hematology	Kashif Ali	3	3
	Stony Brook University Medical Center	Amna Sher	2	2
	Oregon Health & Science University (OHSU)	Emerson Chen	2	1
	Hematology Oncology Clinic	Michael Castine	2	1
	Mayo Clinic Rochester	Wen Ma	4	1
	Oncology Consultants	Julio Peguero	5	3
	Greenville Hospital System	Ki Chung	3	1
	Presbyterian Intercommunity Hospital (PIH)	Lisa Wang	3	2
	Messino Cancer Centers	Christopher Chay	4	3

[a]One patient transferred from Fiona Stanley Hospital. [b]One patient transferred from Florida Cancer Specialists Fort Myers.

Table S2 (online only). Summary of major protocol deviations (intention-to-treat population).

	NALIRIFOX (n=383)	Nab-paclitaxel + gemcitabine (n=387)	All patients (n=770)
Patients with major protocol deviations, n (%)	256 (66·8)	233 (60·2)	489 (63·5)
Study treatment non-compliance	200 (52·2)	153 (39·5)	353 (45·8)
Safety reporting non-compliance	36 (9·4)	43 (11·1)	79 (10·3)
Eligibility criteria deviation	28 (7·3)	48 (12·4)	76 (9·9)
Informed consent non-compliance	38 (9·9)	29 (7·5)	67 (8·7)
Randomisation/Treatment allocation process deviation	20 (5·2)	13 (3·4)	33 (4·3)
Procedures deviation	18 (4·7)	13 (3·4)	31 (4·0)
GCP non-compliance	18 (4·7)	9 (2·3)	27 (3·5)
Prohibited medication/therapy/surgery	14 (3·7)	9 (2·3)	23 (3·0)
Time window deviation	8 (2·1)	8 (2·1)	16 (2·1)
Withdrawal criteria deviation	3 (0·8)	7 (1·8)	10 (1·3)
Combination of minor deviations	0 (0·0)	6 (1·6)	6 (0·8)

GCP, good clinical practice; NALIRIFOX, liposomal irinotecan in combination with 5-fluorouracil, leucovorin, and oxaliplatin.

Table S3 (online only). Subsequent therapy (safety population).

	NALIRIFOX (n=370)	Nab-paclitaxel + gemcitabine (n=379)
Any further subsequent anti-cancer therapy, n (%)	187 (50·5)	206 (54·4)
Systemic anti-neoplastic therapy	187 (50.5)	206 (54·4)
Surgery	1 (0·3)	2 (0·5)
Radiotherapy	2 (0·5)	4 (1·1)

NALIRIFOX, liposomal irinotecan in combination with 5-fluorouracil, leucovorin, and oxaliplatin.

Table S4 (online only). List of anticancer therapies.

Gemcitabine-based	5-fluorouracil-based	Liposomal irinotecan-based
capecitabine;gemcitabine	cisplatin;fluorouracil;folinic acid	fluorouracil;irinotecan hydrochloride trihydrate liposomal
carboplatin;gemcitabine	fluorouracil	irinotecan hydrochloride trihydrate liposomal
cisplatin;gemcitabine	fluorouracil;folinic acid	
erlotinib;gemcitabine	fluorouracil;folinic acid;irinotecan	
gemcitabine	fluorouracil;folinic acid;irinotecan;oxaliplatin	
gemcitabine hydrochloride	fluorouracil;folinic acid;oxaliplatin	
gemcitabine;paclitaxel	uracil;irinotecan hydrochloride trihydrate liposomal	
gemcitabine;paclitaxel nanoparticle albumin-bound	fluorouracil;irinotecan;oxaliplatin	
	fluorouracil;mitomycin	
	fluorouracil;oxaliplatin	
	fluorouracil;irinotecan hydrochloride trihydrate liposomal	
	irinotecan hydrochloride trihydrate liposomal	

Table S5 (online only). Reasons for exclusion from the per-protocol population.

Patient	Reason
05600300002	EC12a: Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before screening
07600900002	EC21: History of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies
07601300003	EC3: Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy that was not palliative radiotherapy or placement of a biliary stent/tube
20300400006	EC22: History of peripheral artery disease (e.g. claudication, Leo Buerger's disease)
25000200007	Randomised but not dosed
25001000008	Randomised but not dosed
27600500006	IC3&IC4: Did not have histologically or cytologically confirmed adenocarcinoma of the pancreas not previously treated in the metastatic setting; initial diagnosis of metastatic disease did not occur ≤6 weeks prior to screening
38000600010	Randomised but not dosed
38000800004	Randomised but not dosed
62000400004	EC18: Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma
64300100004	IC7c: Biological parameters inadequate – haemoglobin was not ≥9g/dL obtained ≤14 days prior to randomisation; randomised but not dosed
64300200006	EC3: Prior treatment of pancreatic cancer in the metastatic setting with surgery, radiotherapy, chemotherapy or investigational therapy that was not palliative radiotherapy or placement of a biliary stent/tube
64300300012	Randomised but not dosed
72400500010	Randomised but not dosed
72400600003	EC5: Localised advanced disease
72400900009	Randomised but not dosed

72401400018	IC3&IC4: Did not have histologically or cytologically confirmed adenocarcinoma of the pancreas not previously treated in the metastatic setting; initial diagnosis of metastatic disease did not occur ≤6 weeks prior to screening
72401700001	Randomised but not dosed
72401700008	EC21: History of interstitial lung disease, history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies
82600400003	IC8a: Hepatic function inadequate - serum total bilirubin was not ≤1.5 times the upper limit of normal
84000100009	Randomised but not dosed
84000800002	EC18: Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma
84002000008	Randomised but not dosed
84002100005	Randomised but not dosed
84002600001	Randomised but not dosed
84004800019	Randomised but not dosed
84004800024	Randomised but not dosed
84005100003	IC8a: Hepatic function inadequate - serum total bilirubin was not ≤1.5 times the upper limit of normal; randomised but not dosed
84006500002	Randomised but not dosed
84006800003	Randomised but not dosed
84006900001	Randomised but not dosed
84007600005	Randomised but not dosed
84007700007	Prohibited concomitant medication
84008300004	Randomised but not dosed
84010200001	EC20a: History of systemic connective tissue disorders (e.g. lupus, scleroderma, arteritis nodosa)

Table S6 (online only). Treatment-emergent adverse events of any grade occurring in ≥10% of patients in either treatment arm (safety population).

TEAE* — No. (%)	NALIRIFOX (n=370)	Nab-paclitaxel + gemcitabine (n=379)	All patients (n=749)
Gastrointestinal disorders			
Diarrhoea	261 (70·5)	139 (36·7)	400 (53·4)
Nausea	220 (59·5)	162 (42·7)	382 (51·0)
Vomiting	147 (39·7)	100 (26·4)	247 (33·0)
Constipation	93 (25·1)	113 (29·8)	206 (27·5)
Abdominal pain	98 (26·5)	77 (20·3)	175 (23·4)
Stomatitis	50 (13·5)	45 (11·9)	95 (12·7)
General disorders and administration site conditions			
Fatigue	120 (32·4)	143 (37·7)	263 (35·1)
Asthenia	114 (30·8)	104 (27·4)	218 (29·1)
Oedema peripheral	52 (14·1)	108 (28·5)	160 (21·4)
Pyrexia	39 (10·5)	87 (23·0)	126 (16·8)
Mucosal inflammation	51 (13·8)	16 (4·2)	67 (8·9)
Nervous system disorders			
Neuropathy peripheral	66 (17·8)	66 (17·4)	132 (17·6)
Dysgeusia	63 (17·0)	58 (15·3)	121 (16·2)
Peripheral sensory neuropathy	56 (15·1)	51 (13·5)	107 (14·3)
Paresthesia	44 (11·9)	33 (8·7)	77 (10·3)

Blood and lymphatic system disorders			
Anaemia	97 (26·2)	153 (40·4)	250 (33·4)
Neutropenia	109 (29·5)	121 (31·9)	230 (30·7)
Thrombocytopenia	50 (13·5)	86 (22·7)	136 (18·2)
Metabolism and nutrition disorders			
Decreased appetite	136 (36·8)	106 (28·0)	242 (32·3)
Hypokalaemia	117 (31·6)	49 (12·9)	166 (22·2)
Dehydration	41 (11·1)	32 (8·4)	73 (9·7)
Investigations			
Neutrophil count decreased	76 (20·5)	71 (18·7)	147 (19·6)
Weight decreased	82 (22·2)	33 (8·7)	115 (15·4)
Platelet count decreased	39 (10·5)	68 (17·9)	107 (14·3)
Alanine aminotransferase increased	45 (12·2)	48 (12·7)	93 (12·4)
Aspartate aminotransferase increased	40 (10·8)	40 (10·6)	80 (10·7)
γ-glutamyltransferase increased	45 (12·2)	34 (9·0)	79 (10·5)
Blood alkaline phosphatase increased	39 (10·5)	31 (8·2)	70 (9·3)
Skin and subcutaneous tissue disorders			
Alopecia	52 (14·1)	119 (31·4)	171 (22·8)
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	25 (6·8)	47 (12·4)	72 (9·6)

Epistaxis	14 (3·8)	43 (11·3)	57 (7·6)

NALIRIFOX, liposomal irinotecan in combination with 5-fluorouracil, leucovorin, and oxaliplatin; TEAE, treatment-emergent adverse event.
*TEAEs are adverse events that occurred or worsened on or after the day of the first dose of study medication and within the 30 days after discontinuation of treatment. Patients with multiple adverse events within a preferred term are only counted once under each category.

Table S7 (online only). Grade ≥3 treatment-emergent adverse events occurring in ≥2% of patients in either treatment arm (safety population).

TEAE* — No. (%)	NALIRIFOX (n=370)	Nab-paclitaxel + gemcitabine (n=379)	All patients (n=749)
Gastrointestinal disorders			
Diarrhoea	75 (20·3)	17 (4·5)	92 (12·3)
Nausea	44 (11·9)	10 (2·6)	54 (7·2)
Vomiting	26 (7·0)	8 (2·1)	34 (4·5)
Constipation	3 (0·8)	8 (2·1)	11 (1·5)
Abdominal pain	16 (4·3)	14 (3·7)	30 (4·0)
Ascites	11 (3·0)	8 (2·1)	19 (2·5)
General disorders and administration site conditions			
Fatigue	23 (6·2)	20 (5·3)	43 (5·7)
Asthenia	33 (8·9)	19 (5·0)	52 (6·9)
Mucosal inflammation	8 (2·2)	1 (0·3)	9 (1·2)
Nervous system disorders			
Neuropathy peripheral	12 (3·2)	22 (5·8)	34 (4·5)
Peripheral sensory neuropathy	13 (3·5)	11 (2·9)	24 (3·2)
Blood and lymphatic system disorders			
Anaemia	39 (10·5)	66 (17·4)	105 (14·0)
Neutropenia	52 (14·1)	93 (24·5)	145 (19·4)

Thrombocytopenia	3 (0·8)	14 (3·7)	17 (2·3)
Leukopenia	4 (1·1)	17 (4·5)	21 (2·8)
Febrile neutropenia	9 (2·4)	9 (2·4)	18 (2·4)
Metabolism and nutrition disorders			
Decreased appetite	32 (8·6)	10 (2·6)	42 (5·6)
Hypokalaemia	56 (15·1)	15 (4·0)	71 (9·5)
Dehydration	12 (3·2)	4 (1·1)	16 (2·1)
Investigations			
Neutrophil count decreased	36 (9·7)	51 (13·5)	87 (11·6)
Weight decreased	11 (3·0)	1 (0·3)	12 (1·6)
Platelet count decreased	3 (0·8)	9 (2·4)	12 (1·6)
Alanine aminotransferase increased	13 (3·5)	12 (3·2)	25 (3·3)
Aspartate aminotransferase increased	11 (3·0)	8 (2·1)	19 (2·5)
γ-Glutamyltransferase increased	23 (6·2)	21 (5·5)	44 (5·9)
Blood alkaline phosphatase increased	11 (3·0)	10 (2·6)	21 (2·8)
White blood cell count decreased	6 (1·6)	18 (4·7)	24 (3·2)
Blood bilirubin increased	14 (3·8)	11 (2·9)	25 (3·3)
Infections and infestations			
Pneumonia	5 (1·4)	13 (3·4)	18 (2·4)
Sepsis	4 (1·1)	9 (2·4)	13 (1·7)

Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	2 (0.5)	8 (2·1)	10 (1·3)
Pulmonary embolism	21 (5·7)	17 (4·5)	38 (5·1)
Vascular disorders			
Hypertension	13 (3·5)	8 (2·1)	21 (2·8)
Renal and urinary disorders			
Acute kidney injury	4 (1·1)	10 (2·6)	14 (1·9)

NALIRIFOX, liposomal irinotecan in combination with 5-fluorouracil, leucovorin, and oxaliplatin; TEAE, treatment-emergent adverse event.
*TEAEs are adverse events that occurred or worsened on or after the day of the first dose of study medication and within the 30 days after discontinuation of treatment. Patients with multiple adverse events within a preferred term are only counted once under each category.

Table S8 (online only). Serious treatment-emergent adverse events of any grade occurring in patients in either treatment arm (safety population).

TEAE* — No. (%)	NALIRIFOX (n=370)	Nab-paclitaxel + gemcitabine (n=379)	All patients (n=749)
Gastrointestinal disorders			
Diarrhoea	23 (6·2)	9 (2·4)	32 (4·3)
Vomiting	22 (5·9)	6 (1·6)	28 (3·7)
Nausea	18 (4·9)	3 (0·8)	21 (2·8)
Abdominal pain	9 (2·4)	8 (2·1)	17 (2·3)
Ascites	6 (1·6)	5 (1·3)	11 (1·5)
Colitis	7 (1·9)	4 (1·1)	11 (1·5)
Constipation	1 (0·3)	6 (1·6)	7 (0·9)
Gastrointestinal haemorrhage	3 (0·8)	4 (1·1)	7 (0·9)
Intestinal obstruction	3 (0·8)	2 (0·5)	5 (0·7)
Ileus	3 (0·8)	1 (0·3)	4 (0·5)
Upper gastrointestinal haemorrhage	1 (0·3)	3 (0·8)	4 (0·5)
Duodenal obstruction	2 (0·5)	1 (0·3)	3 (0·4)
Duodenal stenosis	2 (0·5)	1 (0·3)	3 (0·4)
Duodenal ulcer	3 (0·8)	0 (0·0)	3 (0·4)
Small intestinal obstruction	1 (0·3)	2 (0·5)	3 (0·4)
Gastric haemorrhage	1 (0·3)	1 (0·3)	2 (0·3)

Gastrointestinal toxicity	2 (0·5)	0 (0·0)	2 (0·3)
Haematemesis	2 (0·5)	0 (0·0)	2 (0·3)
Obstruction gastric	1 (0·3)	1 (0·3)	2 (0·3)
Oesophagitis	2 (0·5)	0 (0·0)	2 (0·3)
Pancreatitis acute	0 (0·0)	2 (0·5)	2 (0·3)
Abdominal discomfort	0 (0·0)	1 (0·3)	1 (0·1)
Abdominal pain upper	1 (0·3)	0 (0·0)	1 (0·1)
Diarrhoea haemorrhagic	0 (0·0)	1 (0·3)	1 (0·1)
Duodenal ulcer perforation	1 (0·3)	0 (0·0)	1 (0·1)
Dysphagia	0 (0·0)	1 (0·3)	1 (0·1)
Enterocolitis	1 (0·3)	0 (0·0)	1 (0·1)
Faecaloma	0 (0·0)	1 (0·3)	1 (0·1)
Food poisoning	0 (0·0)	1 (0·3)	1 (0·1)
Gastric fistula	0 (0·0)	1 (0·3)	1 (0·1)
Gastric ulcer haemorrhage	1 (0·3)	0 (0·0)	1 (0·1)
Gastrointestinal disorder	0 (0·0)	1 (0·3)	1 (0·1)
Intestinal pseudo-obstruction	1 (0·3)	0 (0·0)	1 (0·1)
Mesenteric vein thrombosis	1 (0·3)	0 (0·0)	1 (0·1)
Neutropenic colitis	1 (0·3)	0 (0·0)	1 (0·1)
Odynophagia	0 (0·0)	1 (0·3)	1 (0·1)
Oesophageal ulcer	0 (0·0)	1 (0·3)	1 (0·1)

Oesophageal varices haemorrhage	0 (0·0)	1 (0·3)	1 (0·1)
Small intestinal haemorrhage	0 (0·0)	1 (0·3)	1 (0·1)
Terminal ileitis	1 (0·3)	0 (0·0)	1 (0·1)
Infections and infestations			
COVID-19	18 (4·9)	14 (3·7)	32 (4·3)
Sepsis	6 (1·6)	16 (4·2)	22 (2·9)
Pneumonia	7 (1·9)	13 (3·4)	20 (2·7)
Urinary tract infection	3 (0·8)	4 (1·1)	7 (0·9)
Asymptomatic COVID-19	0 (0·0)	3 (0·8)	3 (0·4)
Biliary tract infection	2 (0·5)	1 (0·3)	3 (0·4)
Cellulitis	0 (0·0)	3 (0·8)	3 (0·4)
Febrile infection	1 (0·3)	2 (0·5)	3 (0·4)
Gastroenteritis	3 (0·8)	0 (0·0)	3 (0·4)
Abdominal sepsis	0 (0·0)	2 (0·5)	2 (0·3)
Bacteraemia	1 (0·3)	1 (0·3)	2 (0·3)
Diverticulitis	1(0·3)	1 (0·3)	2 (0·3)
Erysipelas	1 (0·3)	1 (0·3)	2 (0·3)
Escherichia bacteraemia	1 (0·3)	1 (0·3)	2 (0·3)
Septic shock	1 (0·3)	1 (0·3)	2 (0·3)
Suspected COVID-19	0 (0·0)	2 (0·5)	2 (0·3)

Abdominal abscess	0 (0·0)	1 (0·3)	1 (0·1)
Anal abscess	1 (0·3)	0 (0·0)	1 (0·1)
Atypical pneumonia	1 (0·3)	0 (0·0)	1 (0·1)
Bacterial sepsis	0 (0·0)	1 (0·3)	1 (0·1)
Biliary sepsis	0 (0·0)	1 (0·3)	1 (0·1)
COVID-19 pneumonia	0 (0·0)	1 (0·3)	1 (0·1)
Campylobacter colitis	1 (0·3)	0 (0·0)	1 (0·1)
Catheter site infection	0 (0·0)	1 (0·3)	1 (0·1)
Cholangitis infective	0 (0·0)	1 (0·3)	1 (0·1)
Clostridium difficile colitis	1 (0·3)	0 (0·0)	1 (0·1)
Device related bacteraemia	0 (0·0)	1 (0·3)	1 (0·1)
Device related infection	0 (0·0)	1 (0·3)	1 (0·1)
Enterococcal infection	0 (0·0)	1 (0·3)	1 (0·1)
Gallbladder abscess	0 (0·0)	1 (0·3)	1 (0·1)
Gastroenteritis norovirus	1 (0·3)	0 (0·0)	1 (0·1)
Hepatic infection	0 (0·0)	1 (0·3)	1 (0·1)
Hepatitis E	1 (0·3)	0 (0·0)	1 (0·1)
Implant site cellulitis	0 (0·0)	1 (0·3)	1 (0·1)
Infective spondylitis	0 (0·0)	1 (0·3)	1 (0·1)
Large intestine infection	1 (0·3)	0 (0·0)	1 (0·1)
Liver abscess	1 (0·3)	0 (0·0)	1 (0·1)

Peritonitis bacterial	0 (0·0)	1 (0·3)	1 (0·1)
Pneumonia aspiration	0 (0·0)	1 (0·3)	1 (0·1)
Post procedural cellulitis	0 (0·0)	1 (0·3)	1 (0·1)
Staphylococcal bacteraemia	1 (0·3)	0 (0·0)	1 (0·1)
Streptococcal infection	1 (0·3)	0 (0·0)	1 (0·1)
General disorders and administration site conditions			
Pyrexia	8 (2·2)	12 (3·2)	20 (2·7)
Asthenia	7 (1·9)	2 (0·5)	9 (1·2)
Fatigue	7 (1·9)	0 (0·0)	7 (0·9)
General physical health deterioration	1 (0·3)	6 (1·6)	7 (0·9)
Malaise	3 (0·8)	0 (0·0)	3 (0·4)
Oedema peripheral	0 (0·0)	3 (0·8)	3 (0·4)
Mucosal inflammation	1 (0·3)	1 (0·3)	2 (0·3)
Peripheral swelling	0 (0·0)	2 (0·5)	2 (0·3)
Catheter site inflammation	0 (0·0)	1 (0·3)	1 (0·1)
Chest pain	1 (0·3)	0 (0·0)	1 (0·1)
Condition aggravated	0 (0·0)	1 (0·3)	1 (0·1)
Generalised oedema	1 (0·3)	0 (0·0)	1 (0·1)
Inadequate analgesia	0 (0·0)	1 (0·3)	1 (0·1)
Inflammation	1 (0·3)	0 (0·0)	1 (0·1)

Multiple organ dysfunction syndrome	1 (0·3)	0 (0·0)	1 (0·1)
Pain	1 (0·3)	0 (0·0)	1 (0·1)
Performance status decreased	0 (0·0)	1 (0·3)	1 (0·1)
Sudden cardiac death	1 (0·3)	0 (0·0)	1 (0·1)
Sudden death	1 (0·3)	0 (0·0)	1 (0·1)
Metabolism and nutrition disorders			
Dehydration	10 (2·7)	4 (1·1)	14 (1·9)
Hypokalaemia	6 (1·6)	3 (0·8)	9 (1·2)
Decreased appetite	5 (1·4)	2 (0·5)	7 (0·9)
Hypoglycaemia	1 (0·3)	4 (1·1)	5 (0·7)
Hyponatraemia	1 (0·3)	2 (0·5)	3 (0·4)
Adult failure to thrive	0 (0·0)	2 (0·5)	2 (0·3)
Failure to thrive	0 (0·0)	2 (0·5)	2 (0·3)
Hypophosphataemia	1 (0·3)	1 (0·3)	2 (0·3)
Diabetes mellitus inadequate control	0 (0·0)	1 (0·3)	1 (0·1)
Diabetic metabolic decompensation	1 (0·3)	0 (0·0)	1 (0·1)
Electrolyte imbalance	1 (0·3)	0 (0·0)	1 (0·1)
Hypercalcaemia	1 (0·3)	0 (0·0)	1 (0·1)
Hyperkalaemia	0 (0·0)	1 (0·3)	1 (0·1)
Type 2 diabetes mellitus	1 (0·3)	0 (0·0)	1 (0·1)

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	10 (2·7)	7 (1·8)	17 (2·3)
Dyspnoea	2 (0·5)	5 (1·3)	7 (0·9)
Pleural effusion	2 (0·5)	2 (0·5)	4 (0·5)
Pneumonitis	0 (0·0)	2 (0·5)	2 (0·3)
Pneumothorax	1 (0·3)	1 (0·3)	2 (0·3)
Acute respiratory failure	0 (0·0)	1 (0·3)	1 (0·1)
Aspiration	1 (0·3)	0 (0·0)	1 (0·1)
Hydrothorax	1 (0·3)	0 (0·0)	1 (0·1)
Hypoxia	0 (0·0)	1 (0·3)	1 (0·1)
Interstitial lung disease	0 (0·0)	1 (0·3)	1 (0·1)
Lung infiltration	0 (0·0)	1 (0·3)	1 (0·1)
Pneumonitis aspiration	1 (0·3)	0 (0·0)	1 (0·1)
Productive cough	0 (0·0)	1 (0·3)	1 (0·1)
Pulmonary hypertension	0 (0·0)	1 (0·3)	1 (0·1)
Respiratory failure	0 (0·0)	1 (0·3)	1 (0·1)
Blood and lymphatic system disorders			
Anaemia	5 (1·4)	8 (2·1)	13 (1·7)
Febrile neutropenia	7 (1·9)	6 (1·6)	13 (1·7)
Neutropenia	2 (0·5)	1 (0·3)	3 (0·4)

Pancytopenia	1 (0·3)	1 (0·3)	2 (0·3)
Thrombocytopenia	0 (0·0)	2 (0·5)	2 (0·3)
Disseminated intravascular coagulation	0 (0·0)	1 (0·3)	1 (0·1)
Vascular disorders			
Deep vein thrombosis	4 (1·1)	8 (2·1)	12 (1·6)
Hypotension	2 (0·5)	3 (0·8)	5 (0·7)
Embolism	1 (0·3)	3 (0·8)	4 (0·5)
Haemorrhage	0 (0·0)	3 (0·8)	3 (0·4)
Peripheral ischaemia	1 (0·3)	1 (0·3)	2 (0·3)
Embolism arterial	1 (0·3)	0 (0·0)	1 (0·1)
Hypertension	1 (0·3)	0 (0·0)	1 (0·1)
Iliac vein occlusion	0 (0·0)	1 (0·3)	1 (0·1)
Orthostatic hypotension	0 (0·0)	1 (0·3)	1 (0·1)
Peripheral embolism	1 (0·3)	0 (0·0)	1 (0·1)
Venous thrombosis limb	0 (0·0)	1 (0·3)	1 (0·1)
Hepatobiliary disorders			
Cholangitis	4 (1·1)	6 (1·6)	10 (1·3)
Biliary obstruction	6 (1·6)	1 (0·3)	7 (0·9)
Cholestasis	1 (0·3)	2 (0·5)	3 (0·4)
Hyperbilirubinaemia	2 (0·5)	1 (0·3)	3 (0·4)

Cholecystitis	0 (0·0)	2 (0·5)	2 (0·3)
Cholecystitis acute	0 (0·0)	2 (0·5)	2 (0·3)
Bile duct stenosis	0 (0·0)	1 (0·3)	1 (0·1)
Hepatitis	0 (0·0)	1 (0·3)	1 (0·1)
Hepatitis toxic	1 (0·3)	0 (0·0)	1 (0·1)
Hepatotoxicity	1 (0·3)	0 (0·0)	1 (0·1)
Jaundice cholestatic	0 (0·0)	1 (0·3)	1 (0·1)
Nervous system disorders			
Cerebrovascular accident	4 (1·1)	2 (0·5)	6 (0·8)
Ischaemic stroke	4 (1·1)	2 (0·5)	6 (0·8)
Cerebral haemorrhage	2 (0·5)	0 (0·0)	2 (0·3)
Cerebral ischaemia	2 (0·5)	0 (0·0)	2 (0·3)
Aphasia	1 (0·3)	0 (0·0)	1 (0·1)
Cerebral infarction	0 (0·0)	1 (0·3)	1 (0·1)
Embolic stroke	0 (0·0)	1 (0·3)	1 (0·1)
Epilepsy	0 (0·0)	1 (0·3)	1 (0·1)
Generalised tonic-clonic seizure	1 (0·3)	0 (0·0)	1 (0·1)
Hemiparesis	0 (0·0)	1 (0·3)	1 (0·1)
Hypoaesthesia	0 (0·0)	1 (0·3)	1 (0·1)
Metabolic encephalopathy	0 (0·0)	1 (0·3)	1 (0·1)

Myoclonus	0 (0·0)	1 (0·3)	1 (0·1)
Pineal gland cyst	1 (0·3)	0 (0·0)	1 (0·1)
Sciatica	0 (0·0)	1 (0·3)	1 (0·1)
Seizure	1 (0·3)	0 (0·0)	1 (0·1)
Transient ischaemic attack	0 (0·0)	1 (0·3)	1 (0·1)
Tremor	1 (0·3)	0 (0·0)	1 (0·1)
Investigations			
Blood bilirubin increased	5 (1·4)	3 (0·8)	8 (1·1)
Neutrophil count decreased	2 (0·5)	2 (0·5)	4 (0·5)
SARS-CoV-2 test positive	1 (0·3)	2 (0·5)	3 (0·4)
Gamma-glutamyltransferase increased	2 (0·5)	0 (0·0)	2 (0·3)
White blood cell count decreased	1 (0·3)	1 (0·3)	2 (0·3)
Blood alkaline phosphatase increased	1 (0·3)	0 (0·0)	1 (0·1)
Blood glucose abnormal	1 (0·3)	0 (0·0)	1 (0·1)
General physical condition abnormal	1 (0·3)	0 (0·0)	1 (0·1)
Haemoglobin decreased	1 (0·3)	0 (0·0)	1 (0·1)
Platelet count decreased	0 (0·0)	1 (0·3)	1 (0·1)
Renal and urinary disorders			
Acute kidney injury	3 (0·8)	9 (2·4)	12 (1·6)
Haematuria	0 (0·0)	3 (0·8)	3 (0·4)

Renal impairment	1 (0·3)	1 (0·3)	2 (0·3)
Nephrolithiasis	0 (0·0)	1 (0·3)	1 (0·1)
Renal failure	1 (0·3)	0 (0·0)	1 (0·1)
Urinary retention	0 (0·0)	1 (0·3)	1 (0·1)
Urinary tract obstruction	0 (0·0)	1 (0·3)	1 (0·1)
Cardiac disorders			
Atrial fibrillation	0 (0·0)	3 (0·8)	3 (0·4)
Cardiac arrest	1 (0·3)	1 (0·3)	2 (0·3)
Cardiac failure	0 (0·0)	2 (0·5)	2 (0·3)
Acute myocardial infarction	1 (0·3)	0 (0·0)	1 (0·1)
Angina pectoris	1 (0·3)	0 (0·0)	1 (0·1)
Arrhythmia	0 (0·0)	1 (0·3)	1 (0·1)
Atrial flutter	1 (0·3)	0 (0·0)	1 (0·1)
Cardiac failure chronic	0 (0·0)	1 (0·3)	1 (0·1)
Cardiac flutter	0 (0·0)	1 (0·3)	1 (0·1)
Myocardial infarction	0 (0·0)	1 (0·3)	1 (0·1)
Sinus node dysfunction	0 (0·0)	1 (0·3)	1 (0·1)
Tachycardia	1 (0·3)	0 (0·0)	1 (0·1)
Injury, poisoning and procedural complications			
Exposure to SARS-CoV-2	0 (0.0)	4 (1.1)	4 (0.5)

Hip fracture	1 (0·3)	1 (0·3)	2 (0·3)
Fall	1 (0·3)	0 (0·0)	1 (0·1)
Femoral neck fracture	0 (0·0)	1 (0·3)	1 (0·1)
Head injury	1 (0·3)	0 (0·0)	1 (0·1)
Wound	0 (0·0)	1 (0·3)	1 (0·1)
Psychiatric disorders			
Confusional state	1 (0·3)	2 (0·5)	3 (0·4)
Mental status changes	2 (0·5)	0 (0·0)	2 (0·3)
Anxiety	0 (0·0)	1 (0·3)	1 (0·1)
Delirium	1 (0·3)	0 (0·0)	1 (0·1)
Depression	1 (0·3)	0 (0·0)	1 (0·1)
Psychotic disorder	0 (0·0)	1 (0·3)	1 (0·1)
Musculoskeletal and connective tissue disorders			
Back pain	1 (0·3)	1 (0·3)	2 (0·3)
Chest wall haematoma	0 (0·0)	1 (0·3)	1 (0·1)
Myalgia	0 (0·0)	1 (0·3)	1 (0·1)
Pain in extremity	1 (0·3)	0 (0·0)	1 (0·1)
Pathological fracture	0 (0·0)	1 (0·3)	1 (0·1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage	1 (0·3)	1 (0·3)	2 (0·3)

Peritumoural oedema	1 (0·3)	0 (0·0)	1 (0·1)
Tumour pain	0 (0·0)	1 (0·3)	1 (0·1)
Skin and subcutaneous tissue disorders			
Decubitus ulcer	0 (0·0)	1 (0·3)	1 (0·1)
Erythema	0 (0·0)	1 (0·3)	1 (0·1)
Pruritus	0 (0·0)	1 (0·3)	1 (0·1)
Rash	0 (0·0)	1 (0·3)	1 (0·1)
Ear and labyrinth disorders			
Vertigo	2 (0·5)	0 (0·0)	2 (0·3)
Reproductive system and breast disorders			
Penile vein thrombosis	1 (0·3)	0 (0·0)	1 (0·1)
Priapism	1 (0·3)	0 (0·0)	1 (0·1)
Eye disorders			
Retinal vein occlusion	1 (0·3)	0 (0·0)	1 (0·1)
Product issues			
Thrombosis in device	1 (0·3)	0 (0·0)	1 (0·1)

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*TEAEs are adverse events that occurred or worsened on or after the day of the first dose of study medication and within the 30 days after discontinuation of treatment. Patients with multiple adverse events within a preferred term are only counted once under each category.

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