Official Title: A Dose-optimization, Exploratory Phase Ib/II Study to Assess Safety and Efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) Mimetic Debio 1143, When Given in Combination with the Anti-PD-1 Antibody Nivolumab in Patients With Specific Solid Tumors Who Have Progressed During or Immediately After Anti-PD-1/PD-L1 Treatment

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STUDY PROTOCOL

SMARTPLUS-106: Debio 1143 a SMAC Mimetic in Combination with Nivolumab in Patients Failing Prior PD-1/PD-L1 Treatment: A Basket Trial

A dose-optimization, exploratory phase Ib/II study to assess safety and efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) mimetic Debio 1143, when given in combination with the anti-PD-1 antibody nivolumab in patients with specific solid tumors who have progressed during or immediately after anti-PD-1/PD-L1 treatment

Investigational Medicinal Product (IMP): Debio 1143

Investigational Medicinal Product (IMP): Nivolumab

Study Number: Debio 1143-106

EudraCT Number: 2018-003546-16

US IND Number: 105074

SPONSOR:
Debiopharm International SA
Forum "après-demain"
Chemin Messidor 5-7
P.O. Box 5911
CH-1002 Lausanne
Switzerland

Final version No.4, 03 April 2020 incorporating Amendment No. 3

Study Sponsor:	Debiopharm International SA, Ch. Messidor 5-7, P.O. Box 5911, CH-1002 Lausanne, Switzerland
Study Title:	**SMARTPLUS-106: Debio 1143 a SMAC Mimetic in Combination with Nivolumab in Patients Failing Prior PD-1/PD-L1 Treatment: A Basket Trial** A dose-optimization, exploratory phase Ib/II study to assess safety and efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) mimetic Debio 1143, when given in combination with the anti-PD-1 antibody nivolumab in patients with specific solid tumors who have progressed during or immediately after anti-PD1/PD-L1 treatment
Study Number:	Debio 1143-106
Investigational Medicinal Product (IMP):	Debio 1143 in combination with nivolumab
Date	Final version No.4, 03 April 2020 incorporating Amendment No. 3
Principal Investigator:	The full list of investigators and participating sites will be provided separately.

[redacted] Signature [redacted] Date [redacted]

[redacted], [redacted], MD
Debiopharm International SA,
Chemin Messidor 5-7, P.O. Box 5911
CH-1002 Lausanne, Switzerland

Phone: [redacted]
Fax: [redacted]
Email: [redacted]

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STUDY SYNOPSIS

STUDY TITLE	**SMARTPLUS-106: Debio 1143 a SMAC Mimetic In Combination With Nivolumab In Patients Failing Prior PD-1/PD-L1 Treatment: A Basket Trial** A dose-optimization, exploratory phase Ib/II study to assess safety and efficacy of the Second Mitochondrial-derived Activator of Caspases (SMAC) mimetic Debio 1143, when given in combination with the anti-PD-1 antibody nivolumab in patients with specific solid tumors who have progressed during or immediately after anti-PD-1/PD-L1 treatment
STUDY NUMBER	Debio 1143-106
EUDRACT NUMBER	2018-003546-16
US IND NUMBER	105074
STUDY PHASE/ INDICATION	Phase Ib/II / Basket trial in selected solid tumors
PARTICIPATING COUNTRIES AND NUMBER OF SITES	Part A- Up to six active sites in France and Spain Part B- In addition to Part A sites, up to 10 sites in the US. (Full list to be provided separately)
STUDY DESIGN	This study consists of two sequential parts: 1. Part A: a dose-optimization phase Ib 2. Part B: an exploratory phase II basket trial **Part A** has an open-label, multicenter and dose-optimization design applying the classical 3+3 method, aiming at optimizing the Debio 1143 dose in combination with standard doses of nivolumab (OPDIVO®) in order to define a safe recommended phase II dose (RP2D) and to assess its safety and feasibility in pretreated patients with selected advanced/unresectable solid tumors, including: small cell lung cancer (SCLC); squamous cell carcinoma of the head and neck (SCCHN); known microsatellite instability-high (MSI-H), mismatch repair deficiency (MMRd) or other known DNA damage repair (DDR) abnormalities, including homologous recombination deficiency (HRD) in gastrointestinal (GI) cancers; known DNA MMRd/MSI-H, breast cancer (BRCA)-1/2 hereditary or somatic/sporadic mutations, or other DDR abnormalities including HRD in platinum-resistant ovarian, endometrial, primary peritoneal or cervical cancers. Patients must have received at least one prior systemic line of standard treatment and must have progressed or relapsed during or immediately after a prior anti-programmed cell death-1 (PD-1)/ programmed cell death-ligand 1 (PD-L1)-based treatment, given either as a single agent or in combination with standard/approved chemotherapy, tyrosine kinase inhibitors (TKIs) or other monoclonal antibodies (mAbs) that are not known to modulate/inhibit immune checkpoints. Patients with prior cytotoxic T-lymphocyte antigen 4 (CTLA-4) or lymphocyte activation gene-3 (LAG-3) combinations with PD-1/PD-L1 are excluded; any other prior combinations with checkpoint inhibitors (CPI) should be discussed and agreed by the Sponsor before patient inclusion. Eligible patients will enter the study in cohorts of three evaluable patients. The starting dose of Debio 1143 will be 150 mg daily, administered orally for 10 consecutive days every 2 weeks (i.e., Days 1-10 and Days 15-24 of each 28-day cycle [q4w]). The dose will be optimized according to the observed dose limiting toxicities (DLTs), patient treatment compliance, safety/tolerability and pharmacokinetics (PK) data, if applicable. The DLT period is defined as Cycle 1 (i.e., lasting 4 weeks or longer in case of dosing delays). Treatment-related toxicities fulfilling DLT criteria but occurring after Cycle 1 (i.e., delayed DLTs) may also be considered for RP2D definition after discussion and agreement between the Investigators and the Sponsor. Nivolumab will be administered at 240 mg flat dose over at least 30 minutes as an intravenous (IV) infusion on Days 1 and 15 of a 28-day cycle. From Cycle 3, patients may be switched to nivolumab at a dose of 480 mg IV over at least 60 minutes on Day 1 q4w, exclusively upon Investigator request with the Sponsor agreement.

The maximum explored Debio 1143 dose will be 200 mg/d. Neither Debio 1143 dose escalation beyond this threshold, nor any nivolumab dose increases are foreseen in this study.

According to the 3+3 dose-optimization design, if none of the three patients at the starting dose cohort experiences a DLT during Cycle 1, three more patients will be treated at the next dose level. However, if one of the first 3 patients experiences a DLT, 3 more patients will be treated at the same dose level. If ≤ 1 out of 6 evaluable patients experiences a DLT during the first cycle, at the starting dose level, then dose escalation will proceed to the second dose level. If ≥ 2 DLTs are observed during the first cycle among the 3 or 6 evaluable patients treated with the initial dose level, then recruitment will be stopped temporarily or definitively until the reasons for this finding have been clarified. If the dose is increased to the second dose level, 3 to 6 evaluable patients will be included, and the 3+3 design rules will be applied again. If ≤ 1 out of 6 evaluable patients experiences a DLT during the first cycle at the second dose level, this dose will be considered the optimal dose level. If ≥ 2 out of 3 or 6 evaluable patients experience a DLT during the first cycle, at the second dose level, then the initial dose level will be declared the optimal dose, given that < 33% of evaluable patients have experienced a DLT during the first cycle and there are at least 6 evaluable patients treated at this dose level. Patients within a cohort may all start treatment simultaneously.

At least 6 evaluable patients should be treated at the RP2D before Part B of the study may start. Once the RP2D is defined, any patient still receiving treatment can be switched to this RP2D, if deemed appropriate by the Investigator and agreed by the Sponsor.

Table 1: Study treatment starting doses

Dose level	**Debio 1143** orally, daily for 10 days then 4 days off: D1-D10 & D15-D24 q4w (1 cycle= 4 weeks)	**Nivolumab#** flat dose, IV, D1 & D15 q4w (1 cycle=4 weeks)
1 (starting dose)	150 mg	240 mg
2 (higher dose)	200 mg	

D= day; IV= intravenous; q4w= every 4 weeks

From Cycle 3, a switch to 480 mg nivolumab q4w (Day 1 of each 28-day cycle) will be allowed on a per-patient basis, based on the Investigator's judgement and Sponsor agreement. Once the nivolumab dose is switched, this schedule should be maintained until EOT.

Part B is a multicenter, open-label, basket trial using Debio 1143 in combination with nivolumab at the RP2D, as previously defined in Part A, in patients with selected advanced/unresectable solid tumors.

Eligible patients will be simultaneously included, into four cohorts according to tumor type:

Cohort 1: SCLC (including extrapulmonary small-cell carcinomas or large cell neuroendocrine lung carcinoma as per WHO Classification of Lung Tumors of 2015)[1]
Cohort 2: SCCHN (nasopharyngeal carcinomas are excluded)
Cohort 3: GI cancers, including esophageal, gastric, colorectal or pancreatobiliary tumors, with known MSI-H/ MMRd or other known DDR abnormalities (incl. HRD).
Cohort 4: platinum-resistant epithelial ovarian cancer (EOC), endometrial cancer, primary peritoneal cancer (PPC) and cervical cancer, with known MSI-H/ MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other DNA DDR abnormalities (incl. HRD).

The objective of Part B is to assess whether the combination of Debio 1143 with nivolumab is active overall and in each cohort. Early futility stopping rules based on objective response

[1] "The 2015 World Health Organization Classification of Lung Tumors", Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification (J. Thorac. Oncol. 2015;10: 1243-1260)

	(unconfirmed) rate (ORR) will be used. In each cohort, if no unconfirmed response is observed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or Gynecologic Cancer Intergroup (GCIG) criteria (Cohort 4) once the initial 8 evaluable patients have been assessed at least twice after baseline or have discontinued their treatment earlier, futility will be concluded and the recruitment will be stopped in that cohort. If at least one response (unconfirmed) is documented in the initial 8 evaluable patients, recruitment shall continue up to 11 evaluable patients. At least two unconfirmed responses must then be observed in these 11 evaluable patients to continue the recruitment up to 15 evaluable patients in that cohort. A homogeneity test will be conducted in any non-futile cohorts showing a confirmed response rate of at least 15%. If homogeneous response rates are seen across the cohorts, efficacy data will be pooled, and an overall efficacy analysis will be conducted in addition to the analyses by cohort. For the final analysis, first proof of efficacy will be claimed in a given cohort if at least 4 objective responses (confirmed) are reported in the 15 evaluable patients. In the case of insufficient accrual in any cohort (e.g., less than 2 patients in 6 months) despite concrete measures aiming at increasing the recruitment, enrolment may be stopped in that cohort. A Data Safety Monitoring Committee (DSMC), composed at least of all actively involved investigators (or their designees), the Sponsor Medical Director and the Contract Research Organization (CRO) medical monitor as voting members, will meet regularly to overview the clinical safety of the patients and laboratory data and the conduct of the study during both study parts A and B. Ad hoc members may be invited upon needed. During Part A, calls will be scheduled monthly or according to patient recruitment as necessary. A charter will be provided as a separate document. During Part B the DSMC will meet approximately every three months, and more frequently if needed in the event of rapid recruitment. A charter will be provided separately.
STUDY OBJECTIVES	**Primary objectives** Dose-optimization study (Part A): To determine the RP2D taking into account DLT/s in Cycle 1, overall safety/tolerability and PK, by optimizing doses of Debio 1143 when combined with the standard dose of nivolumab, as well as treatment compliance in patients with advanced solid malignancies who failed prior systemic standard treatments. Basket trial (Part B): To evaluate the preliminary anti-tumor activity of Debio 1143 at the RP2D in combination with nivolumab at the standard dose, overall and in each patient cohort. **Secondary objectives** Part A: 1. To assess the PK disposition of Debio 1143 (and its metabolite Debio 1143-MET1) and nivolumab when administered in combination. 2. To assess the anti-tumor activity of Debio 1143 in combination with nivolumab in patients with advanced solid malignancies. Part B: 1. To assess the safety and tolerability of the RP2D of Debio 1143 when given in combination with nivolumab in patients with advanced solid malignancies. 2. To assess the PK disposition of Debio 1143 (including its metabolite Debio 1143-MET1) and nivolumab when administered in combination. **Exploratory objectives** • To explore potential predictive and pharmacodynamic (PDy) biomarkers of Debio 1143 and nivolumab when administered in combination, in blood and tumor tissue [redacted]

	• To explore genetic variations in drug metabolism enzyme and transporter (DMET) genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab. • To explore the exposure/response relationship for efficacy and safety (including PK/PDy correlations, if applicable) of Debio 1143 in combination with nivolumab • To explore correlations between response, clinical parameters, immune correlates, and putative biomarkers, [redacted] • To explore the relationship between Debio 1143 plasma concentrations and QTcF
ENDPOINTS	**Primary:** Part A: • RP2D of Debio 1143 when combined with the standard dose of nivolumab, in patients with advanced solid malignancies who received prior systemic standard treatment and failed a prior PD-1/PD-L1-containing treatment, as per DLT occurrence in less than one-third of evaluable treated patients at the RP2D dose level. Part B: • Confirmed ORR as per RECIST v1.1 and/or GCIG criteria (in Cohort 4, if applicable). **Secondary** (for both study parts unless otherwise specified)**:** • Incidence and severity of TEAEs and clinical laboratory abnormalities, according to NCI-CTCAE v5.0 • Changes in vital signs: systolic/diastolic blood pressure, heart rate (both after at least 5 minutes of supine rest), temperature, and weight; electrocardiograms (ECG) and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) • Incidence of premature treatment discontinuations and treatment modifications due to TEAEs and laboratory abnormalities (i.e., treatment compliance). • Confirmed (Part A) and unconfirmed (Parts A and B) ORR using standard RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable). • Disease control rate (DCR), defined as any response, partial response (PR) or complete response (CR), + stable disease (SD) • Time-related endpoints as median time to response, median duration of response (DOR), median progression-free survival (PFS), PFS rate at 6,12 and 18 months, median overall survival (OS), OS rate at 12 months and 18 months (if data allow) • PK parameters of Debio 1143 and Debio 1143-MET1, as defined in the available population PK disposition model and, if appropriate, post-hoc estimates of areas under the curve (AUCs), $C_{max,}$ and C_{min}; serum concentration versus time profiles of nivolumab and, if deemed appropriate, relevant nivolumab PK parameters derived from a population PK model. **Exploratory:** • Potential predictive and PDy biomarkers of Debio 1143 combined with nivolumab in blood and tumor tissue [redacted] • Best overall response (BOR) evaluation as per iRECIST criteria 2017 guideline for immunotherapeutics • Correlations between PK disposition of Debio 1143 combined with nivolumab and clinical response and/or any tumor metrics • Correlations between PK disposition of Debio 1143 combined with nivolumab and safety profile, and PDy if applicable • Correlations between Debio 1143 and Debio 1143-MET1 plasma concentrations and changes from baseline QTcF. • Correlations between response, clinical parameters, immune correlates and putative biomarkers, [redacted] • Genetic variations in DMET genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab

STUDY POPULATION	Patients with selected advanced/unresectable or metastatic solid tumors, for whom standard therapy has failed, including progression to prior treatments with anti PD-1/PD-L1 given as single agent or in combination with standard/approved chemotherapy, TKIs or other targeted agents, RT, hormonal therapy or any other non-CPI mAbs, but excluding other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoints pathways (i.e., CTLA-4). Any other potential CPI combinations previously administered to the candidate should be discussed and agreed by the Sponsor before patient inclusion. The same indications will be eligible in both study Part A and B. In Part B, separate cohorts are defined as follows. Part A: • Between 3 and 12 patients evaluable for DLT planned. • Patients will be evaluable for DLT if they received at least 70% of Debio 1143 and one planned nivolumab dose during Cycle 1 and were evaluated for DLT or if the patient discontinued treatment earlier due to any toxicity that could be considered a DLT. • Non-evaluable patients will be replaced, as appropriate. Part B: Cohort 1: SCLC (including extrapulmonary small-cell carcinomas or large cell neuroendocrine lung carcinoma, as per WHO Classification of Lung Tumors of 2015)[1] Cohort 2: SCCHN (nasopharyngeal carcinomas are excluded) Cohort 3: GI cancers (including esophageal, gastric, colorectal or pancreatobiliary) with known MSI-H/MMRd or other DDRs abnormalities, including HRD. Cohort 4: platinum-resistant EOC, endometrial cancer, PPC or cervical cancer, with known MSI-H/MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other DNA DDR abnormalities (incl. HRD). • Between 32 (if all cohorts are futile) and 60 evaluable patients (if none of the 4 cohorts is futile). • Patients will be evaluable for efficacy if the two conditions below are met: a. Measurable disease at baseline as per RECIST v1.1 or GCIG criteria (Cohort 4), b. At least one efficacy assessment done, either computed tomography (CT) or magnetic resonance imaging (MRI) for RECIST evaluable patients; or CA-125 dosage performed after baseline, if applicable or treatment discontinuation occurred before the efficacy assessment is done due to treatment failure, defined as any of the following: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening. • Non-evaluable patients will be replaced.
INCLUSION CRITERIA	The same tumor types are eligible in Part A and B. Patients must fulfill all the following criteria (in both Parts A and B, unless specified otherwise): 1. Willing and able to sign a written informed consent form; 2. Male or female ≥18 years of age. 3. Histologically and/or cytologically confirmed advanced/ unresectable or metastatic solid tumor, for one of the following indications. a. SCLC b. SCCHN (nasopharyngeal carcinomas are excluded) c. GI cancers, including esophageal, gastric, colorectal or pancreatobiliary with known MSI-H/MMRd or any other known DDRs abnormalities, including HRD d. Platinum-resistant* EOC, endometrial cancer, PPC or cervical cancer, with known MSI-H/ MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other known DNA DDRs abnormalities (incl. HRD)

	* Platinum-resistant is defined as relapse or progressive disease (PD) occurring within 1 to 6 months (180 days) after a platinum-containing chemotherapy. 4. Have received at least one prior line of standard systemic chemotherapy in the advanced/unresectable cancer setting (standard adjuvant/neoadjuvant treatment is acceptable if relapse occurred within six months of treatment end) and have no established standard therapeutic alternatives 5. Have progressed or relapsed during or after a prior anti-programmed cell death-1 (PD-1)/ programmed cell death-ligand 1 (PD-L1)-based treatment, given either as a single agent or in combination with standard/approved chemotherapy, tyrosine kinase inhibitors (TKIs), radiotherapy (RT) or other monoclonal antibodies (mAbs) that are not known to modulate/inhibit immune checkpoints (CPIs). 6. Minimum washout periods since prior therapy until treatment start (C1D1) (in cases of more than one prior treatment type, whichever has the longest minimum period applies): a. 3 weeks for chemotherapy (6 weeks, specifically for nitrosoureas or mitomycin C containing regimens) b. 4 weeks for any prior mAbs or live vaccines; for investigational mAbs 4 weeks or at least the duration of one treatment cycle whichever is longest c. 3 weeks for prior RT (1 week in case of localized antalgic/hemostatic hypofractionated RT flash) d. 2 weeks for TKIs, hormonal therapy, other anti-cancer treatment not previously specified or investigational agents e. 4 weeks for any major surgery f. Immunosuppressive medication: within 2 weeks, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological/replacement doses, which should never exceed 10 mg/d prednisone, or an equivalent corticosteroid 7. Measurable disease (Part B only) according to RECIST v1.1 and/or GCIG criteria in Cohort #4 (if applicable) and documented PD during or after prior PD-1/PD-L1 based therapy 8. ECOG Performance Status = 0 or 1 9. Adequate hematologic, renal and hepatic function: a. absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, b. platelets $\geq 100 \times 10^9$/L, c. hemoglobin ≥ 9.0 g/dL, d. AST and ALT ≤ 3 x ULN (≤ 5 x ULN if liver metastases are present) e. total bilirubin ≤ 1.5 x ULN, f. serum creatinine ≤ 1.5 x ULN, g. serum albumin ≥ 30 g/L 10. Available archived tumor samples for biomarker analysis obtained after prior PD-1/PD-L1 treatment failure or, if no archived tumor sample is available, patient must be suitable and willing to undergo a percutaneous or endoscopic biopsy without unacceptable major risks before starting study treatment 11. Participants with known central nervous system (CNS) and/or meningeal involvement will be eligible if they are clinically asymptomatic, have completed primary CNS therapy more than 4 weeks before treatment start (such as whole brain RT, stereotactic radiosurgery, or complete surgical resection), and have remained off steroids (including tapering doses) for at least 2 weeks 12. Women of child-bearing potential (WOCBP): a. Negative serum pregnancy test at screening; b. Agreement to use highly effective contraception methods from study entry and for up to 5 months after the last day of study treatment c. Agreement from her male partner to use contraception methods 13. Male patients with WOCBP partners must agree to use highly effective contraception methods from study entry and for up to 5 months after the last day of study treatment

EXCLUSION CRITERIA	Patients must NOT fulfill any of the following criteria (in both Parts A and B, unless specified otherwise): 1. Thoracic or head and neck radiation >30 Gy within the 6 weeks prior to C1D1 2. Have received, in total, more than 3 (i.e. Cohorts 1&2) or 4 (i.e. Cohorts 3&4) lines of prior systemic treatments (including adjuvant or neoadjuvant regimens if relapse within six months prior to C1D1) 3. Active moderate alcohol consumption, at screening, more than 100/140 grams (3.5/4.9 ounces) of alcohol per week for female/ male patients, respectively 4. Liver cirrhosis Child-Pugh score B or C 5. Prior treatment with an anti-CTLA-4 or anti-LAG3 in combination with PD-1/ PD-L1 CPI, unless discussed and agreed with the Sponsor 6. Prior treatment with SMAC mimetics 7. Prior PD-1/PD-L1 discontinuation due to severe immune-related toxicity, not resolved upon adequate steroids/immunosuppressive treatment 8. Requirement of concomitant treatment with any prohibited medication (See Appendix B: Prohibited medications and special warnings) 9. Ongoing toxicity from prior administration of any other investigational drug and/or anti-cancer treatment of > Grade 1 NCI-CTCAE v5.0 before treatment start (except for grade 2 alopecia, stable sensory neuropathy, vitiligo or any endocrinopathy adequately managed by replacement hormonal therapy) 10. Patients with known history of: a. Uncontrolled or symptomatic angina or myocardial infarction, within the last 12 months prior to C1D1 b. Elevated (>ULN) troponins (T or I) or creatine phosphokinase (CPK) > 1.5xULN during screening c. Symptomatic intestinal sub-occlusion d. Infection, active or latent by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) e. Ongoing arrhythmias requiring treatment, including asymptomatic QTc interval as corrected by Fridericia (F) >480 msec f. In patients previously treated with anthracycline-containing chemotherapy or thoracic RT, non-adequate cardiac function with left ventricular ejection fraction (LVEF) <50%, measured by an echocardiogram (ECHO) or a multigated acquisition (MUGA) as per institutional standards g. Active rheumatoid arthritis, active inflammatory bowel disease (IBD), primary sclerosing cholangitis, autoimmune hepatitis, systemic lupus erythematous (SLE), multiple sclerosis or any other ongoing autoimmune disease requiring systemic treatment (excluding vitiligo, mild cutaneous psoriasis and asymptomatic autoimmune endocrinopathy well controlled under hormonal replacement therapy) h. Evidence of active, non–infectious pneumonitis or a history of interstitial lung disease i. Active ongoing infection requiring systemic antibiotic therapy, including active tuberculosis 11. Evidence or clinical suspicion of active bleeding or requirement of red blood cell (RBC) transfusions within 2 weeks prior to C1D1 12. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Debio 1143 or nivolumab or their constituents 13. History of another non-metastatic, low grade malignancy other than the primary tumor within the last 1 year prior to C1D1, except: completely resected non-melanoma skin cancer, second SCCHN tumors, completely resected minimally invasive bladder cancer, low grade prostate cancer, if Prostate-specific antigen (PSA) ≤ 10 ng/mL; non-metastatic localized low grade renal cell carcinoma (RCC) or any previous (non-synchronous) malignancy if related to germ-line mutations linked to either MSI-High (lynch syndrome) or BRCA-1/2 hereditary cancer syndromes, for

	patients included either in cohort 3 or 4. For these indications there are no time restrictions with regard to their occurrence prior to C1D1. 14. Pregnant or lactating females 15. Unable to swallow or retain oral medications 16. Known contraindication to contrast-enhanced MRI and CT 17. Patient unwilling or unable to comply with study visits/assessments
DLT PERIOD AND DEFINITION OF DLTS	The DLT period is defined as Cycle 1*. DLT is defined as any of the following treatment-emergent adverse events (TEAEs) which are possibly, probably or definitely related to the combination treatment and occurring in Cycle 1 (1 cycle=4 weeks): • Any Grade 4 or 5 hematologic toxicity, clinical or laboratory non-hematologic toxicity • Febrile neutropenia any grade, Grade 3 thrombocytopenia if associated with bleeding or requiring platelet transfusion • Grade 2 or higher cardiac or neurologic toxicities, pneumonitis that does not resolve within 3 days after starting steroids at adequate doses or that was recurrent upon steroid tapering or withdrawal, myasthenia gravis, myositis, polymyositis, Guillain-Barre syndrome (excluding peripheral purely-sensory neuropathies) • Grade 2 or higher alanine transaminase (ALT)/ aspartate transaminase (AST) increase with a concurrent increase of total bilirubin ≥2 x upper limit of normal (ULN) and concurrent with alkaline phosphatase (ALP) ≤2 x ULN (Hy's law), in the absence of objective causes of biliary obstruction due to obvious disease-related causes • Any other Grade 3 non-hematologic, treatment-related clinical toxicity lasting 3 or more days despite optimal supportive care, or requiring admission for appropriate medical management; hypersensitivity and/or infusion-related reactions are excluded if not reoccurring after appropriate pre-medication and/or prolonging infusion time • Grade 3 non-hematologic laboratory value (excluding lipase, amylase and/or autoimmune endocrinopathies manageable by replacement therapies) if: a. Symptomatic and b. Medical intervention was promptly required to treat the patient, or c. The abnormality led to hospitalization or d. The abnormality did not resolve to at least Grade 1 within 2 weeks (including the steroid tapering period) despite adequate medical intervention/treatment • A delay of >2 weeks due to drug-related toxicity in initiating Cycle 2 • Unable to complete at least 70% of the scheduled treatment, i.e., more than six Debio 1143 skipped doses in Cycle 1 due to treatment-related toxicity • Required dose reduction in Cycle 1 or on Cycle 2 Day 1 or requirement for treatment withdrawal due to treatment-related toxicity (even if not meeting other DLT criteria) * Any toxicity fulfilling one or more of these criteria but occurring from C2D1, may be defined as delayed DLTs after discussion and agreement between Principal Investigators (PIs), DSMC and the Sponsor, and may be considered for RP2D definition, if appropriate.
INVESTIGATIONAL MEDICINAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION	<u>Investigational products:</u> • Debio 1143 capsules (75 and 100 mg), as bottles of 10 capsules each, oral route. • Nivolumab (OPDIVO®) 10 mg/mL concentrate for solution for infusion, intravenous route (IV). Oral Debio 1143 will be administered at a starting dose of 150 mg/d on Days 1-10 and Days 15-24 every four weeks (q4w). One dose increment of 50 mg (i.e. to 200 mg/d) is planned for the subsequent dose level. No dose escalation beyond 200 mg/d is foreseen in this study. In individual cases of severe toxicity or DLT, the Debio 1143 dose will be reduced by a maximum of up to two reductions of 50 mg each, and to a minimum dose of 100 mg/d.

	Debio 1143 will be administered on site on D1 and D15, immediately before nivolumab. Remaining daily doses are to be taken by the patient at home following relevant medical instructions, except on days where PK samples are planned, during the first cycle, and the third cycle. Administration compliance will be recorded in a patient diary which will be supplied as a separate document. Nivolumab will be administered, as per current prescribing information, at a dose of 240 mg, flat dose by IV infusion over at least 30 minutes on Days 1 and 15, q4w (i.e., 2 infusions per cycle). From Cycle 3 on, patients may be switched to nivolumab infusion at a dose of 480 mg over at least 60 minutes on Day 1 exclusively q4w (i.e., 1 infusion per cycle), upon the Investigator's request and Sponsor approval. Neither lower nor higher doses of nivolumab will be explored; dose reduction or increase will not be allowed. Infusion of nivolumab will be stopped in case of Grade ≥2 hypersensitivity, inflammatory response, or infusion-related reactions. Infusions may be resumed after Grade ≤2 events upon resolution of the events within less than 4 hours and after medical assessment and agreement by a qualified Investigator. Infusion duration will not be shorter than 120 minutes after resumption in all subsequent infusions. Treatment will be withdrawn definitively after the occurrence of any Grade ≥3 infusion-related reactions, hypersensitivity or cytokine-release syndrome. Appropriate standard measures must be in place for the medical management of the patients under these circumstances. Formal premedication is not required. However, premedication might be used after C1D1 administration, if needed on an individual patient basis, per clinical judgment and local institutional guidelines, as appropriate.
TREATMENT DURATION	Participants are planned to be treated with Debio 1143 and nivolumab for up to 52 weeks (13 cycles), until any of the following events occurs: symptomatic PD, asymptomatic but confirmed PD (as per iRECIST), unacceptable toxicity per Investigator judgment and despite up to two dose adjustments, patient withdrawal, or treatment delay greater than 4 and 8 weeks (+1 week tolerance) for Debio 1143 and nivolumab, respectively. Permission to prolong the study treatment for one additional year can be exceptionally granted by the Sponsor, if patients are deriving continuous clinical benefit from the study treatment. Medical justification for extending the treatment and the assessment of the risk/benefit balance must be provided by the Study Investigator and will be discussed with the Sponsor. The decision to further extend study treatment will be re-evaluated on a yearly basis for each patient. Re-treatment criteria are listed in Table 2. From Cycle 2, if a patient does not meet the requirements for treatment continuation on Day 1 of any cycle, both study drugs will be withheld until recovery or for a maximum of 4 and 8 weeks (+1 week tolerance window) for Debio 1143 and nivolumab, respectively. After this delay-period, the patient should withdraw from treatment. If a patient does not meet the requirements for treatment continuation on any days other than D1 (D2-10 or D15-24), treatment will be immediately interrupted and the corresponding Debio 1143 dose (and nivolumab if on D15) will be omitted. Patients should be re-assessed (ideally every 48-72 hours, if clinically indicated) and treatment will only be resumed after all re-treatment criteria are met. All patients who withdraw from treatment for any reason will be followed for safety up to 5 months (± 15 days) after the last nivolumab infusion, complete resolution or stabilization of any ongoing toxicity, unless the patient starts a new treatment, end-of-life-care or withdraws consent. If for any reason, treatment with nivolumab is temporarily withheld, Debio 1143 may be continued; however, at any time, and regardless of the reason, if nivolumab is permanently discontinued then Debio 1143 must also be withdrawn. If for any reason Debio 1143 is withheld temporarily, nivolumab will also be withheld until treatment may be resumed. Patients will not receive any further nivolumab infusions during the study until Debio 1143 treatment is resumed.

Table 2: Re-treatment criteria

Assessment	Debio 1143		Nivolumab
	Days 1 & 15	Days 2-10 or 16-24	Days 1 & 15
ECOG-PS	≤1	≤2	≤1
ANC	≥ 1.5 x10^9/L	≥ 1.0 x10^9/L	-
Platelets	≥ 100x10^9/L	≥ 75 x10^9/L	-
Hemoglobin	≥ 9.0 g/dL	≥ 9.0 g/dL	≥ 9.0 g/dL
Total bilirubin	Grade 1	Grade 2[a]	Grade 1
AST/ALT	Grade 1	Grade 2[a]	Grade 1
Amylase or lipase increases	≤ Grade 3[b]		-
Serum creatinine	≤2.0 x ULN	-	≤ 2.0 x ULN
Non-optimally treated, symptomatic immune-related AEs	-		≤ Grade 1 [c]
Any Debio 1143 drug-related AEs	≤ Grade 1 [c]	≤ Grade 2	-
Cardiac safety /ECG	Baseline status		
βHCG urine pregnancy test (for women of childbearing age)[d]	Negative	-	Negative

ANC: absolute neutrophil count; AST/ALT: aspartate aminotransferase/alanine aminotransferase; AEs: adverse event(s); ECG: electrocardiogram; ECOG-PS: Eastern Cooperative Oncology Group performance status

a) Provided that total bilirubin and/or ALT/AST levels were Grade 1 as per NCI-CTCAE v5.0 at the start of the corresponding cycle.
b) As per NCI-CTCAE v5.0, Grade 3 is defined as amylase or lipase increases up to 5x ULN symptomatic or not; or above 5x ULN but asymptomatic
c) Up to Grade 2 for alopecia, stable sensory neuropathy, fatigue/asthenia, skin toxicity or non-optimally treated nausea, vomiting or diarrhea, or any grade endocrinopathy optimally treated by replacement therapy
d) On every Day 1 for both Debio 1143 and nivolumab

PARTICIPANT DURATION

A 4-week period is planned for patient screening before initiating the study treatment.

The treatment duration for an individual patient is 52 weeks (13 cycles). If a patient is benefiting from the study treatment, exceptional permission to prolong the study treatment might be granted. After the end-of treatment (EOT), patients will be followed every 12 weeks (± 1 week window) until symptomatic or confirmed PD or start of new cancer treatment or end-of-life care, or until the end of the Main study period (lasts until 18 months after LPI or 60 days after last patient last visit [LPLV]), whichever occurs first. For patients who continue study treatment after the Main study period, tumor response assessments will continue at the frequency of local institutional care practice until EOT.

	After PD or start of any new cancer treatment, follow-up for overall survival (OS) will be collected, by telephone, email or mail every 4 months (± 1 month) until the end of the Main study period. There will be up to two visits planned for screening and at least two treatment visits per cycle on D1 and 15 up to Cycle 3, then at least one treatment visit from Cycle 4 onwards if applicable, plus one EOT ± follow-up visit, as applicable. The total number of onsite visits per patient will depend on the total number of cycles delivered which is based on disease progression status, clinical deterioration, start of new cancer treatments or end-of-life care or death whichever occurs first.
STUDY VISITS & ASSESSMENTS	Cf. Figure 'Study plan' and Table 'schedule of assessments'
STUDY PERIOD	First patient included (FPI): ~ Q1-2019 Dose optimization part: ~ 3 months FPI Basket trial part: ~ Q2-2019 Assessment of the primary clinical endpoint for futility: ~ 6-9 months after FPI Complete accrual in non-futile indications: ~ 3-9 months (according to results) Accrual period: ~ from 9 to 18 months (depending on futility assessments) End of the Main study period: 18 months after LPI or 60 days after last patient last visit (LPLV), whichever occurs first Extended study period: Only for patients treated beyond 13 cycles. Starts after the Main study period and lasts until LPLV. End of study (EOS): End of Main study period or End of Extended study period, whichever occurs last. Final analysis (Final CSR): within 1 year of end of the Main study period. Data collected during the Extended study period will be summarized in an addendum to the Final CSR, after the End of Extended study period.

STATISTICAL METHODS	**Sample size** Part A: The sample size will be determined by the number of patients included per dose level and the observed toxicities. Given that (i) a maximum number of two dose levels will be explored, (ii) a classical 3+3 design will be used and (iii) at least 6 evaluable patients need to be treated at the RP2D before the phase II part starts formally, between 3-12 evaluable patients will be included. Part B: Up to 15 evaluable patients will be included in each of the 4 cohorts. In case of no early stopping due to futility and no patient replacement, the total sample size will be 60 patients. **Randomization** Not applicable **Statistical analysis** Part A: There will be no formal interim analysis during dose-optimization, only a review of data when dose increase, repeat or reduction is to be decided at DSMC meetings. The statistical analysis of Part A will be mostly descriptive unless otherwise specified. Part B: The efficacy of Debio 1143 in combination with nivolumab will be tested in each cohort by using the Bayesian posterior probability with early stopping rules for futility. The primary efficacy endpoint will be the confirmed ORR based on RECIST v1.1 and/or GCIG (Cohort 4), if applicable. However, for the futility stopping rules the unconfirmed ORR will be used. The cut-off for the futility analyses is defined as the time when the last ongoing patient from the first 8/11 evaluable patients has performed at least 2 post-baseline tumor assessments or prematurely discontinued. The number of patients included in the interim analyses and the futility boundaries were defined assuming an unconfirmed ORR of 17%, a futility response rate of 5%, a maximum sample size of 15 patients by cohort and a probability confidence threshold for futility of 20%. The futility stopping boundaries are defined as follows: 0 response out of 8 evaluable patients for the first interim analysis and ≤1 response out of 11 evaluable patients for the second interim

analysis. Consequently, if no unconfirmed response is documented as per RECIST v1.1 and/or GCIG (Cohort 4, if applicable) after the 8th patient is assessed, futility will then be concluded, and recruitment will be stopped in the corresponding cohort. If at least one unconfirmed response is documented in the first 8 patients, recruitment shall continue up to 11 patients when a second futility analysis will be conducted. If at least two unconfirmed responses are documented in the first 11 evaluable patients, recruitment will continue up to 15 evaluable patients; otherwise the recruitment will be stopped. For the final efficacy assessment in each cohort, first proof of efficacy will be claimed if at least 4 confirmed responses are reported in the 15 evaluable patients. This efficacy boundary was derived assuming a confirmed ORR of 15% and a probability confidence threshold of efficacy of 80%.

No formal interim analysis will be performed during the futility monitoring. Only the number of patients with unconfirmed responses as per RECIST v1.1 or GCIG criteria will be checked vs. the futility boundaries in each cohort independently.

The final analysis including all the study endpoints will be performed at the end of the Main study period. A homogeneity test will be conducted in the non-futile cohorts showing a confirmed response rate of at least 15%.

In case of homogeneous response rates across the cohorts, efficacy data will be pooled and an overall efficacy analysis will be conducted in addition to the analyses by cohort. Otherwise, efficacy will only be reported by cohort. All other endpoints such as demographics, baseline characteristics, safety, PK, PDy etc. will be presented overall and for each cohort. In case of promising efficacy results, further confirmatory trials will be then envisaged.

Efficacy analysis
Efficacy analysis will be conducted in the efficacy and ITT populations (as defined in section 11.5.4). The main efficacy analysis will be conducted in the efficacy population.

ORR, immune-related BOR, and DCR will be presented using contingency tables. Time-to-response, DOR, PFS and OS medians and rates will be determined using the Kaplan-Meier method.

Safety analysis
Safety analysis will be conducted in the Safety population (as defined section 11.5.2).

TEAEs including those related to study drugs, TEAEs by severity (according to the NCI-CTCAE v5.0 criteria), TEAEs leading to treatment discontinuation and serious adverse events (SAEs) will be summarized by system organ class (SOC) and preferred term (PT) overall and by dose (Part A) and by cohort (Part B).

Data of safety laboratory parameters, vital signs, ECG and ECOG-PS will be presented using descriptive statistics. Shift tables and scatter plots will be provided.

PK analysis
Plasma/serum concentrations and PK parameters will be presented individually and by descriptive statistics. Graphic displays of plasma concentration vs. time curves will be presented individually by patient and as arithmetic and geometric means. Pharmacokinetic parameters will be presented by patient and summarized by dose (Part A) and cohort (Part B) and overall as descriptive statistics. They will also be derived by population PK data.

The relationship between PK disposition and clinical response, PDy, safety and genetic variations in DMET genes will be analyzed by regression methods or association analyses. These relationships will also be evaluated in a dedicated Exposure/Response by population analysis approach where data from several clinical studies with Debio 1143 will be pooled. Such evaluation will be described in a separate report.

Pharmacodynamics analysis
Pharmacodynamics will be presented at baseline and at any scheduled visit with the corresponding fold changes (log2) from baseline by using descriptive statistics. The maximum increase while on-treatment will be similarly presented, along with its fold change from

	baseline. Graphics displaying PDy parameters absolute values and fold changes from baseline will be presented as individual curve and mean (±standard deviation) curve vs. time. Exploratory analyses will be conducted to investigate the relationship between PDy biomarkers, efficacy and safety parameters by using regression methods. **Pharmacogenetic factors/predictive biomarker analysis** Pharmacogenetic factors and predictive biomarkers assessments will be exploratory. The correlation between efficacy, pharmacogenetic factors and predictive biomarkers will be analyzed by regression methods.

Table 1-1 Schedule of assessments

		CYCLE																EOT	Follow-up#	EOS
	Screening	Baseline	1					2		3				4-13		>13[13]				
CYCLE DAY*	-28 to -1	1	3[11]	8	15	17[11]	22	1	15	1	3[11]	15	17[11]	1	15	1	15			
INFORMED CONSENT	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MEDICAL AND MEDICATION HISTORY[12]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
INCLUSION/EXCLUSION CRITERIA	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PHYSICAL EXAMINATION	X[µ]	X	-	-	X	-	-	X	X	X	-	X	-	X	-	X	-	X	-	-
ECOG, VITAL SIGNS	X	X	-	X	X	-	X	X	X	X	-	X	-	X	X	X	-	X	-	-
CONCOMITANT MEDICATIONS	X	X	X	X	X	X	X	X	X	X	-	X	-	X	X	X	-	X	X	-
DIGITAL, TRIPLICATED 12-LEAD ECG[1]	X	X	-	X	X	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
SAFETY LABORATORY SAMPLING[2]	X[2a,b,c,f]	X[2c,e]	X[2d]	X[2c]	X[2c,e]	X[2d]	X[2c]	X[2c,e,f]	X[2c]	X[2c,e,f]	-	X[2c]	-	X[2c,e,f]	-	X[2c,e,f]	-	X[2c,e]	-	-
PREGNANCY TEST[3]	X	X	-	-	-	-	-	X	-	X	-	-	-	X	-	X	-	X	X	-
CT SCAN OR MRI[4]	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	X	-	X	X	-
TUMOR BIOPSY[5]	X	-	-	-	-	-	-	-	-	Optional	-	-	-	-	-	-	-	-	-	-
PK SAMPLING[6]	-	X	X[6a]	X	X	X[6a]	X	-	-	X	X[6a]	X	X[6a]	X[6b]	-	X[6b]	-	X[6b]	-	-
PDY AND PREDICTIVE BM SAMPLING[7]	-	X	-	X	X	-	X	-	-	X	-	-	-	X[7a]	-	-	-	-	-	-
DEBIO 1143 DISPENSING/ACCOUNTABILITY[8]	-	X			X			X	X	X	X	X		X	X	X	-	-	-	-
NIVOLUMAB DISPENSING/ACCOUNTABILITY[9]	-	X	-	-	X	-	-	X	X	X[9a]	-	+/-	-	X[9a]	+/-	X[9a]	+/-	-	-	-
ADVERSE EVENTS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X[10]	-

Cycle: Each cycle is defined as 28 days

EOT: A visit should be performed 30 days (± 5days) after last Debio 1143 dose, unless start of new cancer treatment or end-of-life care before, in which case EOT visit should be ideally scheduled immediately before these events.

Follow-up: A first follow-up (FU) visit is scheduled 90 (± 15) days after last study treatment, a second safety follow-up visit may be scheduled at 5 months (±15 days) after the last nivolumab infusion, provided the first safety follow-up visit did not overlap (± 1 week), and provided that no subsequent anticancer treatment or end-of-life hospice care had been started before. Subsequent visits will be scheduled every 12 weeks (± 1 week) after EOT unless confirmed or symptomatic PD occurred before or any new anticancer treatment or end-of-life care is started, whichever occurs first. Once PD occurs, or start of new treatment, phone calls, email or mail to document survival status will be done every 4 (± 1) months until the end of the Main study period (lasts until 18 months after LPI or 60 days after LPLV, whichever occurs first).

EOS: At the end of the Main study period or at LPLV if patients are ongoing in the Extended study period, whichever occurs last.

* Examinations should be performed in the following order as applicable: physical examination, vital signs, ECG, safety blood/urine samples, followed by blood sampling for PK/PDy according to specific instructions, and other examinations: Note: ECGs always have to be taken before PK/PDy sampling.
Assessments should be performed on schedule, but occasional changes may be allowed. If the study schedule is shifted, both assessments and dosing must be shifted to ensure the collection of data is completed prior to dosing. Windows: Laboratory assessments and clinical examinations: Screening period: -4 days (i.e., day -32); EOT visit: ±5 days; follow up visits ±1week, in case of holidays, vacations; other administrative reasons: ± 3 days in all cycles. Window for CT/MRI assessment = ± 1 week

Assessments for concomitant medications, pregnancy test and AEs will be performed only at the first two FU visits, if applicable. CT scan or MRI assessments will be performed until confirmed iRECIST PD, symptomatic PD or any new anticancer treatment or end-of-life hospice care is started or until EOS whichever occurs first.

μ Height only collected at screening.

1 Digital triplicate 12-lead ECGs will be recorded after 10 minutes of supine rest at the following 3 time points: pre-, 0.5-2h Debio 1143 post-dose (before starting the nivolumab infusion or after nivolumab perfusion was removed) and 4-6 h post-dose ;There should be at least 1 minute between each ECG and all 3 ECGs should be completed within 10 minutes or less. ECG readings must be performed before PK/PDy sampling. ECG reading will be done centrally and also locally for screening purposes.

2 Pre-dose (as per section 8.2.2.5) only required if screening test were performed > 7 days prior to C1D1 or if inclusion/exclusion criteria were not met during screening:

- 2a HIV, HCV and HBV serology testing and CPK and Troponins (I or T whichever is applicable): Only at screening, to be repeated if clinically indicated only.
- 2b FSH/LH and total testosterone (in male) or estrogens (in female patients), free-cortisol (at morning) and ACTH: Only at screening and to be repeated if clinically indicated.
- 2c Hemoglobin, hematocrit, platelets and complete blood cell count and differential counts, creatinine, sodium, potassium, calcium, total bilirubin (if >ULN, then also measure direct bilirubin), ALP, AST, ALT, amylase, lipase, LDH, total protein, albumin, CRP.
- 2d Part A patients (only): Total bilirubin (if >ULN, then direct bilirubin should also be measured), ALP, AST, ALT, and creatinine.
- 2e TSH, FT3 and FT4: At Day 1 and Day 15 in Cycle 1 and every Day 1 of each subsequent cycle.
- 2f CA-125 to be performed at screening within 4 weeks of C1D1, exclusively in applicable patients included in Cohort 4, and to be repeated before start of each new cycle if abnormally elevated before treatment start, unless PD, any new anticancer treatment or end-of-life hospice care is started before.

3 In women of childbearing potential only: blood test at screening (only required if screening test were performed > 7 days prior to C1D1), then urine dipstick test alone would be sufficient, at the beginning of each treatment cycle while on study up to 5 months after EOT.

4 Every 8 weeks (±1 week) from first on-treatment scan until Cycle 10, then from Cycle 13, every 12 weeks (± 1 week) until confirmed iRECIST PD, symptomatic PD or any new anticancer treatment or end-of-life hospice care is started or until the end of the Main study period, whichever occurs first. For patients who continue study treatment in the Extended study period, tumor response assessments will be performed at the frequency of local institutional care practice until EOT. All patients will have CT or MRI at the time of disease progression, if none previously available. CT or MRI done before screening, as part of patient's standard of care and not older than 8 weeks (+1 week tolerance) before C1D1 can be used instead of repeating a new assessment at screening even if done before ICF signature with patient specific agreement, if deemed clinically appropriate by the Investigator.
A contrast enhanced brain CT or MRI is mandatorily at baseline only in SCLC cohort, subsequent brain scans to be done if clinically indicated.

5 Up to 3 tumor tissue samples will be collected:

1) An archived biopsy at diagnosis (before prior PD-1/PD-L1 therapy) = optional;
2) An archived biopsy if collected after prior PD1/PD-L1 or, if not available a fresh biopsy collected at screening will be mandatory;
3) A fresh biopsy collected at end of Cycle 2 (day 28=Day 1 of the following cycle) = optional

6 Timepoints as specified in Table 8-1, Table 8-2 and Table 8-3 and windows of tolerance as specified in Table 8-5.

- 6a Patients included in Part A only.
- 6b Debio 1143 PK, nivolumab PK, and nivolumab ADA sample at C6D1 only. In addition, for patients discontinuing the study at the end of the Main study period, the last nivolumab ADA will be collected at EOT, and for patients entering the Extended study period, the last nivolumab ADA will be collected at C13D1 instead of at EOT.

7 Timepoints as specified in Table 8-4 and windows of tolerance as specified in Table 8-5.

- 7a Only at Cycle 6: PGx ctDNA.

8 Debio 1143 will be taken orally on D1-10 and D15-24 on an empty stomach (patients will fast for 2 h before dosing and for at least 1 h after dosing) at approximately the same time each day. Water is permitted freely. A missed dose can be taken as soon as the patient remembers but no later than 6 h after the planned dose. If >6 h have elapsed, the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. Debio1143 will be given in the hospital (before nivolumab infusion whenever is applicable) during: Cycle 1 on Days 1,3 (only Part A), 8, 15, 17 (only Part A), 22; Cycle 2 on Days 1 and 15; Cycle 3 on Days 1, 3 (only Part A) , 15, and 17 (only Part A); and on Days 1 ± 15 of all subsequent cycles. The rest of the days will be taken at home following relevant medical instructions. A patient's diary to record treatment compliance will be provided as a separate document and it will be reconciled with the returning capsules by the study nurse.

9 Nivolumab will be administered, as per current prescribing information, at a dose of 240 mg, flat dose by IV infusion over at least 30 minutes on Days 1 and 15, every 4 weeks (i.e., 2 infusions in each cycle).

9a From Cycle 3 on, the switch to an administration of 480 mg of nivolumab only on Day 1 of each 28-day cycle is allowed based on the Investigator's judgment and Sponsor's agreement.
± Dispensing of nivolumab will depend on the nivolumab schedule administered from Cycle 3 onwards.

[10] Continuous AE monitoring, with Investigator's assessment and documentation at scheduled study visits up to EOT visit and second follow up visit, if applicable. The SAE reporting period is up to 5 months after the last nivolumab administration. Patients continuing in follow-up (FU) after EOT, in the first and/or second FU visits will have final AEs update of any ongoing toxicity at this time, if applicable, unless start of new anticancer treatment or end-of-life-care, in which case visit should be scheduled ideally before.

[11] For Part B, visits on Cycle 1 and Cycle 3 on Days 3 and 17 will not be performed

[12] Including information on current and previous tobacco and alcohol use/consumption

[13] Only applicable for patients treated beyond Cycle 13

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine transaminase
AMV	assisted mechanical ventilation
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BAL	Bronchoalveolar lavage
BOR	best overall response
BP	blood pressure
bpm	beats per minute
BRCA	breast cancer
C	cycle
CA-125	carbohydrate antigen 125
CAS	Chemical Abstract Service
CBCDA	Carboplatin
CD4+ / CD8+	cluster of differentiation 4/8
CI	confidence interval
CNS	central nervous system
CPI	checkpoint inhibitors
CPK	creatine phosphokinase
CR	complete response
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte antigen-4
CV	coefficient of variation
CYP	cytochrome P450
D	day
DCR	disease control rate
DDR	DNA damage repair
DLCO	diffusing capacity of the lungs for carbon monoxide
DLT	dose limiting toxicity
DMET	drug metabolism enzymes and transporters

DOR	duration of response
DPI	Debiopharm International SA
DSMC	data safety monitoring committee
ECG	electrocardiogram
ECHO	echocardiogram
ECL	electrochemiluminescence
ECOG-PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EOC	epithelial ovarian cancer
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
FPI	first patient included
FSH	follicle-stimulating hormone
FT3	free tri-iodothyronine
FT4	free thyroxine
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRD	homologous recombination deficiency
IAP	inhibitor of apoptosis
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor 1
IgG4	immunoglobulin G4
IL-8	interleukin 8
IMP	investigational medicinal product
INN	International Non-proprietary Name
IRB	Institutional Review Board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVIG	intravenous immunoglobulins

LAG-3	lymphocyte activation gene-3
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOQ	limit of quantification
LPI	last patient-in
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMRd	mismatch repair deficiency
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NFκB	nuclear factor κB
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
Pdy	pharmacodynamic
PFS	progression-free survival
PGx	pharmacogenomics
PGt	pharmacogenetics
PI	principal Investigator
PK	pharmacokinetics
PPC	primary peritoneal cancer
PR	partial response
PRL	prolactin
PSA	Prostate-specific antigen
PT	preferred term
qxw	every x weeks
QTcF	QTc interval as corrected by Fridericia
RBC	red blood cells
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase II dose
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan

SCCHN	squamous cell carcinoma of the head and neck
SCLC	small cell lung cancer
SD	stable disease
SLE	systemic lupus erythematosus
SMAC	second mitochondrial activator of caspase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIL	tumor –infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
TNFa	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
TTP	time to progression
TXL	paclitaxel
ULN	upper limit of normal
USAN	U.S. Adopted Name
WHO	World Health Organization
WOCBP	woman of child-bearing potential

DEFINITION

IMP "A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form."

According to the above definition, the Debiopharm International (DPI) active substance being tested as well as associate or comparator drugs used during the study are to be considered as IMPs.

1. INTRODUCTION

Immune checkpoint inhibition has resulted in impressive response rates and long-term disease control in some cancers and patients.(1, 2) The tumor-derived neo-antigen repertoire plays a key role for immune T-cell reactivity and sensitivity to immune checkpoint inhibition with anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) and anti-programmed cell death 1/-ligand 1 (PD-1/PD-L1) therapies.(3) Patients whose tumors have a high mutation burden (>10 somatic mutations/Mb) and neo-antigen load, such as those with melanoma and lung cancer, have been shown to benefit most from immune checkpoint inhibition.(4-6) Despite the fact that improved progression-free survival (PFS) and overall survival (OS) have been reported with immune checkpoint blockade in several advanced malignancies, only 10-30% of patients respond to treatment and most patients ultimately develop resistance to therapy. Therefore, strategies to expand the extent and quality of response to immune checkpoint inhibition are required to optimize cancer immunotherapy.(7) Combination of immune checkpoint inhibitors (CPI) with compounds that foster anti-tumor immunity and also promote programmed cell death (apoptosis) in tumor cells may have great therapeutic potential to achieve this goal.(8)

2. PHARMACEUTICAL AND BACKGROUND INFORMATION

2.1. Nivolumab

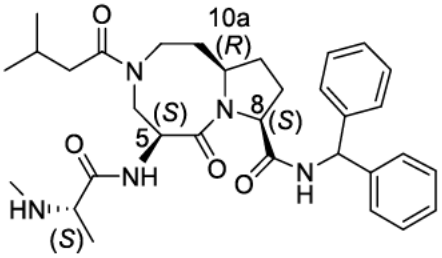
Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody, which binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2. When PD-L1 that is found on tumor cells binds to PD-1 that is found on immune system cells, the PD-1 signaling pathway is activated, inhibiting an immune response. By blocking this interaction, nivolumab allows the immune system to recognize and attack tumor cells. In two pivotal phase I trials in advanced solid tumors, nivolumab showed significant clinical anti-tumor activity and was relatively well tolerated at 10 mg/kg once every 2 weeks (q2w) as monotherapy or in combination with other agents (non-CPIs).(9, 10) This led to several randomized phase III trials of nivolumab monotherapy in advanced cancers including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), classical Hodgkin lymphoma, squamous cell carcinoma of the head and neck (SCCHN) and others.(11) In the pooled dataset of all patients enrolled in these phase III trials and receiving nivolumab 3-10 mg/kg q2w as monotherapy across tumor types (n = 2,578) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 24 months follow-up in NSCLC, no new safety signals were identified.(12, 13)

Efficacy of nivolumab monotherapy was assessed in a recent meta-analysis that included 27 worldwide clinical trials (n=5,551). The pooled objective response rate (ORR), the 6-month PFS and the 1-year OS rates were 26% (95% confidence interval (CI) 21–31), 40% (95% CI 34–46) and 52% (95% CI: 43–62), respectively.(14) In Europe, nivolumab (OPDIVO®) as monotherapy or in combination with ipilimumab is currently indicated for the treatment of advanced melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, SCCHN and urothelial carcinoma. Due to antibody-specific kinetics, a flat dose was derived from the 3 mg/kg q2w dose by multiplying for an average 80 kg weight, thus based on the current prescribing information, a nivolumab infusion at either 240 mg (flat dose) q2w or 480 mg every four weeks (q4w) (starting from Cycle 3) was identified as the recommended phase II dose (RP2D). The two treatment schedules are currently being used in daily oncology practice given the extended terminal half-life of IgG4 antibodies such as nivolumab and the relative lack of potential interactions.(12) It is anticipated that switching the nivolumab schedule as of Cycle 3, from D1, 15 q4w to D1 q4w with the higher dose, if the treating investigator considers this appropriate, is not expected to raise any concerns in regards to efficacy or safety, while simplifying treatment administration and hospital visits and contributing to alleviate patient's time constraints and treatment burden to a significant extent.

2.2. Debio 1143

2.2.1. Chemical structure, formula, and molecular weight

Structural formula:



Molecular formula: $C_{32}H_{43}N_5O_4$

Molecular weight: 561.71 g/mol

2.2.2. International non-proprietary name, brand name, and code name

INN (International Non-proprietary Name):	Not applicable
USAN (U.S. Adopted Name):	Not applicable
CAS (Chemical Abstract Service number):	Not applicable
Company code name	Debio 1143
Former code names:	AT-406, AT-406 free base, SM-406
Chemical name:	(5S,8S,10aR)-N-benzhydryl-5-((S)-2-(methylamino)propanamido)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide

2.2.3. Mechanisms of action

Debio 1143 is an oral monovalent second mitochondrial activator of caspase (SMAC) mimetic that promotes tumor cell apoptosis by blocking the activity of certain members of the inhibitor of apoptosis (IAP) family.(15) IAPs were thought to function primarily by regulating caspases, cysteine proteases that are involved in apoptosis. However, they also influence a multitude of other cellular processes, such as ubiquitin-dependent signaling events that regulate activation of nuclear factor κB (NFκB).(8) IAP inhibitors have been shown to induce systemic cytokines and chemokines such as tumor necrosis factor alpha (TNFa) interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1)(16), enhance cluster of differentiation (CD4+ and CD8+) response (17), and convert pro-tumoral M2 macrophages into a pro-inflammatory M1 phenotype(18). The immuno-modulatory properties of IAP antagonists may therefore work in synergy with those of immunotherapeutic agents.

2.3. Brief summary of non-clinical and clinical data

As single agents, SMAC mimetics have been shown to act on tumor and immune cells to eradicate cancer cells through innate and adaptive immune systems.(17, 18) SMAC mimetics have also been shown to synergize in vivo with immunomodulatory agents, including anti-PD-1 biologics, to either induce TNFa- or interferon-mediated tumor cell death or to stimulate CD8+ killer T-cell activity against glioblastoma, multiple myeloma, colon and mammary carcinoma murine models.(19, 20) In preclinical studies, Debio 1143 has been shown to inhibit cellular proliferation in colorectal and ovarian cancer cell lines (21, 22) and to induce apoptosis in xenograft tumors.(23) In syngeneic mouse tumor models, Debio 1143 has also been

shown to enhance anti-PD-1 mediated tumor growth inhibition by increasing the percentage of activated CD4 and CD8 T-cells in the tumor.(24)

A first-in-man study in 31 patients with advanced cancers evaluated short course Debio 1143 monotherapy (5-900 mg), given orally once daily on days 1-5 (q2w or q3w). Debio 1143 was well tolerated up to the maximum dose of 900 mg, with pharmacodynamic (PDy) effects noted at daily doses >80 mg.(25) Pharmacokinetics (PK) studies demonstrated a mean half-life on Day 1 of 5.2 - 7.1 h, regardless of the dose. The maximum tolerated dose (MTD) was not reached. Common treatment-related adverse events (AE) that occurred with a frequency of >10% included fatigue (26%), nausea (23%), and vomiting (13%).(25) While gastrointestinal (42%) and skin/subcutaneous (29%) AEs were common, most drug-related AEs were mild to moderate in severity and the frequency and grade of AEs were not dose-dependent. Of the 8 patients (26%) with serious adverse events (SAE), none was considered related to Debio 1143. Four patients (13%) discontinued treatment with Debio 1143 due to AEs (alanine transaminase [ALT] increase, cranial nerve disorder, abdominal pain, dyspnea), with only ALT elevation deemed related to treatment.

In combination with carboplatin (CBCDA) and paclitaxel (TXL), short-course Debio 1143 at a dose of 200 mg once daily (Days 1-5, q3w) has been determined to be safe and is the RP2D in combination with chemotherapy.(26) Particularly promising results were observed in heavily pre-treated ovarian cancer patients treated with Debio 1143 in combination with CBCDA and TXL, in which 6 patients out of 18 had confirmed partial response (PR) (33.3%). Extended daily administration of Debio 1143 (Days 1-14, q3w) of 200 to 400 mg daily dosing has also been reported.(15) The extended schedule was found to have good tolerability and a toxicity profile similar to the short-course regimen, with cellular IAP-1 degradation in surrogate tissue noted at all doses evaluated.(15) The MTD was not reached up to 400 mg/d and only one isolated dose limiting toxicity (DLT) of asymptomatic reversible transaminase elevation was observed at 200 mg/d, but not at higher doses.

Extended daily dosing of Debio 1143 is currently being evaluated in combination with concurrent chemo-radiation in patients with locally advanced SCCHN.(27) Debio 1143 at the dose of 200 mg/d on Days 1-14 every 21 days has been determined to be safe and is the selected RP2D in combination with concurrent chemo-radiation.(28) Preliminary findings showed that 10/14 (71.4%) patients had complete response (CR) and 3 (21.4%) additional patients had PR. Double-blind, placebo-controlled, randomized phase II trials (Debio 1143-201B and Debio 1143-203) are ongoing to better address the exact contribution of Debio 1143 to the efficacy and safety of these regimens.

In addition, a phase Ib/II study (Debio 1143-NSCLC-105) of Debio 1143 in combination with avelumab (anti-PD-L1) is ongoing in NSCLC patients naïve to CPI. As of 21st of November 2018, 16 patients were included and treated with Debio 1143 doses ranging from 100 mg daily up to 250 mg daily on Days 1-10 and Days 15-24 q4w with the standard avelumab dose (10 mg/kg on Days 1 and 15 q4w)(29).The MTD was not reached and the RP2D has been defined as 200 mg QD. The study used an adaptive modified continual reassessment method design. Preliminary results showed treatment was well tolerated without any major issues identified so far except for some expected mild grade avelumab infusion-related reactions, which have been well described in the literature. One NSCLC patient, treated at 150 mg/d Debio 1143 had an ongoing confirmed RECIST v1.1 PR at Cycle 6+ as of the cutoff and 5 stable disease (SD) were observed, providing early evidence of clinical activity. Other clinical studies evaluating other CPI combinations are planned to assess the immunomodulatory properties of IAP inhibition.(30)

In summary, as of July 2018 nearly 300 patients have been included in Debio 1143 studies, receiving treatment as single agent in the first-in-human study, or most cases as part of a combination containing either chemotherapy, chemoradiation or immunotherapy. Debio 1143 was given at a daily dose ranging from 400-900 mg/d as single agent without the MTD being reached. Debio 1143 at 200 mg/d can be safely given in combination with carboplatin/paclitaxel, cisplatin, daunorubicin/cytarabine or with concomitant chemo-radiotherapy with cisplatin. In terms of combining Debio 1143 with an anti-PD-L1, preliminary clinical data from the ongoing Debio 1143-NSCLC-105 study, suggest that 150 mg/d is non-toxic and 200 mg/d Debio 1143 combined with standard avelumab is tolerable. PDy evidence of target occupancy and IAP degradation in blood is available from patients treated at doses as low as 120 mg/d.

3. RATIONALE AND RISK BENEFIT ASSESSMENT

Evasion from apoptosis and immune-surveillance have been recognized as two key hallmarks of cancer. A dual combination approach that overcomes both of these barriers has been shown in preclinical models to effectively eradicate tumors. Small-molecule IAP antagonists, known as SMAC mimetics render cancer cells susceptible to cell death and stimulate effector immune cells, resulting in increased anti-tumor immunity.(16) The SMAC mimetic Debio 1143 is expected to expand and enhance patients' response to immune CPIs.

Immune checkpoint inhibition – in particular monoclonal antibodies targeting PD-1/PD-L1 – is changing the treatment paradigm for many cancer types. Pembrolizumab, a PD-1 antagonist is the first drug approved in oncology which is indicated for the treatment of tumors with particular molecular features, such as microsatellite instability-high (MSI-H) or mismatch repair deficiency (MMRd), which cause errors in DNA replication resulting in a high mutation load and likely enhanced neoantigen presentation to immune cells irrespective of their primary tumor origin or location. Nevertheless, only a limited subset of patients responds to single-agent blockade. Combination therapies are often a means of increasing response rates. Furthermore, benefit associated with CPI treatment in patients with malignant melanoma and other tumors was suggested when patients were continuously treated even beyond initial tumor progression.(31, 32) The immunogenic properties of the IAP antagonists provide a good rationale for combining Debio 1143 with immune CPIs such as nivolumab.

In a phase III trial enrolling 423 NSCLC patients with a PD-L1 expression level of 5% or more, nivolumab, as first-line therapy, was well tolerated with 18.0% of patients experiencing grade 3/4 treatment-related toxicity. Among the 75 patients with follow up >13 weeks, median PFS was 4.2 months and the ORR was 26.1% (CR: 2%, PR: 24%), with 38% of patients achieving stable disease (33).

In clinical trials, Debio 1143 monotherapy was well tolerated up to a maximum of 900 mg without reaching the MTD with a schedule of Days 1-5 q2w or q3w. The extended dosing schedule of Debio 1143 (Days 1-14 q3w) also showed good tolerability, with a toxicity profile similar to the short-course regimen, and the MTD not reached with doses up to 400 mg/d. PDy effects were seen with daily doses >80 mg/d. Treatment-related AEs (TEAEs) with a frequency of >10% included fatigue (26%), nausea (23%), and vomiting (13%). Gastrointestinal (42%) and skin/subcutaneous (29%) AEs were common, but most drug-related AEs were mild to moderate in severity and the frequency and grade of AEs were not dose-dependent. More recently, results of a window-of-opportunity trial in patients with SCCHN showed an increased level of tumor-infiltrating lymphocytes (TILs), especially CD8+ T-cells; as well as increased expression of PD-L1 and PD-1 in tumors resected 14-days post-treatment with Debio 1143. [redacted]

The combination of immune CPI with compounds that foster anti-tumor immunity and promote programmed cell death (apoptosis) in tumor cells has strong therapeutic potential and based on their good tolerability, the benefit risk balance is positive.

A combination of Debio 1143 and avelumab, a CPI targeting PD-L1, is currently being tested in patients with solid tumors and NSCLC, using the same schedule as that proposed in this study, Days 1-10 and Days 15-24 q4w. Results available from 16 patients treated up to 21st of November 2018 in the Debio 1143 dose range explored (100-250 mg/d) plus the standard avelumab dose showed an acceptable safety profile without any unexpected toxicities. The MTD was not reached and the RP2D had been defined at 200 mg/d D1-10 and D15-24 combined with avelumab i.v. at 10 mg/kg on D1 and 15, both q4w (29). Preliminary PK/PDy data from this and other studies (i.e., Debio 1143-101/AT-406-C2S-001 and Debio 1143-202 Window-of-Opportunity), show target engagement, adequate tumor distribution and concentrations and potential immunomodulatory properties with the 200 mg/d Debio 1143 dose (some already apparent at 80-100 mg). It also has an acceptable safety profile both as single agent and when combined with a variety of other treatments (concomitant chemo-radiotherapy, carboplatin and paclitaxel, cisplatin weekly, etc). Based on the known safety profile of CPIs and SMAC mimetics, and particularly Debio 1143 when given orally

at 200 mg/d, the risk-benefit ratio for patients treated with the combination as proposed in this study is favorable. See Section 5.3 for the Debio 1143 administration schedule rationale.

Regarding the risk of drug-drug interactions (DDIs), Debio 1143 is transported by P-glycoprotein (P-gp). Accordingly, strong P-gp inhibitors and inducers are prohibited. In addition, in vitro Debio 1143 significantly inhibits CYP 3A4/5 and P-gp and has the potential to induce and downregulate CYP 3A4/5, 2Cs, 2B6, and to downregulate 1A2. The clinical relevance of these phenomena is unknown.

Accordingly, narrow therapeutic range or sensitive CYP 3A substrates are prohibited. Also, narrow therapeutic range or sensitive substrates of P-gp, CYP 2Cs, 2B6 or 1A2 should be closely monitored.

4. STUDY OBJECTIVES

4.1. Primary objectives

4.1.1. Part A

The primary objective of the dose-optimization part of the study is to determine the RP2D taking into account DLT/s in Cycle 1, overall safety/tolerability and PK, by optimizing doses of Debio 1143 when combined with the standard dose of nivolumab, as well as treatment compliance in patients with advanced solid malignancies who failed prior systemic standard treatments.

4.1.2. Part B

The primary objective of the basket trial is to evaluate the preliminary anti-tumor activity of Debio 1143 at the RP2D in combination with nivolumab at the standard dose, overall and in each patient cohort.

4.2. Secondary objectives

4.2.1. Part A

For the dose-optimization part, secondary objectives are to assess the:

1. PK disposition of Debio 1143 (including its metabolite Debio 1143-MET1) and nivolumab when administered in combination.
2. Anti-tumor activity of Debio 1143 in combination with nivolumab in patients with advanced solid malignancies.

4.2.2. Part B

For the basket trial, secondary objectives are to assess the:

1. Safety and tolerability of the RP2D of Debio 1143 when given in combination with nivolumab in patients with advanced solid malignancies.
2. PK disposition of Debio 1143 (and its metabolite Debio 1143-MET1) and nivolumab when administered in combination.

4.3. Exploratory objectives

1. To explore potential predictive and PDy biomarkers of Debio 1143 and nivolumab when administered in combination, in blood and tumor tissue, [redacted]

2. To explore genetic variations in drug metabolism enzyme and transporter (DMET) genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab
3. To explore the exposure/response relationship for efficacy and safety (including PK/PDy correlations, if applicable) of Debio 1143 in combination with nivolumab
4. To explore correlations between response, clinical parameters, immune correlates, and putative biomarkers, [redacted]
5. To explore the relationship between Debio 1143 plasma concentrations and QTcF

5. STUDY DESIGN AND TREATMENT

5.1. Study design

This study will be conducted in two sequential parts, i.e., a dose-optimization phase Ib (Part A) and an exploratory phase II basket (multiple parallel cohorts) trial (Part B), to evaluate Debio 1143 in combination with the standard dose of nivolumab in patients with advanced/unresectable solid malignancies who have progressed during or immediately after anti-PD1/PD-L1 treatment.

A Data Safety Monitoring Committee (DSMC) will overview study conduct during both parts A and B. A full charter will be provided as a separate document.

5.1.1. Part A

Part A has an open-label, multicenter dose-optimization design applying the classical 3+3 method, aiming at optimizing the Debio 1143 dose in combination with standard doses of nivolumab (OPDIVO®) to determine the RP2D taking into account safety/tolerability and PK, as well as the treatment compliance in pretreated patients with advanced solid malignancies including: small cell lung cancer (SCLC); SCCHN; MSI-H, MMRd or other DNA damage repair (DDR) abnormalities, including homologous recombination deficiency (HRD) in gastrointestinal (GI) cancers; known DNA MMRd/MSI-H, breast cancer (BRCA)-1/2 hereditary or somatic/ sporadic mutations, or other DDR abnormalities including HRD in platinum-resistant ovarian, endometrial, primary peritoneal or cervical cancers. Patients must have received at least, one prior systemic line of standard treatment and must have progressed or relapsed during or immediately after a prior anti-programmed cell death-1 (PD-1)/ programmed cell death-ligand 1 (PD-L1) based-treatment, given either as a single agent or in combination with standard/approved chemotherapy, tyrosine kinase inhibitors (TKIs) or other monoclonal antibodies (mAbs) that are not known to modulate/inhibit immune checkpoints. Patients with prior cytotoxic T-lymphocyte antigen 4 (CTLA-4) or lymphocyte activation gene-3 (LAG-3) combinations with PD-1/PD-L1 are excluded; any other prior combinations with checkpoint inhibitors (CPI) should be discussed and agreed by the Sponsor before patient inclusion.

Eligible patients will enter Part A of the study in cohorts of three evaluable patients. The starting dose of Debio 1143 will be 150 mg, daily, administered orally for 10 consecutive days every 2 weeks (i.e., Days 1-10 and Days 15-24 inclusively of each 28-day cycle [q4w]). The dose will be optimized according to the observed DLTs, patient treatment compliance, safety/tolerability and PK data, if applicable.

The DLT period is defined as Cycle 1 (i.e. lasting 4 weeks or longer in case of dosing delays). Treatment-related toxicities fulfilling DLT criteria but occurring after Cycle 1 (i.e., delayed DLTs) may also be considered for RP2D definition after discussion and agreement between the Investigators, DSMC and the Sponsor.

Nivolumab will be administered at 240 mg (flat dose) over at least 30 minutes as an IV infusion on Days 1 and 15 of a 28-day cycle. From Cycle 3, patients may be switched to nivolumab at a dose of 480 mg IV over at least 60 minutes on Day 1 q4w, exclusively upon Investigator request with the Sponsor agreement.

The maximum explored Debio 1143 dose will be 200 mg/d. Neither Debio 1143 dose escalation beyond this threshold nor any nivolumab dose increases are foreseen in this study. In individual cases of severe

toxicity, the Debio 1143 dose may be reduced by a maximum of two decrements of 50 mg/d or up to a minimum dose of 100 mg/d.

According to the 3+3 dose-optimization design, if none of the three patients at the starting dose cohort experiences a DLT, three more patients will be treated at the next dose level. However, if one of the first 3 patients experiences a DLT during Cycle 1, 3 more patients will be treated at the same dose level. If ≤ 1 out of 6 evaluable patients experience a DLT during the first cycle, at the starting dose level, dose escalation will then proceed to the second dose level. If ≥ 2 DLTs are observed during the first cycle among the 3 or 6 evaluable patients treated with the initial dose level, recruitment will then be stopped temporarily or definitively until the reasons for this finding have been clarified. If the dose is increased to the second dose level, 3 to 6 evaluable patients will be included and the 3+3 design rules will be applied again. If ≤ 1 out of 6 evaluable patients experience a DLT during the first cycle at the second dose level, this dose will be considered the optimal dose level. If ≥ 2 out of 3 or 6 evaluable patients experience a DLT during the first cycle at the second dose level, the initial dose level will then be declared the optimal dose, given that < 33% of evaluable patients have experienced a DLT during the first cycle and there are at least 6 evaluable patients treated at this dose level. Patients within a cohort may all start treatment simultaneously.

At least 6 evaluable patients should be treated at the RP2D before Part B of the study may start. Once the RP2D is defined, any patient still receiving treatment can be switched to the RP2D, if deemed appropriate by the Investigator and agreed by the sponsor.

5.1.2. Part B

Part B is a multicenter, open-label, basket trial using Debio 1143 in combination with nivolumab at the RP2D as previously defined in Part A, in patients with advanced/unresectable solid tumors. Eligible patients will be simultaneously included into four cohorts according to tumor type:

- **Cohort 1**: SCLC (including extrapulmonary small-cell carcinomas or large cell neuroendocrine lung carcinoma, as per WHO Classification of Lung Tumors of 2015 (34)
- **Cohort 2**: SCCHN (nasopharyngeal carcinomas are excluded)
- **Cohort 3**: GI cancers, including esophageal, gastric, colorectal or pancreatobiliary tumors, with known MSI-H/ MMRd or other known DDRs abnormalities (incl. HRD).
- **Cohort 4**: platinum-resistant EOC), endometrial cancer, PPC and cervical cancer, with known MSI-H/ MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other known DNA DDRs abnormalities (incl. HRD).

The primary objective of Part B is to assess whether the combination of Debio 1143 with nivolumab is active overall and in each cohort. Early futility stopping rules based on ORR (unconfirmed) will be used. In each cohort, if no unconfirmed response is observed according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or Gynecologic Cancer Intergroup (GCIG) criteria (Cohort 4, if applicable) once the initial 8 evaluable patients have been assessed at least twice after baseline or have discontinued their treatment earlier, futility will be concluded and recruitment will be stopped in that cohort. If at least one response (unconfirmed) is documented in the initial 8 evaluable patients, recruitment shall continue up to 11 evaluable patients. At least two unconfirmed responses must then be observed in these 11 evaluable patients to continue the recruitment up to 15 evaluable patients in that cohort.

A homogeneity test will be conducted in any non-futile cohorts showing a confirmed response rate of at least 15%. If homogeneous response rates are seen across the cohorts, efficacy data will be pooled and an overall efficacy analysis will be conducted in addition to the analyses by cohort. For the final efficacy assessment, first proof of efficacy will be claimed in a given cohort if at least 4 confirmed objective responses are reported in the 15 evaluable patients.

In the case of insufficient accrual in any cohort (e.g. less than 2 patients in 6 months) despite concrete measures aiming at increasing the recruitment, enrolment may be stopped in that cohort.

During part B the DSMC will meet approximately every 3 months, and more frequently if needed in the event of rapid recruitment. A charter will be provided separately.

5.2. DLT period and definition of DLTs

The DLT period is defined as Cycle 1*.
DLT is defined as any of the following treatment-emergent adverse events (TEAEs) which are possibly, probably or definitely related to the combination treatment and occurring in Cycle 1 (1 cycle=4 weeks):

- Any Grade 4 or 5 hematologic toxicity, clinical or laboratory non-hematologic toxicity
- Febrile neutropenia any grade, Grade 3 thrombocytopenia if associated with bleeding or requiring platelet transfusion
- Grade 2 or higher cardiac or neurologic toxicities, pneumonitis that does not resolve within 3 days after starting steroids at adequate doses or that was recurrent upon steroid tapering or withdrawal, myasthenia gravis, myositis, polymyositis, Guillain-Barre syndrome (excluding peripheral purely-sensory neuropathies)
- Grade 2 or higher alanine transaminase (ALT)/ aspartate transaminase (AST) increase with a concurrent increase of total bilirubin ≥2 x upper limit of normal (ULN) and concurrent with alkaline phosphatase (ALP) ≤2 x ULN (Hy's law), in the absence of objective causes of biliary obstruction due to obvious disease-related causes
- Any other Grade 3 non-hematologic, treatment-related clinical toxicity lasting 3 or more days despite optimal supportive care, or requiring admission for appropriate medical management; hypersensitivity and/or infusion-related reactions are excluded if not reoccurring after appropriate pre-medication and/or prolonging infusion time
- Grade 3 non-hematologic laboratory value (excluding lipase, amylase and/or autoimmune endocrinopathies manageable by replacement therapies) if:
    a. Symptomatic and
    b. Medical intervention was promptly required to treat the patient, or
    c. The abnormality led to hospitalization or
    d. The abnormality did not resolve to at least Grade 1 within 2 weeks (including the steroid tapering period) despite adequate medical intervention/treatment
- A delay of >2 weeks due to drug-related toxicity in initiating Cycle 2
- Unable to complete at least 70% of the scheduled treatment, i.e. more than six Debio 1143 skipped doses in Cycle 1 due to treatment-related toxicity
- Required dose reduction in Cycle 1 or on Cycle 2 Day 1 or requirement for treatment withdrawal due to treatment-related toxicity (even if not meeting other DLT criteria)

*Any toxicity fulfilling one or more of these criteria but occurring from C2D1, may be defined as delayed DLTs after discussion and agreement between principal Investigators (PIs) and the Sponsor, and may be considered for RP2D definition, if appropriate.

5.3. Study treatments

Debio 1143: rationale for dose regimen

Since Debio 1143 is a chemosensitizer, radiosensitizer and immunosensitizer, its schedule of administration in clinical trials is adapted to the standard treatment used in the combination.

A 10-day on / 4-days off schedule given every 2 weeks (i.e., repeated twice in a 4-week cycle) of Debio 1143 was selected to optimize the activity of the combination with standard nivolumab. This schedule is being tested in an ongoing Debio 1143-NSCLC-105 study in combination with avelumab (NCT03270176). The 4-day wash-out period allows recovery from potential Debio 1143-related toxicity and gives a lower

cumulative dose per cycle than regimens using 14 days q3w (14 days on and 7 days off) while providing similar dose-density and intensity. As of 31 July 2018 (IDB cut-off), up to 13 patients had been treated in the Debio 1143-NSCLC-105 study: all 4 planned dose levels (150 to 250 mg/d) had been explored without reaching a formal MTD. No unexpected toxicities were observed and the 200 mg/d dose is currently being expanded formally.

In the first-in-human phase I single-agent trial, Debio 1143 was well tolerated up to doses of 900 mg/d on Days 1-5 every 3 weeks (q3w) and up to 400 mg/d Days 1-14 q3w. The MTD was not reached for either of these schedules. The prolonged dosing schedule of Debio 1143 with a total cumulative dose of 5600 mg/cycle showed good tolerability, with an acceptable toxicity profile and treatment compliance, similar to the short-course regimen at the highest explored dose level (i.e., total cumulative dose of 4500 mg/cycle). PDy demonstration of target occupancy and linear PK were observed within the explored dose range, even at doses as low as 120 mg/d. High interpatient variability was seen, but without drug-accumulation. The dose of 200 mg/d was chosen as the RP2D when Debio 1143 was combined with both cisplatin-based chemo-radiation (100 mg/m^2 IV on Day 2 q3w) in patients with locally advanced SCCHN, and with carboplatin and paclitaxel q3w in patients with NSCLC, triple-negative breast cancer or ovarian cancer [cf. section 6.2.1.4.5 of Debio 1143 Investigator's Brochure and (28)]. It is therefore expected that a Debio 1143 starting dose of 150 mg/d, given orally on Days 1-10 and Days 15-24 q4w, with a dose-intensity of 750 mg/week and a maximal cumulative dose of 3000 mg per cycle is tolerable, relevant in terms of biological target engagement and feasible as single agent and in combination with standard dose of nivolumab.

Given that a linear dose-effect response was not observed above 120 mg/d in the single agent mechanistic studies, and that no further PDy effects are expected when the Debio 1143 dose is increased, dose escalation beyond 200 mg/d is not planned in this study.

Study treatments

Patients will receive oral Debio 1143 at a starting dose of 150 mg once daily on Days 1-10 and Days 15-24 every 4 weeks (q4w) along with nivolumab at a flat dose of 240 mg IV on days 1 and 15 of a 28-day cycle (with a possible switch to one dose at 480 mg q4w from Cycle 3) (cf. Table 5-1). On Days 1 and 15, Debio 1143 will be administered on site, immediately before the nivolumab infusion. Remaining daily doses are to be taken by the patient at home following relevant medical instructions, except on days where PK samples are planned, during the first cycle, and the third cycle. For nivolumab administration, specific precautionary measures outlined in section 7.6.2 must be applied.

Table 5-1 Days of treatment for each treatment cycle

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Debio 1143	X	X	X	X	X	X	X	X	X	X	-	-	-	-	X	X	X	X	X	X	X	X	X	X	-	-	-	-
Nivolumab	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X[1]	-	-	-	-	-	-	-	-	-	-	-	-	-

[1] From Cycle 3 onwards, patients may switch to nivolumab infusion of 480 mg IV on D1 q4w, if appropriate as per Investigator request and upon Sponsor agreement. After switching to the D1q4w schedule, this schedule must be maintained thereafter.

In Part A, the Debio 1143 starting dose will be 150 mg/d and up to one dose increment of 50 mg will be allowed. No dose escalation beyond 200 mg/d is foreseen in this study under any circumstances. If 200 mg/d is defined as the optimal RP2D, any patients still ongoing with active treatment at a lower Debio 1143 dose at this time may increase their dose to the RP2D, if the investigator considers it appropriate and accepted by the Sponsor.

Patients remaining on treatment after Cycle 2 is completed may have the nivolumab infusion switched from Cycle 3 onwards to one infusion every 4 weeks instead of two infusions, thus receiving nivolumab at 480 mg intravenously on Day 1 q4w. This switch will be allowed on a per-patient basis, based on the

Investigator's judgement and Sponsor agreement. Once the nivolumab dose is switched, this schedule should be maintained until end of treatment (EOT). Switch back to the initial schedule is not permitted.

Table 5-2 Study treatment starting doses

Dose level	**Debio 1143** orally, daily for 10 days then 4 days off: D1-D10 & D15-D24 q4w (1 cycle= 4 weeks)	**Nivolumab#** flat dose, IV, D1 & D15 q4w (1 cycle=4 weeks)
1 (starting dose)	150 mg	240 mg
2 (higher dose)	200 mg	

D= day; IV= intravenous; q4w= every 4 weeks

From Cycle 3, a switch to 480 mg q4w (Day 1 of each 28-day cycle) will be allowed on a per-patient basis, based on the Investigator's judgement and Sponsor's agreement. Once the nivolumab dose is switched, this schedule should be maintained until EOT.

In Part B, patients will receive Debio 1143 at the RP2D established in Part A, in combination with nivolumab at the standard dose. Per-patient dose adjustments of Debio 1143 will be considered according to the severity of any eventual observed toxicity (See Section 5.4)

Participants are planned to be treated with Debio 1143 and nivolumab for up to 52 weeks (i.e., 13 cycles), until any of the following events occurs: symptomatic progressive disease (PD), asymptomatic but confirmed PD (as per iRECIST), unacceptable toxicity (per Investigator judgment and despite up to two dose adjustments), patient withdrawal, or treatment delay greater than 4 and 8 weeks (+1 week tolerance) for Debio 1143 and nivolumab, respectively (see section 8.3.2.1 for details).

Permission to prolong the study treatment for one additional year can be exceptionally granted by the Sponsor, if patients are deriving continuous clinical benefit from the study treatment. Medical justification for extending the treatment and the assessment of the risk/benefit balance must be provided by the Study Investigator and will be discussed with the Sponsor. The decision to further extend study treatment will be re-evaluated on a yearly basis for each patient.

5.4. Dose modifications

For participants without DLT in the previous cycle and/or unacceptable toxicity, in the absence of symptomatic disease progression or confirmed iRECIST PD, the combination therapy can be continued unchanged as long as re-treatment criteria are met (cf. Table 5-3).

Table 5-3 Re-treatment criteria

Assessment	Debio 1143		Nivolumab
	Days 1 and 15	Days 2-10 or 16-24	Days 1 & 15
ECOG-PS	≤1	≤2	≤1
ANC	≥ 1.5 x10^9/L	≥ 1.0 x10^9/L	-
Platelets	≥ 100 x10^9/L	≥ 75 x10^9/L	-
Hemoglobin	≥ 9.0 g/dL	≥ 9.0 g/dL	≥ 9.0 g/dL
Total bilirubin	grade 1	grade 2[a]	grade 1
AST/ALT	grade 1	grade 2[a]	grade 1
Amylase or lipase increases	≤ Grade 3[b]		-
Serum creatinine	≤ 2.0 x ULN	-	≤ 2.0 x ULN
Non-optimally treated, symptomatic immune-related AEs	-		≤ Grade 1[c]
Any Debio 1143 drug-related AEs	≤ Grade 1[c]	≤ Grade 2	-
Cardiac safety/ ECG	Baseline status		
βHCG urine pregnancy test (for women of childbearing age)[d]	Negative	-	Negative

ANC: absolute neutrophil count; AST/ALT: aspartate aminotransferase/alanine aminotransferase; AEs: adverse event(s); ECG: electrocardiogram; ECOG-PS: Eastern Cooperative Oncology Group performance status

a) Provided that total bilirubin and/or ALT/AST levels were Grade 1 as per NCI-CTCAE v5.0 at the start of the corresponding cycle.
b) As per NCI-CTCAE v5.0, Grade 3 is defined as amylase or lipase increases up to 5x ULN symptomatic or not; or above 5x ULN but asymptomatic
c) Up to Grade 2 for alopecia, stable sensory neuropathy, fatigue/asthenia, skin toxicity or non-optimally treated nausea, vomiting or diarrhea or any grade endocrinopathy optimally treated by replacement therapy
d) On every Day 1 for both Debio 1143 and nivolumab

From Cycle 2, if a patient does not meet the requirements for treatment continuation on Day 1 of any cycle, both study drugs will be withheld until recovery or for a maximum of 4 and 8 weeks (+1 week tolerance window) for Debio 1143 and nivolumab, respectively. After this delay-period, treatment should be withdrawn. If a delay occurs in initiating Cycle 2 and is due to any toxicity related to study drug, it will be considered as a DLT.

If a patient does not meet the requirements for treatment continuation on any day other than D1 (D2-10 or D15-24) of any cycle, treatment will be immediately interrupted and the corresponding Debio 1143 dose (and nivolumab if on D15) will be omitted. Patients should be re-assessed, ideally, every 48-72 hours, if clinically indicated, and treatment will only be resumed after all re-treatment criteria are met. On D1, treatment can be delayed more than 3 days if required; in this case, the assessment schedule will shift accordingly, and all assessments planned for D1 will be performed on the day treatment is re-started. However, if treatment is interrupted during any day other than D1 and the re-treatment criteria are not met within 72 hours, treatment will be resumed only on D1 of the next cycle.

A maximum delay of 4 and 8 weeks (+1-week tolerance) for Debio 1143 and nivolumab, respectively, is allowed. After this delay-period, treatment will be withdrawn. Patients withdrawing from treatment for any reason will be followed for safety up to 5 months (±15 days) after the last nivolumab infusion, complete resolution or stabilization of any ongoing toxicity, unless the patient starts a new treatment, end-of-life-care or withdraws consent.

Patients experiencing immune-related AEs, that require withholding nivolumab infusions temporarily until resolution to at least Grade 1, may withhold nivolumab for a maximal period of up to 8 weeks (±1 week

tolerance). During this period, patients may continue to receive Debio 1143 as per protocol, if appropriate. Patients requiring more than 8 weeks (±1 week) of nivolumab interruption and those who permanently discontinue nivolumab for any reason, will discontinue Debio 1143 permanently and will be withdrawn from the study. The nivolumab dose will not be adjusted under any circumstances.

Patients experiencing any treatment-related grade 4 toxicity (clinically or laboratory, excluding grade 4 amylases and/or lipase and/or non-febrile neutropenia) will withdraw from treatment definitively without further reduction (see section 8.3.2.1 for details).

Patients experiencing any other treatment-related toxicity fulfilling applicable DLT criteria (as shown below) at any time during the study must stop treatment and may only resume treatment after adequate recovery to re-treatment criteria.

Treatment must be re-started with a Debio 1143 dose reduction. Individual patients may have up to two dose adjustments of 50 mg/d (each one) up to a minimum dose of 100 mg/d Debio 1143 (i.e. 1st dose reduction 150 mg/d, 2nd dose reduction 100 mg/day). Patients still requiring a dose adjustment with a dose of 100 mg/d will be withdrawn from the study. Once adjusted, Debio 1143 dose will not be re-escalated under any circumstances.

Up to 2 dose reductions must be implemented in the event of any of the following:

- Any Debio 1143-related Grade 4 hematologic toxicity
- Debio 1143-related febrile neutropenia any grade, or Grade 3 thrombocytopenia if associated with bleeding or requiring platelet transfusion
- Debio 1143-related grade 2 or higher alanine transaminase (ALT)/ aspartate transaminase (AST) increase with a concurrent increase of total bilirubin ≥2 x upper limit of normal (ULN) and concurrent with alkaline phosphatase (ALP) ≤2 x ULN (Hy's law), in the absence of objective causes of biliary obstruction due to obvious disease-related causes
- Any Grade 3, treatment-related, non-hematologic clinical toxicity lasting 3 or more days despite optimal supportive care, or requiring admission for appropriate medical management; hypersensitivity and/or infusion-related reactions are excluded if not reoccurring after appropriate pre-medication and/or prolonging infusion time
- Grade 3 non-hematologic laboratory value (excluding lipase, amylase and/or autoimmune endocrinopathies manageable by replacement therapies)
- A delay of >2 weeks due to drug-related toxicity in initiating subsequent cycles, or a second delay lasting >24 h but <2 weeks
- Unable to complete at least 70% of the scheduled treatment, i.e. more than six Debio 1143 skipped doses during any cycle due to treatment-related toxicity or more than 2 treatment interruptions >24 h but <6 days

If for any reason Debio 1143 is withheld temporarily, nivolumab will also be withheld until treatment may be resumed. Patients discontinuing Debio 1143 definitively for any reason will also discontinue nivolumab study treatment.

Patients requiring no more than 1 treatment interruption per cycle and for not more than 3 consecutive days, may resume treatment without dose adjustments. Patients requiring one interruption greater than 3 days, or more than one interruption during any given cycle, may resume treatment only after full recovery and adjustment of Debio 1143 dose upon the Sponsor's agreement (if applicable).

Patients interrupting treatment or delaying the start of a new cycle due to any Grade 3 treatment-related toxicity will resume treatment after Debio 1143 adjustment (except Grade 3 neutropenia, thrombocytopenia, non-optimally treated fatigue, diarrhea, or nausea). Patients experiencing any Grade 4 treatment-related toxicity will immediately stop treatment without any possible therapy resumption.

Omitted Debio 1143 doses will not be re-administered under any circumstances. Every new cycle D1 will start with the Debio 1143 dose. In case of any cycle delays (Day 1 delayed greater than 72 hours), all

subsequent doses will be administered according to the new planning, if feasible (i.e. Day 1-10 followed by Day 11-14 pause).

6. STUDY POPULATION

All patients included in the study must have selected advanced/unresectable or metastatic solid tumors, and must have received at least one prior systemic line of standard treatment and have progressed or relapsed during or immediately after a prior anti-PD-1/PD-L1-based treatment, given either as a single agent or in combination with standard/approved chemotherapy, TKIs or other mAbs that are not known to modulate/inhibit immune checkpoints. Patients with prior CTLA-4 or LAG-3 combinations with PD-1/PD-L1 are excluded; any other prior CPI combinations should be discussed and agreed by the Sponsor before patient inclusion.

In Part A:

- Between 3 and 12 evaluable patients are planned.
- Non-evaluable patients will be replaced, as appropriate.

In Part B:

- **Cohort 1**: SCLC (including extrapulmonary small-cell carcinomas or large cell neuroendocrine lung carcinoma, as per WHO Classification of Lung Tumors of 2015 (34)
- **Cohort 2:** SCCHN (nasopharyngeal carcinomas are excluded)
- **Cohort 3:** GI cancers (including esophageal, gastric, colorectal or pancreatobiliary) with known MSI-H/MMRd or other DDR abnormalities, including HRD.
- **Cohort 4:** platinum-resistant EOC, endometrial cancer, PPC or cervical cancer, with known MSI-H/ MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other DNA DDR abnormalities (incl. HRD).
- Between 32 evaluable patients (if all cohorts are futile) and 60 evaluable patients (if none of the 4 cohorts is futile) (see section 11.1 for details on sample size).
- Non-evaluable patients will be replaced.

6.1. Inclusion criteria

The same tumor types are eligible in Part A and B.

All patients must fulfil all the following criteria (both Parts A and B, unless specified otherwise):

1. Willing and able to sign a written informed consent form;
2. Male or female ≥18 years of age.
3. Histologically and/or cytologically confirmed advanced/ unresectable or metastatic solid tumor for one the following indications:
    a. SCLC
    b. SCCHN (except nasopharyngeal carcinoma)
    c. GI cancers, including esophageal, gastric, colorectal or pancreatobiliary with known MSI-H/MMRd or any other known DDRs abnormalities, including HRD
    d. Platinum-resistant* EOC, endometrial cancer, PPC or cervical cancer, with known MSI-H/ MMRd, hereditary/somatic mutations of the BRCA1 and BRCA2 genes or other known DNA DDRs abnormalities (incl. HRD)
    * Platinum-resistant is defined as relapse or progressive disease (PD) occurring within 1 to 6 months (180 days) after a platinum-containing chemotherapy.
4. Have received at least one prior line of standard systemic chemotherapy in the advanced/unresectable cancer setting (standard adjuvant/neoadjuvant treatment is acceptable if

relapse occurred within six months of treatment end) and have no established standard therapeutic alternatives.

5. Have progressed or relapsed during or after a prior anti-programmed cell death-1 (PD-1)/ programmed cell death-ligand 1 (PD-L1)-based treatment, given either as a single agent or in combination with standard/approved chemotherapy, tyrosine kinase inhibitors (TKIs), radiotherapy (RT) or other monoclonal antibodies (mAbs) that are not known to modulate/inhibit immune checkpoints (CPIs)
6. Minimum washout periods since prior therapy until treatment start (C1D1) (in cases of more than one prior treatment type, whichever has the longest minimum period applies):
    a. 3 weeks for chemotherapy (6 weeks, specifically for nitrosoureas or mitomycin C containing regimens);
    b. 4 weeks for any prior mAbs or live vaccines; for any investigational mAbs 4 weeks or at least the duration of one treatment cycle whichever is longest
    c. 3 weeks for prior RT (1 week in case of localized antalgic/hemostatic hypofractionated RT flash)
    d. 2 weeks for TKIs, hormonal therapy, other anti-cancer treatment not previously specified or investigational agents
    e. 4 weeks for any major surgery
    f. Immunosuppressive medication: within 2 weeks, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological/replacement doses, which should never exceed 10 mg/d prednisone, or an equivalent corticosteroid
7. Measurable disease (Part B only) according to RECIST v1.1 or GCIG criteria in Cohort #4 (if applicable) and documented PD during or after prior PD-1/PD-L1 based therapy
8. ECOG Performance Status = 0 or 1
9. Adequate hematologic renal and hepatic function:
    a. absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L,
    b. platelets $\geq 100 \times 10^9$/L,
    c. hemoglobin ≥ 9.0 g/dL,
    d. AST and ALT ≤ 3 x ULN ($\leq$ 5x ULN if liver metastases are present),
    e. total bilirubin ≤ 1.5 x ULN,
    f. serum creatinine ≤ 1.5 x ULN,
    g. serum albumin ≥ 30 g/L
10. Available archived tumor samples for biomarker analysis obtained after prior PD-1/PD-L1 treatment failure or, if no archived tumor sample is available, patient must be suitable and willing to undergo a percutaneous or endoscopic biopsy without unacceptable major risks before starting study treatment.
11. Participants with known central nervous system (CNS) and/or meningeal involvement will be eligible if they are clinically asymptomatic, have completed primary CNS therapy more than 4 weeks before treatment start (such as whole brain RT, stereotactic radiosurgery, or complete surgical resection), and have remained off steroids (including tapering doses) for at least 2 weeks
12. Women of child-bearing potential (WOCBP):
    a. Negative serum pregnancy test at screening;
    b. Agreement to use highly effective contraception methods from study entry and for up to 5 months after the last day of study treatment
    c. Agreement from her male partner to use contraception methods
13. Male patients with WOCBP partners must agree to use highly effective contraception methods from study entry and for up to 5 months after the last day of study treatment

6.2. Exclusion criteria

Any of the following would render a patient ineligible for inclusion (in both Parts A and B, unless specified otherwise):

1. Thoracic or head and neck radiation >30 Gy within the 6 weeks prior to C1D1;
2. Have received, in total, more than 3 (i.e. Cohorts 1&2) or 4 (i.e. Cohorts 3&4) lines of prior systemic treatments (including adjuvant or neoadjuvant regimens if relapse within six months prior to C1D1);
3. Active moderate alcohol consumption, at screening, more than 100/140 grams (3.5/4.9 ounces) of alcohol per week for female and male patients, respectively
4. Liver cirrhosis Child-Pugh score B or C
5. Prior treatment with an anti-CTLA-4 or anti-LAG3 in combination with PD-1/ PD-L1 CPI, unless discussed and agreed with the Sponsor
6. Prior treatment with SMAC mimetics
7. Prior PD-1/PD-L1 discontinuation due to severe immune-related toxicity, not resolved upon adequate steroids/immunosuppressive treatment
8. Requirement of concomitant treatment with any prohibited medication (See Appendix B: Prohibited medications and special warnings)
9. Ongoing toxicity from prior administration of any other investigational drug and/or anti-cancer treatment of > Grade 1 NCI-CTCAE v5.0 before treatment start (except for grade 2 alopecia, stable sensory neuropathy, vitiligo or any endocrinopathy adequately managed by replacement hormonal therapy)
10. Patients with known history of:
    a. Uncontrolled or symptomatic angina or myocardial infarction, within the last 12 months prior to C1D1
    b. Elevated (>ULN) troponins (T or I) or creatine phosphokinase (CPK) > 1.5xULN during screening
    c. Symptomatic intestinal sub-occlusion
    d. Infection, active or latent by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV)
    e. Ongoing arrhythmias requiring treatment, including asymptomatic QTc interval as corrected by Fridericia (F) >480 msec
    f. In patients previously treated with anthracycline-containing chemotherapy or thoracic RT, non-adequate cardiac function with left ventricular ejection fraction (LVEF) <50%, measured by an echocardiogram (ECHO) or a multigated acquisition (MUGA) as per institutional standards
    g. Active rheumatoid arthritis, active inflammatory bowel disease (IBD), primary sclerosing cholangitis, autoimmune hepatitis, systemic lupus erythematous (SLE), multiple sclerosis or any other ongoing autoimmune disease requiring systemic treatment (excluding vitiligo, mild cutaneous psoriasis and asymptomatic autoimmune endocrinopathy well controlled under hormonal replacement therapy)
    h. Evidence of active, non–infectious pneumonitis or a history of interstitial lung disease
    i. Active ongoing infection requiring systemic antibiotic therapy, including active tuberculosis
11. Evidence or clinical suspicion of active bleeding or requirement of red blood cell (RBC) transfusions within 2 weeks prior to C1D1
12. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Debio 1143 or nivolumab or their constituents
13. History of another non-metastatic, low grade malignancy other than the primary tumor within the last 1 year prior to C1D1, except: completely resected non-melanoma skin cancer, second SCCHN tumors, completely resected minimally invasive bladder cancer, completely resected ≤ pT1N0 invasive breast cancer, low grade prostate cancer if PSA ≤ 10 ng/mL, non-metastatic localized low grade RCC or any previous (non-synchronous) malignancy if related to germ-line mutations linked to either MSI-High-(lynch syndrome) or BRCA-1/2 hereditary cancer syndromes, for patients included either in cohort 3 or 4. For these indications there are no time restrictions with regards to occurrence prior to C1D1.
14. Pregnant or lactating females
15. Unable to swallow or retain oral medications
16. Known contraindication to contrast-enhanced MRI and CT
17. Patient unwilling or unable to comply with study visits/assessments

6.3. Patient replacement

Part A

Patients will be evaluable for DLT, if they received at least 70% of Debio 1143 (i.e., a maximum of 6 missed Debio 1143 doses) and at least one nivolumab dose as planned in Cycle 1 and were evaluated for DLT or if the patient discontinued treatment early due to any toxicity that could be considered a DLT.

Non-evaluable patients will be replaced, as appropriate (see section 11.5.1).

Part B

Patients will be evaluable for efficacy if the following two conditions are met:

- Measurable disease at baseline as per RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable),
- At least one efficacy assessment, either computed tomography (CT) or magnetic resonance imaging (MRI) for RECIST evaluable patients, or CA-125 dosage performed after baseline, if applicable, or treatment discontinuation occurred before the efficacy assessment was done due to treatment failure, defined as any of the following: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening.

Non-evaluable patients will be replaced.

7. CLINICAL SUPPLIES

7.1. Investigational medicinal products

7.1.1. Debio 1143

Debio 1143 will be provided by the Sponsor as size 1 hard gelatin capsules (75 mg yellow, 100 mg white opaque) containing API powder along with starch as excipient, for oral administration.

7.1.2. Nivolumab

Commercially available nivolumab (Opdivo®) will be provided by the Sponsor.

7.2. Packaging and storage of IMPs

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice (GMP) guidelines.

7.2.1. Packaging

Debio 1143 hard gelatin capsules will be packed in opaque high density polyethylene bottles with a sealed child-resistant closure. Each bottle will contain 10 capsules of either 75 mg yellow capsules or 100 mg white capsules.

Nivolumab (Opdivo®) commercial presentations, 1 x 4 mL vials, 1 x 10 mL vials and/or 1 x 24 mL vials.

7.2.2. Labeling

Debio 1143 bottles containing 75 mg capsules will have a yellow label, those with 100 mg capsules will have a white one. Commercial pack Nivolumab (Opdivo®) will be overlabelled to dispense study related information as appropriate per local regulations, storage conditions and expiry date in local languages. Label text will comply with local health authority requirements in each participating country.

7.2.3. Storage

Debio 1143 capsules should be stored at a controlled temperature of 15-25°C, protected from direct heat and contact with water. It will be shipped and dispensed at ambient temperature. Do not freeze.

Nivolumab must be shipped and stored at 2-8°C until use. Do not freeze.

7.3. Dispensing and accountability of IMPs

The IMPs and certificates of analysis will be provided to the Investigators by and under the responsibility of the Sponsor, who will also ensure release of the IMPs as per current GMP guidelines. Any documentation required by local health authorities for import of the IMPs will be appropriately submitted.

The Investigator/pharmacist at each study site will inventory and acknowledge receipt of all IMP shipments. The IMPs accompanied by analytical reports when appropriate, must be kept in a locked area with access restricted to designated study personnel, and must be stored in accordance with the manufacturer's instructions.

The Investigator/pharmacist at each study site will keep accurate records of the IMP (and other study-related drugs) dispensed. These records will specify dates and amounts dispensed, to and by whom (drug dispensing list), and report any IMPs accidentally or deliberately destroyed.

Each dispensing of study drug will be documented by recording the patient's number, and date dispensed on the Drug Accountability Form in the electronic case report form (eCRF)/electronic data capture (EDC) system.

At study closure, unused IMPs will be counted and returned to the Sponsor or destroyed with their written permission. Any discrepancies between the IMPs returned and the expected balance must be justified.

Unused IMPs must not be discarded or used for any purpose other than the present study. Throughout the study, the Sponsor's monitor/representative will collect the drug accountability forms along with any unused IMPs in the original packaging.

7.4. Patient numbering

7.4.1. Screening number

During the screening period (between Day –28 to –1), each potential study patient will be identified by a unique screening number which is displayed when the patient is first recorded in the eCRF via the internet-based application. The screening number allows the patient's data to be entered into the eCRF and subsequently ensures an expedited process when s/he is ready to start the study.

The Screening # consists of a unique 6-digit identifier. The first 3 digits represent the number of the study center and digits 4-5-6 identify the screening order of the subject at the center (starting at 001). Screening #106001, for example, identifies the first subject (001) screened at study center 106. The second subject screened at the same study center will be given Screening # 106002, etc.

If a screened patient fulfils all eligibility criteria and none of the exclusion criteria, the Investigator or designated study coordinator will request enrollment of the patient via the eCRF on study Day 1. Enrollment should not be requested before the patient is fully eligible and ready to start treatment.

7.5. Blinding and unblinding methods

Not applicable, as this is an open-label study.

7.6. Method of administration and compliance

7.6.1. Debio 1143

Debio 1143 capsules are ready to use and will be taken orally once daily for 10 consecutive days every 2 weeks of a 28-day cycle (Days 1 to 10 and Days 15 to 24 q4w).

Patients should fast 2 hours before dosing and should fast at least 1hour post-dose. Water is permitted freely. Beyond the onsite visits, study medication will be self-administered by patients at home and should be taken at approximately the same time each day. If a dose is forgotten, the patient may take the dose later in the day but no later than 6 h after normal intake time. If the delay exceeds 6 h, the patient must wait until the next scheduled administration. A double dose should not be taken to make up for a missed dose.

If a patient vomits after study medication intake, the patient should not take another dose, but wait until the next scheduled dose. If vomiting persists, the patient should contact the Investigator. Relevant medical instructions should be given to the patient, specifically to not replace any missing doses and to not extend treatment beyond Days 10 or 24, during each cycle for any reason. In addition, the patient should be instructed to record any occurrences of vomiting in the diary card.

Patients' compliance will be verified on Day 1 of each cycle and on days when PK sampling is scheduled during Cycles 1 and 3, if applicable. Compliance will be measured by direct visual supervision at dosing by the Investigator or his/her designee when administered at the hospital, or by means of a diary card to be filled out after each dose when taken at home (the number of capsules, date and time of dosing will be recorded). The diary card will be checked by the Investigator or his/her designee at each study visit. Any change in the daily dosing of Debio 1143, must be appropriately reflected in the patient's diary by the Investigator or his/her designee, such as dose reduction, dose omissions, and treatment resumption, as applicable.

7.6.2. Nivolumab

7.6.2.1. Pre-infusion procedures

Nivolumab will be administered at 240 mg (flat dose) as an IV infusion, over at least 30 min, on D1 and D15 q4w (1 cycle=4 weeks and two infusions) or 480 mg over at least 60 min, on D1 q4w (1 cycle=4 weeks and one infusion) from Cycle 3.

For instructions on preparation of nivolumab infusion, please refer to locally approved labelling.

A preparation manual will describe in detail the infusion bags and medical devices to be used for the preparation of the dilution and subsequent administration.

Formal premedication is not required. However, premedication might be used after C1D1 administration, if needed, on an individual patient basis, per clinical judgment and local institutional guidelines, as appropriate.

7.6.2.2. Peri- and post-infusion procedures

For the infusion, patients must be observed according to standard applicable institutional guidelines, if applicable, or for approximately 90 minutes post-infusion, in an area with resuscitation equipment and emergency agents. At all times during nivolumab treatment, immediate emergency treatment of an infusion-related reaction or a severe hypersensitivity reaction according to institutional standards must be assured.

Infusion of nivolumab will be stopped in case of Grade ≥2 hypersensitivity, inflammatory response, or infusion-related reactions. Infusions may be resumed after Grade ≤2 events upon resolution of the events within less than 4 hours and after medical assessment and agreement by a qualified Investigator. Infusion duration will not be shorter than 120 minutes after resumption in all subsequent infusions.

Treatment will be withdrawn definitively after the occurrence of any Grade ≥3 infusion-related reactions, hypersensitivity or cytokine-release syndrome. Appropriate standard measures must be in place for the medical management of the patients under these circumstances.

Recommendations on how to manage infusion-related reactions and severe hypersensitivity reactions according to the NCI are outlined in section 7.6.2.3.

When a reaction does not resolve completely after 4 hours despite appropriate medical management, the ongoing infusion will not be resumed. Upon Investigator judgement and agreement, next scheduled infusions should be performed at a slower infusion rate (i.e., 120-180 minutes) and pre-medications with standard anti-H1, non-steroidal anti-inflammatory drugs (NSAIDs) and/or low dose steroids might be considered as per standard institutional guidelines.

See section 7.6.2.4 for details on the management of immune-related AEs and sections 5.4 and 7.6.2.3 for other (not immune-related) adverse drug reactions (ADRs) potentially requiring nivolumab discontinuation or temporarily withhold.

7.6.2.3. Management of infusion-related reactions

Symptoms of infusion-related reactions may be fever, chills, rigors, diaphoresis, hyper or hypotension and/or headache. These symptoms should be managed according to Table 7-1.

Table 7-1 Treatment modification for symptoms of infusion-related reactions associated with nivolumab

NCI-CTCAE grade and description	Treatment modification for nivolumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	• The total infusion time for nivolumab should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	• Stop nivolumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 and monitor closely for any worsening.
Grade 3 – severe Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. **Grade 4 – life-threatening** Life-threatening consequences; urgent intervention indicated.	• Stop the nivolumab infusion immediately and disconnect infusion tubing from the patient. • Patients have to be withdrawn immediately from nivolumab treatment and must not receive any further nivolumab treatment.

If a patient experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the patient must discontinue nivolumab. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

7.6.2.4. Management of immune-related adverse events

Since inhibition of PD-1/PD-L1 stimulates the immune system, immune-related AEs may occur. Adequate management and treatment of immune-related AEs provided below is mainly based on American Society

of Clinical Oncology (ASCO) practice guidelines recommendations (35) (but not only), depending upon severity (i.e., NCI-CTCAE grading), in general:

- Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring
- Grade 1 to 2 (persistent): manage similar as to high -grade AE (grade 3 to 4)
- Grade 3 to 4: treat with high dose corticosteroids

Treatment of immune-related AEs should follow ASCO guidelines which are summarized in Table 7-2.

Table 7-2 Management of immune-related AEs

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Gastrointestinal immune-related AEs: diarrhea and/or colitis		
Grade 1 Diarrhea: <4 stools/day over baseline Colitis: asymptomatic	• May continue nivolumab therapy • Evaluate symptomatic treatment (e.g. loperamide)	• Close monitoring for symptoms worsening • Educate patient to report if worsening immediately • If worsens: treat as Grade 2 or 3/4 • GI consultation may be needed for persistent cases (e.g. more than 4 weeks)
Grade 2 Diarrhea: 4 to 6 stools per day over baseline; IV fluids indicated <24 h; not interfering with activities of daily living Colitis: abdominal pain; blood in stool	• Withhold temporarily nivolumab therapy until resolution to Grade 1 • Symptomatic treatment if infection is ruled out • Consider GI consultation • Consider 1 mg/kg/day prednisone or equivalent	• If improves to Grade ≤1: resume nivolumab therapy • If persists ≥3 to 5 days or recurs: treat as Grade 3 or 4
Grade 3 to 4 Diarrhea (grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; interfering with activities of daily living Colitis (grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs **Grade 4**: life-threatening, perforation	• Withhold temporarily nivolumab therapy for Grade 3, if first occurrence. • Permanently discontinue study treatment for Grade 4 or recurrent Grade 3. • 1 to 2 mg/kg/day prednisone IV or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy • Consider early infliximab treatment (5-10 mg/kg) if symptoms are steroids-refractory after 2-3 days.	• If improves: continue steroids until Grade 1, then taper over at least 4-6 weeks; resume nivolumab therapy following steroids taper (for initial Grade 3). • If worsens, persists ≥2 to 3 days, or recurs after initial improvement: add infliximab (5-10 mg/kg, if no contraindication)

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Skin immune-related AEs		
Grade 1 to 2	• Continue nivolumab therapy • Symptomatic therapy and advise to avoid sun exposure (for example, oral antihistamines, topical emollients and/or medium to high-potency topical steroids, as appropriate)	• If persists >1 to 2 weeks or recurs: consider withholding nivolumab therapy until resolution to Grade ≤ 1 and monitor weekly; consider skin biopsy • Consider 0.5 to 1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume nivolumab therapy following steroids taper • If worsens: treat as Grade 3 to 4
Grade 3	• Withhold temporarily nivolumab therapy for Grade 3 first occurrence. • Permanently discontinue study treatment for recurrent Grade 3. • Consider skin biopsy • Dermatology consultation • 1 to 2 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections	• If improves to Grade ≤1: taper steroids over at least 1 month; resume nivolumab therapy following steroids taper (for initial Grade 3)
Grade 4 Life threatening consequences or all severe rashes unmanageable with prior interventions	• Permanently discontinue study treatment • Admission and urgent dermatology consultation • IV (methyl)prednisolone 1-2 mg/kg or equivalent • Add prophylactic antibiotics for opportunistic infections • If bullous pemphigoid is diagnosed, treatment with rituximab maybe considered instead of long-term steroids	• Slow tapering over more than one month upon resolution

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Pulmonary immune-related AEs: Pneumonitis		
Grade 1 Asymptomatic, radiographic changes confined to one lobe or <25% of lung parenchyma only	• Consider withholding nivolumab therapy if radiologic evidence of pneumonitis progression • Monitor oximetry, history and physical exam + chest radiography weekly • Consider pulmonary and infectious disease consultations	• Re-assess CT scan if available at baseline at least 3-4 weeks, spirometry/ diffusing capacity of the lungs for carbon monoxide (DLCO) • Resume nivolumab upon radiologic improvement or resolution • If no improvement: treat as Grade 2 or Grade 3 to 4
Grade 2 Symptomatic, involves more than one lobe or 25-50% of lung parenchyma	• Withhold nivolumab therapy until resolution to Grade 1 or less • Pulmonary and infectious disease consultations • Monitor symptoms daily, consider hospitalization • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic/empirical antibiotics for opportunistic infections • Consider bronchoscopy with bronchoalveolar lavage (BAL)	• Re-assess every 3 days • If improves: when symptoms return to Grade ≤1, taper steroids by 5-10 mg/wk over 4-6 wks and then resume nivolumab therapy following steroids taper • If not improving after 48-72 h of steroids or worsening: treat as Grade 3 to 4
Grade 3 to 4 **Grade 3**: Severe new symptoms; New / worsening hypoxia; **Grade 4:** Life-threatening	• Permanently discontinue study treatment • Hospitalize • Pulmonary and infectious disease consultations • 1.0 to 2.0 mg/kg/day prednisone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy with BAL ± lung biopsy	• If improves to Grade ≤1: taper steroids over at least 4-6 weeks. • Add infliximab 5 mg/kg or mycophenolate mofetil IV 1.0 g twice daily or IV immunoglobulins for 5 days or cyclophosphamide, if not improving after 48 h of prior steroids

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Hepatic immune-related AEs: Liver Test Elevation		
Grade 1 Asymptomatic, AST or ALT up to 3.0 x ULN (1.5 – 3.0 x baseline if baseline was abnormal) or total bilirubin up to 1.5 x ULN (>1.0 - 1.5 x baseline if baseline was abnormal)	• Continue nivolumab therapy • Educate the patient to report symptoms immediately	• Continue liver function monitoring at least once or twice weekly • If worsens: treat as Grade 2 or Grade 3 to 4, as appropriate
Grade 2 Asymptomatic AST or ALT >3 to 5 x ULN (>3.0 - 5.0 x baseline if baseline was abnormal) and / or total bilirubin >1.5 to ≤3 x ULN (> 1.5 – 3.0 x baseline if baseline was abnormal)	• Withhold nivolumab therapy temporarily • Increase frequency of monitoring to every 3 days • Advise to stop unnecessary medications and known hepatotoxic drugs • May consider low dose prednisone (≤10 mg/d or equivalent) • Symptomatic patients may consider prednisone 0.5-1.0 mg/kg/d or equivalent	• If returns to Grade ≤1: resume routine monitoring, may resume nivolumab therapy after steroids tapering. • If elevations persist ≥3 to 5 days, or if worsen: treat as Grade 3 to 4 • If improvement on steroids consider tapering over 4-6 weeks (re-escalate if needed)
Grade 3 to 4 (immune-related possible, probable or likely) AST or ALT > 5 x ULN (>5.0 x baseline if baseline was abnormal) and /or total bilirubin >3 x ULN or symptomatic liver failure (e.g. ascites, coagulopathy, encephalopathy or coma)	• Permanently discontinue study treatment • Increase frequency of monitoring to every 1 to 2 days • Start immediately 1 to 2 mg/kg/day (methyl)prednisolone or equivalent • Add prophylactic antibiotics for opportunistic infections • Consult hepatologist if no improvement on steroids • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	• If returns to Grade ≤1: taper steroids over at least 1 month • If does not improve in ≥3 to 5 days, worsens or rebounds: add mycophenolate mofetil or azathioprine or other non-hepatotoxic systemic immunosuppressants • Avoid use of infliximab in the context of suspected immune-mediated hepatitis

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Renal immune-related AEs		
Grade 1	• Consider holding nivolumab therapy, while excluding alternative causes	• Re-assess renal function regularly • If worsens: treat as Grade 2, 3 or 4
Grade 2	• Withhold nivolumab therapy temporarily • Nephrology consultation • Increase frequency of monitoring to every 2-3 days • 0.5 to 1.0 mg/kg/day prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy	• If returns to Grade ≤1: Taper steroids over at least 1 month, and resume nivolumab therapy following steroids taper • If worsens or no improvement on steroids: 1-2 mg/kg/d prednisone or equivalent and treat as Grade 3-4
Grade 3-4	• Permanently discontinue study treatment • Monitor creatinine daily 1-2 mg/kg/d prednisone or equivalent. • Add prophylactic antibiotics for opportunistic infections • Consider renal biopsy • Nephrology consultation	• If returns to Grade ≤1: Taper steroids over at least 4 weeks and consider mycophenolate mofetil
Cardiac immune-related AEs (myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure and vasculitis)		
Grade 1 Any abnormal cardiac biomarker testing, including abnormal ECG	• Withhold nivolumab temporarily until further work-up to exclude alternative causes • Hospitalize • Consult cardiologist to establish etiology and rule out immune-mediated myocarditis • Guideline-based supportive treatment as per cardiology consultation* • Consider early starting of high-dose steroids (1-2 mg/kg/d orally or IV depending on situation)	• Consider permanent nivolumab discontinuation even upon resolution

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Grade ≥2 Grade 2 : any abnormal test with mild symptoms	• Permanently discontinue study treatment • Guideline-based supportive treatment and further workup as appropriate as per cardiology consultation* • Start 1-2 mg/kg/d (methyl)prednisolone IV or equivalent • In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management	• Once improving, taper steroids over at least 4-6 weeks • If no immediate improvement or worsening, consider methylprednisolone at 1 g/d and/or add additional immunosuppressants either mycophenolate mofetil, infliximab, antithymocyte globulin
Endocrine immune-related AEs		
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• May continue nivolumab therapy • Endocrinology consultation if needed • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. • Rule out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	• Continue hormone replacement/suppression and monitoring of endocrine function, as appropriate
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	• Withhold nivolumab therapy • Consider hospitalization • Endocrinology consultation • Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate • Rule out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	• Resume nivolumab once symptoms improve to Grade ≤ 1 or patient stabilizes with hormone replacement • Continue hormone replacement/suppression and monitoring of endocrine function, as appropriate
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum free thyroxine (FT4) with inappropriate low thyroid-	• Resume nivolumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
	stimulating hormone (TSH) and/or low serum cortisol with inappropriate low adrenocorticotropic hormone (ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH)/ insulin-like growth factor 1 (IGF-1), prolactin (PRL), testosterone in men, estrogens in women) • Hormone replacement/ suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue nivolumab if mild symptoms with normal MRI. Repeat the MRI 1 month later • Withhold nivolumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	replacement) • In addition, for hypophysitis with abnormal MRI, resume nivolumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. • Continue hormone replacement/suppression therapy as appropriate.
Neurologic immune-related AEs		
Grade 1 neurologic toxicities or **Grade ≤2** peripheral neuropathy or mood changes	• Withhold nivolumab therapy temporarily • Close monitoring for worsening symptoms	• If persistent: initiate prednisone or equivalent at 1.5 mg/kg/day • Consider resuming nivolumab therapy after discussion with the patient about the benefit/risk balance. If peripheral neuropathy improves to Grade ≤ 1 and does not reoccur after steroids taper: resume nivolumab therapy

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Grade 3-4 and/or any other Grade 2 other than peripheral neuropathy, mood changes	• Permanently discontinue study treatment • Patient's hospital admission in facilities with availability of assisted mechanical ventilation (AMV) • Urgent neurologic and intensive care consultation • Initiate therapy with high-dose IV steroids and other symptomatic and supportive treatment as needed	
Musculoskeletal immune-related AEs		
Grade 1	• Continue nivolumab therapy • If CPK is elevated and/or symptomatic: start oral corticosteroids and treat as Grade 2	
Grade 2	• Withhold nivolumab temporarily and may resume upon resolution to Grade 1 • Add low doses of prednisone <10 mg • Rheumatologic or neurologic consultations	• If worsened: treat as Grade 3
Grade 3-4 or if CPK≥ Grade 2	• Permanently discontinue study treatment • Hospital admission in facilities with availability of AMV • Urgent neurologic and intensive care consultation • Start immediately 1mg/kg prednisone or equivalent • Consider further supportive symptomatic treatment including plasmapheresis if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia) • Referral for neurology or rheumatology admission	

NCI-CTCAE grade v5.0	Suggested management	Suggested follow-up
Hematologic immune-related toxicities (out of immune diseases such as autoimmune hemolytic anemia, acquired thrombocytopenia)		
Grade 1	• May continue nivolumab therapy	• Monitor for improvement closely (i.e., weekly)
Grade 2	• Withhold nivolumab therapy temporarily • Start prednisone at 1.5 mg/kg/d	• May resume nivolumab if improvement or no worsening after steroids tapering
Grade 3 – 4	• Permanently discontinue study treatment • Hematologic consultation and consider hospitalization • Initiate prednisone at 1 mg/kg/d or equivalent • Start rituximab therapy and IVIG (if applicable) • Consider blood transfusion as per existing guidelines	
Ocular immune-related toxicities		
Grade 1 asymptomatic	• Continue nivolumab therapy • Refer to ophthalmology	• If symptomatic: add local treatment if indicated
Grade 2	• Withhold nivolumab therapy temporarily • Urgent ophthalmology referral • Initiate topical steroids and consider systemic corticosteroids • Re-treat after return to Grade 1 or less	• May resume nivolumab once off systemic corticosteroids, which are purely indicated for ocular AEs, or once corticosteroids for other concurrent systemic immune reaction AEs have been reduced to ≤ 10 mg
Grade 3 – 4	• Permanently discontinue study treatment • Urgent ophthalmology referral • Initiate systemic corticosteroids 1-2 mg/kg or IV (methyl)prednisone • Consider infliximab as per specialist evaluation	

*Local guidelines or e.g. American College of Cardiology (ACC) or American Heart Association (AHA) guidelines
European Society of Cardiology (ESC) guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
AHA guidelines website: https://professional.heart.org/professional/GuidelinesStatements/UCM_316885_Guidelines-Statements.jsp

7.7. Concomitant therapy

Administration of concomitant medications/therapies to the patient during the study period must be reported on the concomitant medications page of the eCRF. A medication or therapy is defined as concomitant when administered between the date of signature of informed consent and end of study (EOS). Information to be reported on the eCRF includes: i) international non-proprietary name and trade name, ii) dosage information (dose, unit, frequency, route), iii) dates of administration, and iv) reasons for use.

7.7.1. Permitted medications

Permitted medications are:

- Supportive therapies to treat any emergent serious condition notably including medications against pain, nausea, vomiting, and diarrhea (per the Investigator's decision).
- Granulocyte colony-stimulating factor (G-CSF) and erythropoietic agents (per the Investigator's decision).
- Transfusions and blood-derived products as per local institutional guidelines.
- Bisphosphonates or denosumab as per local institutional guidelines in patients with symptomatic bone metastases, or malignant hypercalcemia or with increased risk of bone fractures.
- Steroids or anti-histaminic drugs according to local institutional standard protocols or guidelines (if any) for allergic reactions Grade ≥2 or prophylactically after C1D1.
- Patients requiring prolonged systemic steroids administration for any emerging medical cause at doses in excess of physiological replacement doses or more than prednisone 10 mg/d, should discontinue study treatment according to risk/benefit evaluation.
- Levetiracetam and pregabalin (per the Investigator's decision).
- Treatment of pain should be done according to severity and recommended drugs. Study-specific guidelines will be available.
- Any other medication for the well-being of the patient except those mentioned as prohibited medications at the Investigator's discretion.
- The use of oral contraceptives should be carefully evaluated during study treatment as well as the use of other drugs reported to cause liver injury.

7.7.2. Prohibited medications

Attention should be paid to treatment that could influence the intended effects or mask side effects of study treatment. Use of drugs reported to cause liver injury should be carefully evaluated.

Concomitant use (until the EOT visit) of the following drugs and treatment modalities is prohibited (see Appendix B: Prohibited medications for the full list), except if they are indicated to treat any TEAEs related to study treatment ([i.e. anti-TNF-α therapy]). In this case, administration of these drugs is allowed and must be documented after interrupting Debio 1143 treatment.

- Strong P-gp inhibitors or inducers (see Appendix B: Prohibited medications)
- Anti-TNF-α therapy (e.g, adalimumab [Humera®], etanercept [Enbrel®], infliximab [Remicade®], etc.)
- Other investigational agents other than mAbs within a 2-week period prior to initial dosing or while receiving Debio 1143
- Systemic corticosteroids, exceeding 10 mg/d of prednisolone or equivalent or physiological replacement doses of hydrocortisone. Note: topical corticosteroids for any indication, megestrol, or inhaled corticosteroids for reactive airway disease are permitted.

- Alcohol dependency defined as drinking greater than 100/140g (3.5/4.9 ounces) of alcohol per week for female/male patients, respectively
- Grapefruit juice or grapefruit-containing products and St John's Wort containing products
- Narrow therapeutic range or sensitive CYP 3A substrates or other drugs on the prohibited medication list (see Appendix B: Prohibited medications).

Restrictions also apply for P-gp substrates during Debio 1143 on-treatment periods (see Appendix B: Prohibited medications). In addition, narrow therapeutic range or sensitive CYP 2Cs (2C8, 2C9, 2C19), 2B6 or 1A2 substrates should be closely monitored. A list of drugs that are sensitive substrates of CYPs is available from website resources such as: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007); http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Finally, considering that the potential of Debio 1143 to prolong the QTc interval has not yet been fully characterized, caution should be exercised when using Debio 1143 with drugs having a known risk of QTc prolongation (refer to product label or Arizona CERT database at website: http://www.crediblemeds.org). Monitoring of patients' electrolyte levels is strongly recommended.

7.7.3. Contraceptive measures

Based on its mechanism of action and data from animal studies, it is known that nivolumab can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Human IgG4 is known to cross the placental barrier. Nivolumab therefore has the potential to be transmitted from the mother to the developing fetus, with greater effects during the second and third trimesters of pregnancy. Nivolumab is not recommended during pregnancy and in women of childbearing potential (WOCBP) not using effective contraception.(12)

Animal reproductive studies have not been conducted with Debio 1143. Therefore, it is not known if Debio 1143 or its metabolites are excreted in milk or can cross the placenta. Thus, pregnant or nursing women should not receive Debio 1143. Women of childbearing potential and their partners who are included in a clinical trial of Debio 1143 must take adequate contraceptive measures.

WOCBP patients and male patients, whose partners are WOCBP, enrolled in this clinical trial must take adequate contraceptive measures through defined periods during and after study treatment as specified below.

WOCBP patients and male patients whose partners are WOCBP must:

- Agree to use one highly effective method of contraception as described below. Contraception will be required from study entry up to 5 months after the last day of study treatment, or
- Agree to practice complete sexual abstinence, when this is in line with the preferred and usual lifestyle of the patient (note: periodic abstinence [e.g., calendar, ovulation, symptothermal post-ovulation methods] and withdrawal are not acceptable methods of contraception) from study entry up to 5 months after the last day of study treatment.

Highly effective methods of birth control include:

- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)*.

- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)*.
- Bilateral tubal ligation.
- Vasectomized partner.
- Double barrier methods (not highly effective, but acceptable)

*Note: If hormonal contraception is chosen, the use of a barrier method (preferably male condom) is mandatory due to potential risk of CYP 3A4/5 induction by Debio 1143 that may reduce hormonal contraception efficacy.

WOCBP are non-surgically sterile women whose date of last menstruation is within 12 months before the date of the screening visit.

8. STUDY ENDPOINTS, ASSESSMENTS, AND PROCEDURES

8.1. Endpoints

8.1.1. Primary endpoints

8.1.1.1. Part A

The primary endpoint of part A is the RP2D of Debio 1143 when combined with the standard dose of nivolumab, in patients with advanced solid malignancies who received prior systemic standard treatment and failed a prior PD-1/PD-L1-containing treatment, as per DLT occurrence in less than one-third of evaluable treated patients at the RP2D dose level.

8.1.1.2. Part B

The primary endpoint of part B is the confirmed ORR as per RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable).

8.1.2. Secondary endpoints

Secondary endpoints for both study parts (unless otherwise specified) are:

- Incidence and severity of TEAEs and clinical laboratory abnormalities, according to NCI-CTCAE version 5.0 criteria
- Changes in vital signs: systolic/diastolic blood pressure, heart rate (both after at least 5 minutes of supine rest), temperature, and weight; ECG and ECOG-PS
- Incidence of premature treatment discontinuations and treatment modifications due to AEs and laboratory abnormalities (i.e., treatment compliance)
- Tumor response determined according to RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable):
    - Confirmed (Part A) and unconfirmed (Parts A and B) ORR
    - Disease control rate (DCR), defined as any response, partial or complete (PR or CR) + stable disease (SD)
    - Time-related endpoints as median time to response, median DOR, median PFS, PFS rate at 6, 12 and 18 months, median OS, OS rate at 12 months and 18 months (if data allow)

- PK parameters of Debio 1143 and Debio 1143-MET1 as defined in the available population PK model (36) and, if appropriate, post-hoc estimates of areas under the curve (AUCs), C_{max}, and C_{min}; serum concentration versus time profiles of nivolumab and, if deemed appropriate, relevant nivolumab PK parameters derived from a population PK model. (37)

8.1.3. Exploratory endpoints

Exploratory endpoints are:

- Potential predictive and PDy biomarkers of Debio 1143 combined with nivolumab, in blood and tumor tissue [redacted]
- Best overall response (BOR) evaluation using the novel iRECIST 2017 guideline for immunotherapeutics
- Correlations between PK disposition of Debio 1143 combined with nivolumab and clinical response and/or any tumor metrics
- Correlations between PK disposition of Debio 1143 combined with nivolumab and safety profile, and PDy if applicable
- Correlations between Debio 1143 and Debio 1143-MET1 plasma concentrations and changes from baseline QTcF.
- Correlations between response, clinical parameters, immune correlates and putative biomarkers, [redacted]
- Genetic variations in DMET genes associated with differences in the PK disposition of Debio 1143 in combination with nivolumab.

8.2. Study assessments

8.2.1. Efficacy

Tumors will be assessed according to either RECIST version 1.1 guidelines by CT scan or MRI imaging of the target/non target lesions (38), and/or GCIG criteria using the serum marker CA-125 for Cohort 4, if applicable.(39)

CT scan and MRI will be performed at screening, then every 8 weeks (± 1-week tolerance window) during the first 10 cycles, then every 12 weeks (± 1 week) from Cycle 13 until symptomatic PD or confirmed iRECIST PD or start of any new cancer treatment or end-of-life care or end of the Main study period, whichever occurs first. For patients who exceptionally continue study treatment after completion of 13 cycles, tumor response assessments will continue at 12-week intervals (± 1 week window) until the end of the Main study period, and thereafter at the frequency of local institutional care practice until PD, start of any new anticancer therapy, death or EOT.

Imaging will be performed as per site standard but whenever possible using contrast agent at screening and during treatment

CA-125 dosages will be performed at screening exclusively in patients included in Cohort 4. In case of abnormally elevated levels before treatment start, these dosages will be repeated on Day 1 of each subsequent cycle.

In case of response, efficacy assessments will be repeated 4 weeks later after first documentation (+ 1-week tolerance window). All patients will have an efficacy assessment (CT scan/MRI or serum CA-125 dosage) at the time of disease progression and/or treatment discontinuation, whichever occurs first.

As an exploratory analysis, tumor response will also be assessed using the iRECIST criteria (novel modified RECIST v1.1 guideline for immunotherapeutics).(40) These exploratory analyses will be described in the SAP.

Patients with asymptomatic, but radiologically observed unconfirmed PD as per iRECIST, may continue the study treatment, upon both the Investigator's request and the Sponsor's agreement, until PD is confirmed as per iRECIST or symptoms occurs or Investigator/patient decision to withdraw treatment, whichever occurs first.

8.2.1.1. Measurability of tumor lesions

Patients must have at least one measurable tumor lesion, according to the RECIST version 1.1 criteria (38) and/or GCIG criteria (Cohort 4), if applicable.(39)

As per RECIST v1.1 guidelines, measurable tumor lesions must be measured in at least one dimension (longest diameter in the plane of measurement is to be recorded except for measurable lymph nodes) with a minimum size of:

- 10 mm by CT scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: ≥15 mm in short axis when assessed by CT scan (slice thickness ≤5 mm). Only the short axis is measured.

As per GCIG criteria (Cohort 4, if applicable), patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

8.2.1.2. Methods of tumor assessment

The choice of the imaging method for tumor assessment is taken by the site, based on local feasibility and clinical adequacy. However, the same method of assessment and the same technique must be used throughout the trial for any given patient. Extent of disease evaluation by institutional guidelines per RECIST includes CT scan with IV contrast of the thorax, abdomen, and pelvis as well as other anatomical areas as appropriate (i.e., CNS imaging for symptomatic SCLC patients, if appropriate). Of note, all known or suspected disease-involved areas assessed at screening should be at least, included in all subsequent assessments. MRI may be used to assess sites of disease not adequately imaged by CT or in patients known to have an allergy to iodine-containing contrast or moderate to severe renal impairment (calculated creatinine clearance <50 ml/min^{-1}).

For Cohort 4 exclusively, extent of disease evaluation by the GCIG criteria includes a monthly dosage of the serum tumor marker CA-125, if applicable, in patients without RECIST measurable disease in ovarian cancer, fallopian cancer, PPC, and/or endometrial cancer with elevated CA-125.

8.2.1.3. Tumor response criteria

For the evaluation of target lesions by the RECIST v1.1 criteria, following definitions will be applied (38):

- **CR**: Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. CR must be confirmed by repeat assessments performed no less than 28 days after the criteria for response are first met to qualify as CR.
- **PR:** At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameter. PR must be confirmed by repeat assessments performed no less than 28 days after the criteria for response are first met to qualify as PR.

- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for disease progression, taking as reference the smallest sum diameter while on study.

As per the GCIG criteria (Cohort 4, if applicable), a CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample for patients whose CA-125 level was greater than twice the upper limit of the reference range when they started treatment.

Progressive disease definitions are provided in Appendix C: Response to treatment criteria.

8.2.2. Safety

Safety assessments will include vital sign measurements, physical examination findings, clinical laboratory results, ECOG-PS, ECGs, AE monitoring, and concomitant medications. The schedule of assessments is presented in Table 8-6.

8.2.2.1. Adverse events and concomitant medications

AEs will be monitored and recorded throughout the study, from the time the informed consent form (ICF) is signed until up to 5 months after last nivolumab administration provided no new anti-cancer or end-of-life care was started earlier. Ideally an EOT visit should be planned immediately before whenever is feasible.

AEs will be graded according to NCI-CTCAE version 5.0 (see section 9).

Concomitant medications and procedures, including blood transfusions, will be recorded from signing informed consent through EOS. Alternative cancer therapies will also be recorded during OS follow-up.

8.2.2.2. Physical examination, ECOG score, and vital signs

A complete physical examination will be performed at screening, on Days 1 and 15 of the first three cycles, and then on Day 1 of remaining cycles and at EOT. The ECOG-PS will always be measured along with vital signs comprising systolic/diastolic blood pressure, heart rate (both after at least 5 minutes of supine rest), temperature, and weight at screening, on Days 1, 8, 15, and 22 of Cycle 1, and on Days 1 and 15 of other cycles and at EOT. Height will be recorded only at screening. On dosing days, all assessments should be performed predose.

8.2.2.4. 12-lead ECG

High-quality, digital triplicate 12-lead ECGs will be recorded after 10 minutes of supine rest at screening. High-quality, digital triplicate 12-lead ECGs will be recorded after 10 minutes of supine rest on Day 1 of Cycle 1 and Cycle 3 and on Days 8, 15 and 22 of Cycle 1 at the following 3 time points: pre-, 0.5-2h Debio 1143 post-dose (before starting the nivolumab infusion or after nivolumab perfusion was removed) and 4-6 h post-dose. ECG readings must be performed prior to PK/PDy sampling. There should be at least 1 minute between each ECG and all 3 ECGs should be completed within 10 minutes. Reading will be done centrally by a dedicated team. For eligibility purposes, the screening reading will be done also locally by the investigator or a cardiologist will be consulted if clinically indicated.

8.2.2.5. Safety laboratory

Safety laboratory measurements are scheduled at screening, C1D1 pre-treatment (only required if screening test were performed > 7 days prior to C1D1 or if inclusion/exclusion criteria were not met during screening),

on Days 3 (Part A only), 8, 15, 17 (Part A only), and 22 of Cycle 1, on Days 1 and 15 of Cycle 2 and 3, on Days 1 of any other subsequent cycle and at EOT. On dosing days, samples will always be collected predose and results reviewed prior to nivolumab infusion, if applicable. All measurements will be performed locally.

On Days 3 and 17 of Cycle 1 for patients included in Part A only, serum will be collected and measured for total bilirubin (if >ULN: direct bilirubin should also be measured), alkaline phosphatase (ALP), AST, ALT and creatinine.

For all other visits mentioned above, blood/serum will be measured for the following panels:

- **Hematology:** Hemoglobin, hematocrit, complete blood count (incl. differential) and platelets
- **Chemistry:** Creatinine, sodium, potassium, calcium, total bilirubin (if >ULN: direct bilirubin should also be measured), ALP, AST, ALT, amylase, lipase, lactate dehydrogenase (LDH), total protein, albumin and C-reactive protein (CRP)

In addition, the following laboratory measurements will be collected:

- on Days 1 and 15 of Cycle 1 and Days 1 of each subsequent cycle:

TSH, free triiodothyronine (FT3), free thyroxine (FT4),

- At screening, the following will also be measured: HIV, HBV, and HCV serology, CPK and troponins, FSH/LH and total testosterone (in males) or estrogens (in pre-menopausal female patients, meaning those whose last menstruation occurred within 12 months of screening date), free-cortisol (at morning) and ACTH. These dosages could be repeated if clinically indicated.

For applicable patients included in Cohort 4, CA-125 dosages will be performed at screening within 4 weeks of C1D1 and will be repeated on Day 1 of each subsequent cycle, if abnormally elevated levels are obtained before treatment start. Patients are evaluable as per GCIG criteria only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

8.2.2.6. Pregnancy test

For WOCPBP, a serum test measuring β-HCG will be performed at screening. A predose urine pregnancy test at the beginning of each cycle (at C1D1 only required if screening test were performed > 7 days prior to C1D1) will be performed as well while on treatment and up to 5 months after of the last study dose, if patients is ongoing follow up.

8.2.3. Pharmacokinetics

PK samples will be collected as described below for determination of Debio 1143 and Debio 1143-MET1 plasma concentration, and of nivolumab serum concentrations. In addition, samples will be collected to allow for determination of nivolumab anti-drug antibodies (ADA), if deemed appropriate to support PK data interpretation. After completion of the analysis, the remaining PK samples may be stored for up to a maximum of 15 years after the end of the study and, if required, may be used for metabolic profiling, for further bioanalytical investigations (such as method cross-validation and protein binding), for a retrospective examination of safety laboratory tests or proteins involved in the metabolism or the pharmacological effects of Debio 1143 or nivolumab.

For all PK samples, exact sampling time must be recorded. PK samples will be taken in both parts of the study but will differ depending on the administration schedule of nivolumab (i.e., every 15 days throughout the study or every 4 weeks after Cycle 2).

Sampling days and times for PK are listed in: Table 8-1, Table 8-2 and Table 8-3.

- For the determination of Debio 1143 and Debio 1143-MET1, during Cycle 1 PK samples are to be collected for Part A on Days 1, 3, 8 15, 17 and 22 and for Part B on Days 1, 8, 15 and 22. During Cycle 3, PK samples will be collected for Part A on Days 1, 3, 15 and 17 and for Part B on Days 1 and 15. During Cycle 6 on Day 1 (in both parts A and B). On Days 1, 8, 15, and 22 of Cycle 1, and on Days 1 and 15 of Cycle 3 there are at least two PK samplings on the same day. Samples will be analyzed for Debio 1143 and Debio 1143-MET1 using a validated LC/MS/MS method with a lower limit of quantification (LOQ) of 2.5 ng/mL for both compounds.
- For the determination of nivolumab, during Cycle 1 PK samples are to be collected for Part A on Days 1, 3, 8, 15, 17 and 22 and for Part B on Days 1, 8, 15 and 22. During Cycle 3, PK samples will be collected for Part A on Days 1, 3, 15 and 17 and for Part B on Days 1 and 15. During Cycle 6 on Day 1 (in both parts A and B). On Days 1 and 15 of Cycles 1 and 3 there are at least two PK samplings on the same day. Nivolumab serum concentrations will be determined using a validated electrochemiluminescence (ECL) immunoassay with a lower LOQ of 100 ng/mL.
- For ADA, blood is taken predose on Days 1 and 15 of Cycle 1 and 3, on Day 1 of Cycles 6 and at EOT for both Parts A and B. For patients entering the Extended study period, the last nivolumab ADA will be collected at C13D1 instead of at EOT.

If deemed appropriate to support PK data interpretation, samples will be analyzed for serum ADA entities using a validated immunoassay following a tiered testing approach.

For all PK measurements, the windows of tolerance for sample collection are provided in Table 8-5.

Table 8-1 Sampling days and times for PK on Cycle 1

	Cycle 1																		
Cycle day	**1**					**3**	**8**				**15**					**17**	**22**		
Time [h]	**0***	**0.5[1]**	**1.5[2]**	**4[3]**	**8[4]**	**0***	**0***	**1.5**	**4[3]**	**8[4]**	**0***	**0.5[1]**	**1.5[2]**	**4[3]**	**8[4]**	**0***	**0***	**1.5**	**4[3]**
Part A																			
Nivolumab PK	X	-	X	-	X	X	X	-	-	-	X	-	X	-	X	X	X	-	-
Debio 1143 PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nivolumab ADA	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-
Part B																			
Nivolumab PK	X	-	X	-	-	-	X	-	-	-	X	-	X	-	-	-	X	-	-
Debio 1143 PK	X	-	X	X	-	-	X	X	-	-	X	-	X	-	-	-	X	X	X
Nivolumab ADA	X	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-

* To be performed prior to Debio 1143 administration; At the time of the safety laboratory assessment;
[1] Just before start of nivolumab infusion;
[2] At the end of nivolumab infusion;
[3] 4 hours after Debio 1143 administration;
[4] 8 hours after Debio 1143 administration.

Table 8-2 Sampling days and times for PK (for Cycle 3 exclusively, irrespective of nivolumab schedule switch)

	Cycle 3										
Cycle day	**1**					**3**	**15**				**17**
Time [h]	**0***	**0.5[1]**	**1.5[2]**	**4[3]**	**8[4]**	**0***	**0***	**1.5[2]**	**4[3]**	**8[4]**	**0***
Part A											
Nivolumab PK	X	-	X	-	X	X	X	X[#]	-	-	X
Debio 1143 PK	X	X	X	X	X	X	X	X	X	X	X
Nivolumab ADA	X	-	-	-	-	-	X	-	-	-	-
Part B											
Nivolumab PK	X	-	X	-	-	-	X	X[#]	-	-	-
Debio 1143 PK	X	-	X	X	-	-	X	X	-	-	-
Nivolumab ADA	X	-	-	-	-	-	X	-	-	-	-

* To be performed prior to Debio 1143 administration;
[1] Just before start of nivolumab infusion;
[2] At the end of nivolumab infusion for patients receiving 240 mg Nivolumab on Day 1 and Day 15 (q4w) or 1.5 hours after Debio 1143 administration for patients receiving 480 mg nivolumab on Day 1 (q4w);
[3] 4 hours after Debio 1143 administration;
[4] 8 hours after Debio 1143 administration;
[#] PK done for patients remaining under 240 mg nivolumab on Day 1 and Day 15 (q4w),

Table 8-3 Sampling day and times (for Cycle 6 and EOT exclusively, irrespective of nivolumab switch of schedule)

Cycle	6		EOT[2]
Cycle day	1		
Time [h]	0*	1.5[1]	
Part A and B			
Nivolumab PK	X	-	-
Debio 1143 PK	X	X	-
Nivolumab ADA	X	-	X

* To be performed prior to Debio 1143 administration;
[1] At the end of nivolumab infusion;
[2] At the time of the safety laboratory assessment; For patients entering the Extended study period, the last nivolumab ADA will be collected at C13D1 instead of at EOT.

8.2.4. Pharmacodynamics and predictive biomarkers

Tumor biopsies will be collected as follows:

1. An archived biopsy collected at diagnosis and before any prior PD-1/PD-L1 therapy will be provided, if available.
2. An archived biopsy collected after prior PD-1/L1 therapy will be provided; if not available a percutaneous or endoscopic biopsy will be mandatorily collected during screening.
3. A percutaneous or endoscopic biopsy will be performed (to collect fresh tumor tissue) at the end of Cycle 2, if consented and feasible (optional).

PDy and potentially predictive biomarkers in tumor biopsies may include, but are not limited to [redacted] and markers of cell death and proliferation.

Blood samples for PDy measurements will be collected on Days 1 (pre- and 4 h post-dose Debio 1143), 8, 15 and 22 (always predose) of Cycle 1, and on Day 1 of Cycle 3. PDy and potentially predictive biomarkers in blood [redacted]

For all PDy and biomarker measurements, the windows of tolerance for sample collection are provided in Table 8-5.

8.2.5. Pharmacogenomics and pharmacogenetics

Blood samples will be collected for mRNA analyses (pharmacogenomics [PGx] PAX gene) at baseline and on Day 15 of Cycle 1 and on Day 1 of Cycle 3. Blood for circulating tumor DNA (PGx ctDNA) will be collected on Day 1 of Cycle 1, 3 and 6. A blood sample will be collected at baseline to explore genetic variations in DMET genes (pharmacogenetics [PGt]) associated with differences in the PK disposition of Debio 1143 in combination with nivolumab.

Back-up samples for PDy, PGx, and PGt will be stored in a sample storage facility pending use for further investigations within the scope of the above- mentioned procedures. The maximum storage period will be 15 years.

DNA and RNA samples for future analyses that are not yet defined will be de-identified and re-coded for improved protection of patient confidentiality and stored for 15 years.

Table 8-4 Sampling days and times for PDy and biomarkers

Cycle	**1**					**3**	**6**
Cycle day	**1**		**8**	**15**	**22**	**1**	**1**
Time [h]	**0 h**	**4 h**					
[redacted]	X[1]	X	X[1]	X[1]	X[1]	X[1]	-
Predictive biomarkers	X[1]	-	-	-	-	-	-
PGt	X[1]	-	-	-	-	-	-
PGx PAX gene	X[1]	-	-	X[1]	-	X[1]	-
PGx ctDNA	X[1]	-	-	-	-	X[1]	X[1]

[1] Pre-dose

Table 8-5 Windows of tolerance for PK, PDy and biomarker samples

Time point	**0* (pre-dose)**	**0.5[1]**	**1.5[2]**	**4[3]**
Window of tolerance (nivolumab, Debio 1143, ADA, PDy and biomarkers)	[-2h – 0h] before D1143 intake. No tolerance after D1143 intake	Preferred ± 10 min Acceptable ± 15 min	[-5 min – 30 min] before/after end of nivolumab infusion	± 30 min

* To be performed prior to Debio 1143 administration (i.e. pre-dose samples);
[1] Just before start of nivolumab infusion;
[2] At the end of nivolumab infusion;
[3] 4 hours after Debio 1143 administration;

8.3. Study procedures

8.3.1. Study plan

A visit assessment schedule is presented in Table 8-6 and a detailed timetable for visits, and PK, PDy are detailed in Table 8-1, Table 8-2 and Table 8-3.

Study procedures must be performed according to the planned time schedule with strict adherence to visit intervals. All patients enrolled in the study will attend the study visits as indicated in the study plan.

Prior to conducting any of the screening tests, the Investigator or designee will fully explain the study to the prospective patient and provide him/her with a copy of the Patient Information Leaflet/ICF.

If the patient is willing to participate in the study, s/he and the Investigator or designee will both sign the document. Of note, CT or MRI scans done before screening, as part of the patient's standard of care, if within the accepted window up to 8 weeks (±1 week) before C1D1, can be used instead of repeating a new assessment at screening even if it was done before ICF signature, with patient specific agreement, if deemed clinically appropriate by the Investigator. A separate ICF will be signed for participation in the PGx part of the study (section 8.2.4).

Patients will attend the screening visit(s) within 4 weeks prior to the first treatment cycle. The patient's suitability for the study will be confirmed by the inclusion/exclusion criteria (see section 6).

Table 8-6 Schedule of assessments

		CYCLE																EOT	Follow-up[#]	EOS
	Screening	Baseline	1					2		3				4-13		>13[13]				
CYCLE DAY*	-28 to -1	1	3[11]	8	15	17[11]	22	1	15	1	3[11]	15	17[11]	1	15	1	15			
INFORMED CONSENT	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MEDICAL AND MEDICATION HISTORY[12]	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
INCLUSION/EXCLUSION CRITERIA	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PHYSICAL EXAMINATION	X[µ]	X	-	-	X	-	-	X	X	X	-	X	-	X	-	X	-	X	-	-
ECOG, VITAL SIGNS	X	X	-	X	X	-	X	X	X	X	-	X	-	X	X	X	-	X	-	-
CONCOMITANT MEDICATIONS	X	X	X	X	X	X	X	X	X	X	-	X	-	X	X	X	-	X	X	-
DIGITAL, TRIPLICATED 12-LEAD ECG[1]	X	X	-	X	X	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
SAFETY LABORATORY SAMPLING[2]	X[2a,b,c,f]	X[2c,e]	X[2d]	X[2c]	X[2c,e]	X[2d]	X[2c]	X[2c,e,f]	X[2c]	X[2c,e,f]	-	X[2c]	-	X[2c,e,f]	-	X[2c,e,f]	-	X[2c,e]	-	-
PREGNANCY TEST[3]	X	X	-	-	-	-	-	X	-	X	-	-	-	X	-	X	-	X	X	-
CT SCAN OR MRI[4]	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	X	-	X	X	-
TUMOR BIOPSY[5]	X	-	-	-	-	-	-	-	-	Optional	-	-	-	-	-	-	-	-	-	-
PK SAMPLING[6]	-	X	X[6a]	X	X	X[6a]	X	-	-	X	X[6a]	X	X[6a]	X[6b]	-	X[6b]	-	X[6b]	-	-
PDY AND PREDICTIVE BM SAMPLING[7]	-	X	-	X	X	-	X	-	-	X	-	-	-	X[7a]	-	-	-	-	-	-
DEBIO 1143 DISPENSING/ACCOUNTABILITY[8]	-	X			X			X	X	X	X	X		X	X	X	-	-	-	-
NIVOLUMAB DISPENSING/ACCOUNTABILITY[9]	-	X	-	-	X	-	-	X	X	X[9a]	-	+/-	-	X[9a]	+/-	X[9a]	+/-	-	-	-
ADVERSE EVENTS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	X[10]	-

Cycle: Each cycle is defined as of 28 days

EOT: A visit should be performed 30 days (± 5days) after last Debio 1143 dose, unless start of new cancer treatment or end-of-life care before, in which case EOT visit should be ideally scheduled immediately before these events.

Follow-up: A first follow-up (FU) visit is scheduled 90 (± 15) days after last study treatment, a second safety follow-up visit may be scheduled at 5 months (±15 days) after the last nivolumab infusion, provided the first safety follow-up visit did not overlap (± 1 week), and provided that no subsequent anticancer treatment or end-of-life hospice care had been started before. Subsequent visits will be scheduled every 12 weeks (± 1 week) after EOT unless confirmed or symptomatic PD occurred before or any new anticancer treatment or end-of-life care is started, whichever occurs first. Once PD occurs, or start of new treatment, phone calls, email or mail to document survival status will be done every 4 (± 1) months until the end of the Main study period (lasts until 18 months after LPI or 60 days after LPLV, whichever occurs first).

EOS: At the end of the Main study period or at LPLV if patients are ongoing in the Extended study period, whichever occurs last.

* Examinations should be performed in the following order as applicable: physical examination, vital signs, ECG, safety blood/urine samples, followed by blood sampling for PK/PDy according to specific instructions, and other examinations: Note: ECGs always have to be taken before PK/PDy sampling.
Assessments should be performed on schedule, but occasional changes may be allowed. If the study schedule is shifted, both assessments and dosing must be shifted to ensure the collection of data is completed prior to dosing. Windows: Laboratory assessments and clinical examinations: Screening period: -4 days (i.e., day -32); EOT visit: ±5 days; follow up visits ±1week, in case of holidays, vacations; other administrative reasons: ± 3 days in all cycles. Window for CT/MRI assessment = ± 1 week

Assessments for concomitant medications, pregnancy test and AEs will be performed only at the first two FU visits, if applicable. CT scan or MRI assessments will be performed until confirmed iRECIST PD, symptomatic PD or any new anticancer treatment or end-of-life hospice care is started or until EOS whichever occurs first.

µ Height only collected at screening.

1 Digital triplicate 12-lead ECGs will be recorded after 10 minutes of supine rest at the following 3 time points: pre-, 0.5-2h Debio 1143 post-dose (before starting the nivolumab infusion or after nivolumab perfusion was removed) and 4-6 h post-dose ;There should be at least 1 minute between each ECG and all 3 ECGs should be completed within 10 minutes or less. ECG readings must be performed before PK/PDy sampling. ECG reading will be done centrally and also locally for screening purposes.

2 Pre-dose (as per section 8.2.2.5) only required if screening test were performed > 7 days prior to C1D1 or if inclusion/exclusion criteria were not met during screening:

- 2a HIV, HCV and HBV serology testing and CPK and Troponins (I or T whichever is applicable): Only at screening, to be repeated if clinically indicated only.
- 2b FSH/LH and total testosterone (in male) or estrogens (in female patients), free-cortisol (at morning) and ACTH: Only at screening and to be repeated if clinically indicated.
- 2c Hemoglobin, hematocrit, platelets and complete blood cell count and differential counts, creatinine, sodium, potassium, calcium, total bilirubin (if >ULN, then also measure direct bilirubin), ALP, AST, ALT, amylase, lipase, LDH, total protein, albumin, CRP.
- 2d Part A patients (only): Total bilirubin (if >ULN, then direct bilirubin should also be measured), ALP, AST, ALT, and creatinine.
- 2e TSH, FT3 and FT4: At Day 1 and Day 15 in Cycle 1 and every Day 1 of each subsequent cycle.
- 2f CA-125 to be performed at screening within 4 weeks of C1D1, exclusively in applicable patients included in Cohort 4, and to be repeated before start of each new cycle if abnormally elevated before treatment start, unless PD, any new anticancer treatment or end-of-life hospice care is started before.

3 In women of childbearing potential only: blood test at screening (only required if screening test were performed > 7 days prior to C1D1), then urine dipstick test alone would be sufficient, at the beginning of each treatment cycle while on study up to 5 months after EOT.

4 Every 8 weeks (±1 week) from first on-treatment scan until Cycle 10, then from Cycle 13, every 12 weeks (± 1 week) until confirmed iRECIST PD, symptomatic PD or any new anticancer treatment or end-of-life hospice care is started or until the end of the Main study period whichever occurs first. For patients who continue study treatment in the Extended study period, tumor response assessments will be performed at the frequency of local institutional care practice until EOT. All patients will have CT or MRI at the time of disease progression, if none previously available. CT or MRI done before screening, as part of patient's standard of care and not older than 8 weeks (+1-week tolerance) before C1D1 can be used instead of repeating a new assessment at screening even if done before ICF signature with patient specific agreement, if deemed clinically appropriate by the Investigator.
A contrast enhanced brain CT or MRI is mandatorily at baseline only in SCLC cohort, subsequent brain scans to be done if clinically indicated.

5 Up to 3 tumor tissue samples will be collected:

1) An archived biopsy at diagnosis (before prior PD-1/PD-L1 therapy) = optional;
2) An archived biopsy if collected after prior PD1/PD-L1 or, if not available a fresh biopsy collected at screening will be mandatory;
3) A fresh biopsy collected at end of Cycle 2 (day 28=Day 1 of the following cycle) = optional

6 Timepoints as specified in Table 8-1, Table 8-2 and Table 8-3 and windows of tolerance as specified in Table 8-5.

- 6a Patients included in Part A only.
- 6b Debio 1143 PK, nivolumab PK, and nivolumab ADA sample at C6D1only. In addition, for patients discontinuing the study at the end of the Main study period, the last nivolumab ADA will be collected at EOT, and for patients entering the Extended study period, the last nivolumab ADA will be collected at C13D1 instead of at EOT.

7 Timepoints as specified in Table 8-4 and windows of tolerance as specified in Table 8-5.

- 7a Only at Cycle 6: PGx ctDNA.

8 Debio 1143 will be taken orally on D1-10 and D15-24 on an empty stomach (patients will fast for 2 h before dosing and for at least 1 h after dosing) at approximately the same time each day. Water is permitted freely. A missed dose can be taken as soon as the patient remembers but no later than 6 h after the planned dose. If >6 h have elapsed, the missed dose should be skipped and the next dose taken according to the regular dosing schedule. A double dose should not be taken to make up for a missed dose. Debio1143 will be given in the hospital (before nivolumab infusion whenever is applicable) during: Cycle 1 on Days 1,3 (only Part A), 8, 15, 17 (only Part A), 22; Cycle 2 on Days 1 and 15; Cycle 3 on Days 1, 3 (only Part A) , 15, and 17 (only Part A); and on Days 1 ± 15 of all subsequent cycles. The rest of the days will be taken at home following relevant medical instructions. A patient's diary to record treatment compliance will be provided as a separate document and it will be reconciled with the returning capsules by the study nurse.

9 Nivolumab will be administered, as per current prescribing information, at a dose of 240 mg, flat dose by IV infusion over at least 30 minutes on Days 1 and 15, every 4 weeks (i.e., 2 infusions in each cycle).

- 9a From Cycle 3 on, the switch to an administration of 480 mg of nivolumab only on Day 1 of each 28-day cycle is allowed based on the Investigator's judgment and Sponsor's agreement.

± Dispensing of nivolumab will depend on the nivolumab schedule administered from Cycle 3 onwards.

[10] Continuous AE monitoring, with Investigator's assessment and documentation at scheduled study visits up to EOT visit and second follow up visit, if applicable. The SAE reporting period is up to 5 months after the last nivolumab administration. Patients continuing in follow-up (FU) after EOT, in the first and/or second FU visits will have final AEs update of any ongoing toxicity at this time, if applicable, unless start of new anticancer treatment or end-of-life-care, in which case visit should be scheduled ideally before.

[11] For Part B, visits on Cycle 1 and Cycle 3 on Days 3 and 17 will not be performed

[12] Including information on current and previous tobacco and alcohol use/consumption

[13] Only applicable for patients treated beyond Cycle 13

8.3.2. Study discontinuation

For patients prematurely discontinuing the study, date and reason of withdrawal must be recorded in the eCRF. Only non-evaluable patients will be replaced, as appropriate.

8.3.2.1. End of treatment

Treatment with Debio 1143 will be continued until any of the following occurs:

1. Unacceptable toxicity [including, treatment-related NCI-CTCAE v5.0 grade 4 laboratory abnormalities (excluding hematological and/or non-febrile asymptomatic neutropenia/leukopenia)] that does not resolve with appropriate standard medical measures; or intercurrent illness that would, in the opinion of the Investigator, affect assessments of clinical status to a significant degree or compromise the patient's safety;
2. Permanent discontinuation of nivolumab;
3. Treatment delay greater than 4 and 8 weeks (+1-week tolerance) for Debio 1143 and nivolumab, respectively;
4. Need to discontinue Debio 1143 due to toxicity despite dose reduction to 100 mg/d;
5. Prohibited medication as indicated in section 7.7.2 is required/used during the course of the trial. In the event a patient is found to be taking a prohibited medication during the trial, the site should immediately contact the medical monitor. The decision to withdraw the patient will be made in conjunction with the Sponsor;
6. If a critical protocol violation occurs that may preclude safety continuation of the study for the patient, the Sponsor's trial manager will be contacted to discuss if the patient has to be withdrawn from treatment;
7. Symptomatic disease progression documented by RECIST v1.1 or by GCIG criteria (Cohort 4, if applicable) in RECIST non-evaluable patients. However, patients may continue study treatment if, in the Investigator's opinion, there is reasonable evidence of ongoing clinical benefit or suggestion of "pseudoprogression" without excess risk of toxicity or complications for the patients.
8. Confirmed disease progression as per iRECIST;
9. Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study;
10. Withdrawal of patient's consent;
11. Pregnancy or breast-feeding a baby;
12. Start of any subsequent anti-neoplastic therapy (excluding palliative symptomatic localized RT up to 36 Gy total doses for alleviating symptoms e.g. pain, intracranial hypertension, which may continue upon the Sponsor's agreement, if appropriate). These patients will continue only in the OS follow-up.

Patients who discontinue treatment for any of the reasons above will have an EOT visit performed 30 days (± 5 days) after the last Debio 1143 administration date, but prior to any further therapeutic intervention, whenever possible, otherwise an EOT visit should be ideally scheduled immediately before these events. Results of these assessments are to be recorded in the eCRF, together with the reason for treatment discontinuation.

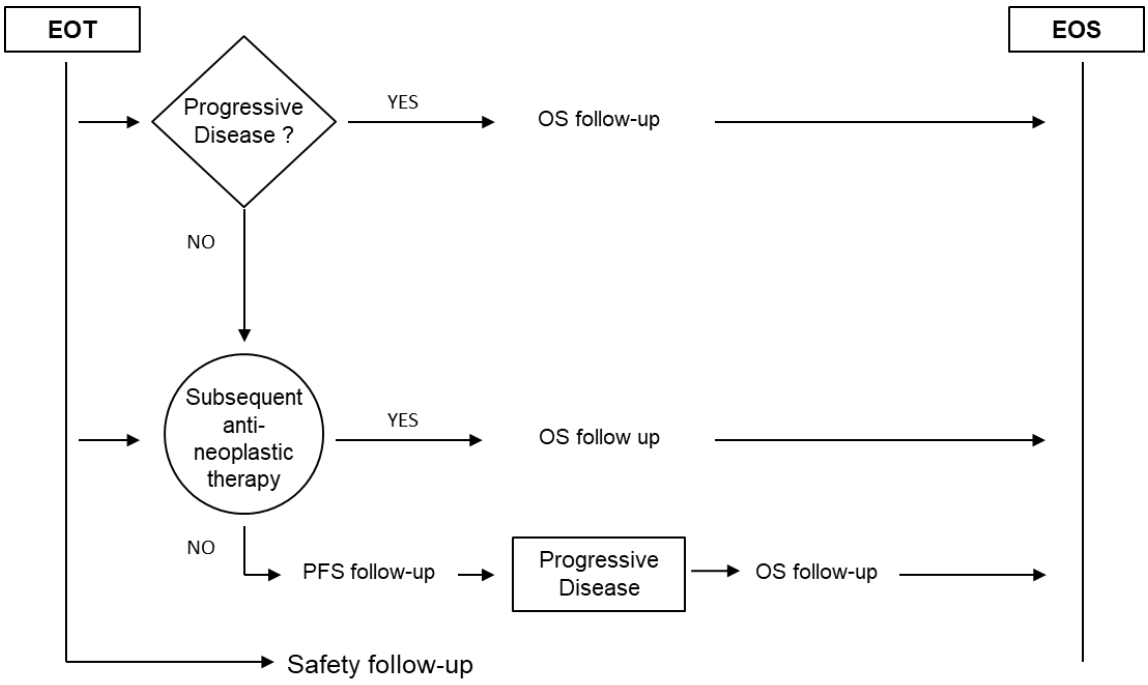
Patients who are taken off study treatment due to AEs are to be treated and followed up according to accepted medical practice. All pertinent information concerning the outcome of such treatment is to be recorded in the eCRF.

8.3.2.2. Follow-up

Patients with confirmed PD at the EOT visit will have an safety follow-up of 5 months (±15 days) planned after the last nivolumab infusion, provided no new cancer treatment or end-of-life care has been started, otherwise this visit may be done immediately before if any of these occur. Patients without PD documented at the EOT visit will continue in follow-up for efficacy every 12 weeks (± 1-week window) until PD or start of new treatment or end-of-life care, whichever occurs first. After PD or new cancer treatment or end-of-life care starts, patients will not attend more onsite visits, however, they and/or relatives may be contacted (by telephone, email or mail) every 4 (± 1) months to update the survival status until the end of the Main study period (18 months have elapsed since the LPI was included in the study or 60 days after LPLV, whichever occurs first).

- Follow-up assessments comprise onsite visits:
- Safety: For all patients, one first safety follow-up visit will be conducted 90 days (±15 days) after last study treatment; a second safety follow-up visit will be scheduled at 5 months (±15 days) after the last nivolumab infusion, provided the first safety follow-up visit did not overlap (± 1 week), and if the patient is still alive and no further anticancer treatment has been started yet..
- Efficacy: Patients without evidence of PD at EOT will be assessed for PD by appropriate methods (CT scan or MRI, and clinically) every 12 weeks (±1 week) until symptomatic PD or confirmed iRECIST PD or start of any new cancer treatment or end-of-life care or the end of the Main study period, whichever occurs first. For patients who continue study treatment after the Main study period, tumor response assessments will continue at the frequency of local institutional care practice until PD, start of any new anti-cancer therapy, death or EOT, whichever occurs first.
- Survival calls/contact: All patients alive after symptomatic progression or confirmed iRECIST PD or start of new anti-cancer treatment will be contacted (by telephone, e-mail or mail) every 4 (± 1) months until the end of the Main study period. In case patients cannot be reached, the primary physician or the patient's partner or family may be contacted by the Investigator or designee.

The following scheme summarizes the temporal relationship between EOT and EOS:



EOS will occur at the End of Main study period or End of Extended study period, whichever occurs last. After the End of Main study period no OS follow-up will be performed for patients in the Extended study period.

8.4. Study duration and EOS

The study duration for an individual patient completing 13 cycles, will be 52 weeks plus up to 5 months for safety follow-up after EOT, excluding a 4-week screening period. Patients will attend the EOT as well as any follow-up visits, if applicable.

Permission to prolong the study treatment for one additional year can be exceptionally granted by the Sponsor, if patients are deriving continuous clinical benefit from the study treatment. Medical justification for extending the treatment and the assessment of the risk/benefit balance must be provided by the Study Investigator and will be discussed with the Sponsor. The decision to further extend study treatment will be re-evaluated on a yearly basis for each patient.

The total number of onsite visits per patient will depend on the total number of cycles delivered which is based on disease progression, clinical deterioration, investigator criteria, unacceptable toxicity or death whichever occurs first.

The EOS will occur at the End of Main study period or End of Extended study period, whichever occurs last.

The Sponsor will make every effort to supply Debio 1143 and nivolumab to patients who benefit from continued treatment; Safety of the patients will be monitored and Health authorities will be notified per regulatory requirements.

Patients will discontinue the study for any of the following reasons:

1. Patient withdrawal of consent;
2. Patient lost to follow-up;
3. Start of end-of-life care;
4. Death;
5. Sponsor or Institutional Review Board (IRB)/ Independent Ethics Committee(s) (IEC) decides to terminate early the study;
6. Completion of Main study period, or completion of Extended study period, as applicable.

9. ADVERSE EVENTS

The Investigator is responsible for detection and documentation of events meeting the criteria and definition of an AE/SAE as provided in this protocol. At each safety evaluation during the study, the Investigator or designee will collect information on unusual manifestations or AEs and SAEs and will record them on the AE page of the eCRF. Their nature, severity, duration, treatment, and relationship with the IMPs as assessed by the Investigator will be recorded. The Investigator will also indicate whether study treatment was discontinued and how the event evolved.

9.1. Definitions and assessment criteria

9.1.1. Adverse event

An AE is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Thus, any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

In particular:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form, instead of signs, symptoms or abnormal laboratory values.
- Pregnancy is not to be considered as an AE; however, it must be monitored as described in Section 9.5.
- Each new episode of a chronic disease (e.g., hay fever, allergy, etc.) from the screening visit should be reported as a new AE.

AEs are illnesses, signs or symptoms (including abnormal laboratory findings) occurring or worsening in the course of the study. AEs can be serious or non-serious. They may or may not lead to the withdrawal of the patient from the study.

9.1.2. Serious adverse event

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

- Results in death;
- Is life threatening (i.e., puts the patient at immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect, or
- Is otherwise medically significant: Important medical events that may not immediately be life threatening or result in death or hospitalisation, but that jeopardize the patient or require intervention to prevent one of the outcomes listed in the definitions above shall also be considered as serious.

All AEs that do not correspond to the definition of SAE are considered as non-serious.

9.1.3. Unexpected or expected adverse events

An unexpected AE is an event whose nature or severity is not consistent with information on the condition under study and/or not consistent with the applicable product information, i.e. the Investigator Brochure.

All AEs that are suspected to be related to the IMP(s) and that are both unexpected and serious are considered to be Suspected Unexpected Serious Adverse Reactions (SUSARs).

9.1.4. Severity of adverse events

AEs will be graded by the Investigator or designee according to NCI-CTCAE, version 5.0.

If a particular AE's severity is not specifically graded by this guidance document, the Investigator is to revert to the general definitions of grades 1 to 5 and to use his or her best medical judgment:

- **Grade 1 (mild):** Causing no limitation of usual activities, the patient may experience slight discomfort.
- **Grade 2 (moderate):** Causing some limitation of usual activities, the patient may experience annoying discomfort.
- **Grade 3 (severe):** Causing inability to carry out usual activities, the patient may experience intolerable discomfort or pain.
- **Grade 4:** Life-threatening
- **Grade 5:** fatal

9.1.5. Relatedness to IMPs

The Investigator or designee will determine the relationship between the AE and the IMPs according to the following criteria:

Reasonable causal relationship:

A clinical event, including laboratory test abnormality,

- Where time relationship to drug administration is at least reasonable, and
- Where other causes (e.g. underlying disease) may not by themselves explain the event, and/or
- Where a clinically reasonable response occurs on withdrawal (dechallenge).

No reasonable causal relationship:

A clinical event, including laboratory test abnormality,

- Where time sequence to drug administration is not reasonable, or
- Where other causes (e.g. underlying disease) can by themselves provide plausible explanations.

9.1.6. Adverse events of special interest

AESIs are

1. for Debio 1143:
    a. AST or ALT increases >3 ULN associated with total bilirubin >2 ULN and ALP <2 ULN
    b. Lipase or amylase increases >5 ULN
    c. Any QTcF prolongation above 30 ms compared to baseline on at least two consecutive readings or other ECG abnormalities such as Torsade de Pointe, ventricular tachycardia, ventricular fibrillation, flutter or any other new cardiac abnormality at the ECG or during the physical examination considered as clinically significant.
2. for nivolumab:
    a. Any AEs that are suspected to be immune-related or infusion-related including drug hypersensitivity, immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies such as: thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus, pituitary disorders; or immune-related

nephritis and renal dysfunction and other immune-related AEs such as: myositis, myocarditis, Guillain-Barré syndrome or uveitis of any grade

All AESIs, occurring after treatment start on C1D1 must be reported to the sponsor in the appropriate eCRF pages. When reporting these cases, it has to be specified in the eCRF whether the case is serious or non-serious. If the AESI(s) is/are serious or considered to be a DLT, then it has to be properly reported within 24 hours of acknowledgement and all applicable SAEs reporting guidelines should be followed (as described in section 9.2) including the reason why it is considered serious.

9.2. Reporting of serious adverse events to the Sponsor

9.2.1. Reporting during the study

The Investigator must notify the Sponsor/Clinical Research Organization (CRO) **of all SAEs within 24 hours of awareness** by completing the AE form provided in the eCRF. Once the AE is selected as a Serious event and the form is saved in the eCRF an email notification will be sent automatically to the Sponsor's Pharmacovigilance department.

If for any reasons the eCRF is not available, as a back-up option the SAE can be declared by e-mail using the Debiopharm International (DPI) paper 'SAE Report form', or by telephone.

1. When reported by e-mail, the 'SAE Report form' will be sent to the following e-mail address: '[redacted]' ([redacted]) or CRO email address if applicable.
2. When reported by telephone, the DPI Pharmacovigilance Officer will be notified as specified in the site study file.

This should be followed by the completion of the AE form in the eCRF as soon as possible

The processes are fully described in separate guidelines and will be provided to investigators with the protocol.

Notification of SAEs does not depend on their relationship with the IMP(s). All SAEs regardless of their relationship with the study drugs and occurring until the last study visit will be reported as described above.

9.2.2. Reporting post-study

Any SAE occurring up to 5 months from the last nivolumab infusion date will be reported in the appropriate eCRF pages and within one day of SAE awareness as described in section 9.2.1

9.3. Follow-up of serious adverse events

All SAEs, regardless of severity, must be followed up:

- To resolution (the patient's health has returned to the baseline status or all variables have returned to normal), or
- Until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event), or
- Until the event is otherwise explained regardless of whether the patient is still participating in the study.

Some events, such as metastases, are often ongoing; however, once these events have been determined by the principal Investigator to be stable or chronic, he/she may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor of any follow-up information in the eCRF pages within 24 hours of new information awareness (see section 9.2.1).

9.4. Procedure for SAE communication

If required by applicable local regulations, the Investigator will promptly notify the relevant IRB/IEC (in addition to the Sponsor) of any SAE (including post-study SAEs and follow-up information) that occurred at their site or was brought to their attention by the Sponsor. The Investigator will verify that the IRB/IEC acknowledges receipt of the notification.

In case of Suspected Unexpected Serious Adverse Reactions (SUSARs), unusual increase in the frequency or the severity of expected SAEs or new safety data which could have an impact on the overall expectedness of a SAR or change in the safety profile of the investigational product(s) that requires the informed consent to be updated, the Sponsor will prepare investigator safety reports according to regulatory requirements relating to safety reporting.

This report will be communicated by the Sponsor to all the investigators involved in clinical studies with Debio-1143 to ensure that any ongoing subjects can be promptly informed.

9.5. Pregnancies

Pregnancies should be avoided during the study. Any patient who nevertheless becomes pregnant must be followed-up until pregnancy outcome is known.

Pregnancies shall be reported from the Investigational site to the Sponsor using a Pregnancy Report Form. The same process and timelines as defined for SAE reporting apply (section 9.2.1). In case of serious outcomes experienced by the parent and/or the fetus/child (definition of 'seriousness' in section 9.1.2), the events should be reported as SAEs using the SAE report form. This procedure applies to pregnancies in female patients as well as to those in female partners of male patients.

10. MONITORING AND STUDY COMMITTEES

10.1. Monitoring

The study Sponsor is Debiopharm International S.A (DPI), Lausanne, Switzerland.

A designated Contract Research Organization (CRO) will perform site monitoring.

At mutually convenient times during the study, the Investigator will let DPI or its representative review all eCRFs and related source documentation, i.e., patient office, hospital, clinic, and laboratory records.

At timely intervals, and at the closing of the study, all IMPs will be accounted for and dispensing records made available to DPI or its representative (see also sections 7.3 and 7.6).

In case eCRFs require support information, DPI may request copies of patient records or other source documents. All the necessary steps will then be taken to protect patient identity. Adherence to local and national laws governing protection of patient identity will be ensured.

10.2. Study committees

10.2.1. Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) will overview study conduct during both parts A and B. It will be composed of at least all actively involved investigators (or their designee), the Sponsor Medical Director and the CRO medical monitor as voting members and will meet regularly to overview the clinical safety of the patients, laboratory data and the conduct of the study. Ad hoc members may be invited as needed.

During Part A, calls will be scheduled monthly or according to patient recruitment as necessary. A charter will be provided as a separate document.

During part B the DSMC will meet approximately every three months, but more frequently if needed due to rapid recruitment. A charter will be provided separately.

11. DATA MANAGEMENT AND STATISTICAL ANALYSIS

11.1. Sample size

- Part A

The sample size will be determined by the number of patients included per dose level and the observed toxicities. Given that (i) a maximum number of two dose levels will be explored, (ii) a classical 3+3 design will be used and (iii) at least 6 patients need to be treated at the RP2D before the phase II part starts formally, between 3-12 evaluable patients will be included. Patients non-evaluable for DLT will be replaced as appropriate.

- Part B

The efficacy of Debio 1143 in combination with nivolumab will be assessed in each cohort using the Bayesian posterior probability with early stopping rules for futility. The primary efficacy endpoint will be the confirmed ORR based on RECIST v.1.1 and/or GCIG (Cohort 4, if applicable). Assuming a futility response rate of 5% below which the response is considered not clinically meaningful and a true response rate of 15% which is considered clinically meaningful, with a maximum sample size of 15 patients per cohort, a cohort will be declared successful if there is at least 80% probability that the true response rate is >= 15%, which corresponds to 4 responses or more. A cohort will be declared futile if there is sufficiently low probability (20%) that the true response rate exceeds 5%. The first futility assessment will be performed after the first 8 patients are assessed and the second one after 11 patients. Futility assessment will be performed using the unconfirmed responses.

The total sample size will be between 32 (if all cohorts are futile) and 60 evaluable patients (if none of the 4 cohorts is futile) and no patient replacement occurs.

11.2. Data management and handling

11.2.1. Data capture, verification and validation

Data entry, verification and validation will be captured using an electronic data capture (EDC) system. EDC system is a web-based computerized system designed for the collection of clinical data in electronic format (electronic case report forms (eCRF)); accessed via an Internet URL link.

EDC system access (username and password) will be provided upon completion and confirmation of prerequisite training. Username and passwords are personal and confidential and must not be shared.

The Investigator and/or designee will accurately, completely, and in a timely manner enter the required study data into the eCRFs. One eCRF will be completed for each patient.

Validation of the eCRF data is performed by i) automatic EDC system checks and ii) other data review tools, such as data listings. Data validation may result in the generation of queries. A query is a request for further information or clarification which may lead to data change. All queries (automatic and manual) will be generated and tracked within the EDC system until resolution. Manual queries can be raised directly into the EDC system by the clinical study team depending on the assigned EDC role throughout the duration of the study.

CRA review, source data verification, is conducted on an ongoing basis and is confirmed in the EDC system. In general, the CRA review is focused on the quality and integrity of the eCRF data.

Data management review is conducted on an ongoing basis, includes the review of all automatic system generated queries and is confirmed in the EDC system. In general, data management review is focused on the completeness and coherency of the eCRF data, and also includes reconciliation of external data versus eCRF data.

Medical review is conducted on an ongoing basis. In general, this review is focused on the completeness and coherency of the safety data.

The EDC system audit trial captures all eCRF data related activities such as: data entry, data modifications, data verification, data lock, e-signature etc.

eCRF data will be extracted from the EDC system into SAS® on a periodic basis and at defined study timepoints for statistical analysis.

11.2.2. Missing data handling for statistical analysis

For missing or partial AEs and concomitant medications dates, conservative conventions will be applied in order to assign the events to corresponding periods. AE will be considered as treatment emergent and the medications will be considered as concomitant if the missing/partial dates cannot definitively exclude the treatment period.

Dates of remote events (e.g., medical history) may be partially incomplete, as the day and/or month may be unknown. Any missing day will be replaced by the 15th and any missing month by June.

Imputation of missing data will be described in detail in the statistical analysis plan.

11.3. Handling of values below (or above) a threshold

To derive PK parameters and for summary statistics (except for calculations involving logarithmic transformations), plasma levels reported as below the LOQ will be considered as 0 when they occur before the first quantifiable concentration. When a plasma level is below LOQ between two quantifiable concentrations within a dosing interval, it will be set to ½ LOQ.

For summary statistics where calculation involves logarithmic transformations (including geometric mean calculation), plasma levels below LOQ will be set to ½ LOQ.

For pharmacodynamics parameters and safety laboratory tests, values below or above the limit of detection will be substituted with the lower/upper limit of detection.

11.4. Handling of unscheduled assessments or retests

The unscheduled assessments and the retests performed before the treatment start will be included in the definition of the baseline which is the last value before the treatment start between the planned assessments, unscheduled assessments and retests.

After treatment start, the unscheduled assessments and retests will be used only in the derivation of endpoints that are not related to a specific timepoint (e.g. worst laboratory parameter level on-treatment). In the timepoint analyses, the original/planned values will be used.

11.4.1. Derived parameters and endpoints

11.4.1.1. Efficacy

Patients without any new anticancer therapy or PD will be assessed for anti-tumor efficacy every 8 weeks (±1 week) during the first 10 cycles and then every 12 weeks (± 1 week) from Cycle 13 onwards until PD occurs or start of a new cancer treatment or end-of-life-care or until the end of the Main study period whichever occurs first. For patients who continue study treatment after the Main study period, tumor

response assessments will continue at the frequency of local institutional care practice until PD, start of any new anti-cancer therapy, death or EOT, whichever occurs first.

Response according to RECIST version 1.1 (38) or GCIG criteria (39) (Cohort 4 for RECIST non-evaluable patients) will be assessed in the efficacy and ITT populations. CR and PR must be demonstrated by objective tumor assessment (CT scan/MRI or CA-125 dosage) and confirmed 4 weeks later. All patients will have a CT scan/MRI or CA-125 dosage at the time of PD. Tumor response will also be assessed by using the novel modified RECIST v1.1 guideline for immunotherapeutics, iRECIST.(40) These exploratory analyses using iRECIST guideline will be presented in detail in the SAP.

In case of premature discontinuation with SD at the EOS visit, this SD will be included in the derivation of efficacy parameters only if the assessment has been performed at least 35 days after treatment start.

The start of a systemic new anti-cancer therapy without prior disease progression could potentially impact the tumor activity observed, hence potentially biasing the evaluation of Debio 1143 anti-tumor activity. As a consequence, no further efficacy data will be collected after the start of any new anti-cancer treatment, except for OS, at least until study data cut-off.

The confirmed response will be used in the primary ORR analysis while a secondary analysis will be performed using the unconfirmed response.

- **Objective response** is derived as any PR or CR recorded after the start of study treatment until disease progression/recurrence is documented, a new systemic anti-cancer therapy is started or analysis cut-off, whichever occurs first.
- **BOR** is the best response (CR, PR, stable disease or disease progression) recorded after the start of study treatment until disease progression/recurrence is documented, a new systemic anti-cancer therapy is started or analysis cut-off, whichever occurs first.
- **Disease control** is derived as any CR, PR or stable disease reported during the study
- **Duration of response** is the time from documentation of tumor response to disease progression, start of a systemic new anti-cancer therapy or analysis cut-off, whichever occurs first.
- **PFS duration** is defined as the time elapsed between treatment initiation and tumor progression or death from any cause, whichever occurs first. Censoring to the last assessment will be applied in the following situations: a) lost to follow-up, b) no progression before analysis cut-off, c) start of a new systemic anti-cancer therapy. The median PFS and the PFS rate at 6, 12 and 18 months will be derived from the Kaplan-Meier curves.
- **OS** is defined as the time elapsed between treatment initiation and death from any cause. In the main analysis, censoring to the last assessment will be applied in the following situations: a) lost to follow-up, b) alive at analysis cut-off. A sensitivity analysis will be performed by censoring the OS at the time of start of a new systemic anti-cancer therapy. The median OS and the OS rate at 12 months will be derived from the Kaplan-Meier curves.

11.4.1.2. Safety

A TEAE is any new, related or non-related, undesirable medical occurrence or change of an existing condition in a patient that occurs during the treatment-emergent period, starting or worsening on or after the first study drug administration and up to 5 months (±15 days) after last nivolumab infusion, or the earliest date of new anticancer therapy – 1 day, whichever occurs first.

11.4.1.3. Pharmacokinetics

Based on sparse plasma concentrations, Debio 1143 and Debio 1143-MET1 PK parameters will be evaluated from the population PK disposition model available to date (36) via a population approach with nonlinear mixed effects modelling using NONMEM® (ICON Solutions). If appropriate, post-hoc estimates

of AUCs, C_{max} and C_{min} will be derived for Debio 1143 and Debio 1143-MET1. Inter- and intra-individual PK variability will be assessed by pooling data of this study with those of other clinical trials.

For nivolumab, serum concentration versus time profiles will be analyzed. If deemed appropriate, nivolumab concentrations will be integrated in a population PK model (37) to estimate relevant PK parameters.

These population PK analyses will be described in a separate analysis plan and reported separately.

If data allow, a non-compartmental PK analysis for Debio 1143 and Debio 1143-MET1 may also be performed using Phoenix™ WinNonlin® (Certara L.A.). As appropriate, this analysis will also be described in a separate analysis plan.

11.4.1.4. Coding

Medical history, AEs, concomitant treatments and/or procedures, and surgeries will be coded per SOC and PT using the last available version of the Medical Dictionary for Regulatory Activities (MedDRA). Past and concomitant medications will be coded per anatomical therapeutic chemical (ATC) class levels 2 and 4 using the last available World Health Organization (WHO) Drug Dictionary.

11.5. Selection of patients for statistical analysis

11.5.1. RP2D population (part A only)

Patients will be considered as not evaluable for DLTs and excluded from the RP2D population, if they did not receive at least 70% of Debio 1143 (i.e., a maximum of 6 missed Debio 1143 doses) and at least one nivolumab dose as planned in Cycle 1 for any reason other than DLT.

Patients not evaluable for DLT will be replaced if there are less than 3 evaluable patients by cohort.

If a treatment modification during the DLT period leads to a potentially non-evaluable patient, the final decision regarding the patient's evaluability will be taken only at the end of his/her DLT period. If the patient experiences a DLT, he/she will be considered as evaluable regardless his/her exposure.

11.5.2. Safety population

The safety population is defined as enrolled patients who received at least one dose of any study drug.

11.5.3. ITT population

The intention-to-treat (ITT) population will include all enrolled patients who took at least one dose of any study drug. This is to exclude the patients who took no trial medication. Therefore, the ITT population is identical with the current Safety population.

11.5.4. Efficacy population

The efficacy population is defined as patients who have:

- measurable disease according to RECIST v1.1 and/or GCIG criteria (Cohort 4, if applicable)

  and

- a baseline tumor assessment and at least one post-baseline tumor assessment, either CT or MRI for RECIST evaluable patients, or CA-125 dosage performed after baseline, if applicable,

  or

- treatment discontinuation occurred before the efficacy assessment was done due to treatment failure, defined as: death, unacceptable toxicity, clinical deterioration and/or symptoms worsening

Patients with treatment failure will not be replaced and will be included in the efficacy population.

In case of non-permitted concomitant treatments or critical protocol violations that may affect the patient benefit/risk balance (i.e., non-eligibility criteria), efficacy data assessed after such protocol violations will be excluded from the efficacy analysis, as appropriate, but the patient will be kept in the efficacy population. This will be described in detail in the statistical analysis plan (SAP).

11.6. Statistical analysis

The statistical analysis described below corresponds to what is foreseen during the planning of this study. If during the study, circumstances should arise that render this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, a different analysis may be performed. Therefore, the definitive statistical analysis will be described in the SAP. Any deviations from this plan, reasons for such deviations, and all alternative or additional statistical analyses that may be made, will be described in the final report.

Ordinal and continuous data will be presented, in the form of descriptive statistics, as number of patients, mean, standard deviation, minimum, median, maximum, and 95% confidence interval (CI). In addition, for PK parameters (see section 11.6.4.5), the geometric mean, 90% CIs of geometric means, the standard deviation of the geometric means, and geometric coefficient of variation (CV%) will be presented if applicable. Categorical data will be presented, using contingency tables with absolute and relative frequencies.

For Part A, the results will be reported overall and by dose, while for Part B, the results will be reported by cohort and overall (except for efficacy in case of heterogeneous data and futile cohorts).

All data analyses will be performed using the statistical softwares SAS®, R, NONMEM®, and Phoenix™ WinNonlin®.

11.6.1. Part A

Due to the nature and design of the study, the statistical analysis of the dose-optimization part will be mostly descriptive unless otherwise specified.

11.6.2. Part B

Part B of the study is an exploratory basket trial intended to assess the preliminary efficacy of Debio 1143 in combination with nivolumab in four indications and promising efficacy results should be further evaluated in subsequent trials. Due to the exploratory nature of the trial, there will be no formal hypotheses testing.

Bayesian posterior probability will be used for the early stopping rules for futility and to assess the efficacy. The claim of efficacy will be based on the primary endpoint (confirmed ORR), while the futility stopping rules will use the unconfirmed ORR.

Recruitment will be stopped in the futile cohorts. A homogeneity test will be conducted in the non-futile cohorts showing a confirmed response rate of at least 15%. In case of homogeneous response rates across the cohorts, efficacy data will be pooled and all the efficacy endpoints will be reported overall and by cohort. Otherwise, the efficacy will be reported by cohort only. The efficacy of the futile cohorts and of the cohorts with less than 15% response rate will be reported separately.

All other endpoints such as demographics, baseline characteristics, safety, PK, PDy, etc. will be presented overall and for each cohort.

11.6.3. Interim analyses

Part A

No formal interim analysis will be performed during the dose-optimization part; review of ongoing data will be done when dose increase, repeat or decrease is to be decided at DSMC meetings.

Part B

There will be two interim futility analyses in each cohort. The cut-off for the futility analyses is defined as the time when the last ongoing patient from the first 8/11 evaluable patients has at least 2 post-baseline tumor assessments or prematurely discontinued.

No formal interim analysis will be performed during the futility monitoring. Only the number of patients with, at least, unconfirmed responses as per RECIST v1.1 and/or GCIG criteria (if applicable) will be checked vs. the futility boundaries in each cohort independently.

Bayesian posterior probability of the unconfirmed objective rate will be used for the early stopping rules for futility.

A general confirmed response rate of 15% is considered as promising, justifying further development. This corresponds to approximatively 17% unconfirmed response rate. On the other hand, 5% is considered to be the general futility response rate (unconfirmed).

Assuming a probability confidence threshold for futility stopping of 20%, and a maximum sample size of 15 patients by cohort, the futility stopping boundaries are defined for each cohort as follows:

- 0 unconfirmed response out of 8 evaluable patients for the first interim analysis and
- ≤1 unconfirmed response out of 11 evaluable patients for the second interim analysis.

Consequently, if no unconfirmed objective response is documented as per RECIST v1.1 and/or GCIG criteria (if applicable) after the 8th evaluable patient is assessed, futility will then be concluded and the recruitment will be stopped in the corresponding cohort. In case at least one unconfirmed response is documented in the first 8 evaluable patients, recruitment shall continue up to 11 evaluable patients and a second futility analysis will be conducted. If at least two unconfirmed responses are documented in the first 11 evaluable patients, the recruitment will continue up to 15 evaluable patients; otherwise the recruitment will be stopped. The early stopping for futility is binding.

11.6.4. Final analysis

The final analysis will be performed within one year of the End of the Main study period (which lasts until 18 months after LPI or 60 days after last LPLV, whichever occurs first).

Data collected after the Main study period for patients entering the Extended study period, will be summarized using descriptive statistics and included in an addendum to the Final CSR.

The main study results will be presented separately for both study parts. An exploratory analysis will be conducted by pooling demographics, baseline characteristics and safety, data from both study parts. In addition, if homogeneity tests allow, and any specific cohort population is adequately represented in Part A, efficacy data form both study parts may be pooled exploratory, as appropriate.

In Part B, according to the Bayesian posterior probability used in each non-futile cohort at the final efficacy assessment conducted in the 15 evaluable patients, the first proof of efficacy will be claimed if at least four confirmed responses are reported in these 15 evaluable patients. This efficacy boundary was derived assuming a confirmed ORR of 15% and a probability confidence threshold of efficacy of 80%.

A homogeneity test of the primary endpoint will be conducted in the non-futile cohorts showing a confirmed response rate of at least 15%. In case of homogeneous response rates across the cohorts, efficacy data will be pooled and all the efficacy endpoints will be reported overall and by cohort. Otherwise, the efficacy will

be reported by cohort only. The efficacy of the futile cohorts and of the cohorts with less than 15% response rate will be reported separately.

All other endpoints such as demographics, baseline characteristics, safety, PK, PDy, etc. will be presented overall and for each cohort.

11.6.4.1. Disposition of patients, demographic and baseline data

Disposition of patients enrolled and treated will be presented with reasons for patient discontinuation if applicable. The number of patients at each study visit will be tabulated. Frequency distribution of adherence to the visit schedule and assessments will be given according to the protocol schedule.

Demographic and baseline data will be summarized overall and by dose for each study population. Ordinal and continuous data will be presented as descriptive statistics, i.e. median, mean, standard deviation, min-max and 95% CI. Characteristics of baseline categorical parameters will be presented as contingency tables with absolute frequencies and percentages, and with 95% CI where applicable.

Medical history and prior anti-cancer treatments will be presented for the safety population as the number/proportion of patients and the number of mentions. Medical history and prior anti-cancer treatments will be classified by the MedDRA dictionary, per SOC and PT and/or by the WHO drug dictionary by ATC class levels 2 and 4.

11.6.4.2. Investigational medicinal product, concomitant medication, and illnesses

Extent of exposure

Extent of exposure will be summarized in the safety, efficacy and RP2D populations for Debio 1143 as follows:

- The number of administrations and total cumulative dose will be summarized as descriptive statistics;
- Treatment delays and dose reductions will be summarized as descriptive statistics;

For nivolumab, the extent of exposure will be summarized in the safety, efficacy and RP2D populations as follows:

- The number of cycles and total cumulative dose will be summarized as descriptive statistics;
- Treatment delays and dose reductions will be summarized as descriptive statistics;
- The treatment-specific window used for the selection of the “exposure on-treatment period” safety and efficacy assessments is defined as:
- Debio 1143: last administration + 5 half lives (~32 hours)
- Nivolumab: last administration + 14 or 28 days as applicable (depending on nivolumab schedule used in last cycle)

Concurrent diseases, concomitant medications, procedures and surgeries will be presented in the Safety population as the number/proportion of patients and the number of mentions. Concomitant procedures and surgeries will be classified by the MedDRA dictionary, per SOC and PT. Concomitant medications will be presented using the WHO drug dictionary by ATC class levels 2 and 4.

Concomitant medications will be split into three categories: pre-medications (medications administered only before treatment start), co-medications (medications administered during investigational product administration) and post-medications (new anticancer therapies started after treatment stop). If applicable, procedures and surgeries will be split as pre-, concomitant, and post-treatment.

11.6.4.3. Efficacy

The efficacy analysis will be presented in the efficacy and ITT population. The main analysis will be conducted in the efficacy population.

The Bayesian posterior probability will be used to preliminary assess the primary efficacy endpoint: the confirmed ORR as per RECIST v1.1 and/or GCIG criteria, if applicable. The unconfirmed ORR will be used for the early futility stopping rules.

The main metrics of the Bayesian efficacy monitoring via posterior probability are the following:

- Denote θ as the response rate. The prior distribution of θ is: $\theta \sim \text{Beta}(a_0, b_0)$
- Let R be the number of responses in n observations, $R \sim Binomial\ (\theta, n)$.
- The posterior distribution of θ given observed r responses and $n-r$ no responses is: $\theta \mid r, n \sim \text{Beta}(a_0+r, b_0+n-r)$.
- For efficacy monitoring, the following decision rules are introduced:
  1. Early stopping for futility: let θ_{fut} be the reference response rate for futility monitoring and P_{fut} be the probability confidence threshold for futility. The trial should be stopped early and the treatment is declared inefficacious if
  $$Prob(\theta \leq \theta_{fut} \mid r, n) > P_{fut}.$$
  2. Criterion for declaring efficacy: let $\theta_{eff,\ final}$ be the reference response rate for declaring efficacy at the final stage, and $P_{eff,}$ be the probability confidence threshold for final efficacy. The treatment is declared efficacious at the end of the trial if
  $$Prob(\theta > \theta_{eff,final} \mid r, n) \geq P_{eff,final}.$$

In this trial, the metrics are the following:

Table 11-1 Metrics and corresponding values

Metric	Value
Reference response rate for futility monitoring (θfut)	0.05
Probability confidence threshold for futility stopping ($Pfut$)	0.2
Reference response rate for efficacy ($\theta eff,final$)	0.17 for confirmed ORR and 0.17 for unconfirmed ORR
Probability confidence threshold for declaring efficacy ($Peff,final$)	0.8
Prior distribution for theta: Beta (a0,b0)	(0.5, 0.5)
Maximum number of patients by cohort	15

The early futility stopping boundaries are the following:

Table 11-2 Futility Early stopping boundaries

# Patients (inclusive)	# Responses (inclusive) are considered futile	Actions
8	0	Early stopping
9	0	Early stopping
10	0	Early stopping
11	0 | 1	Early stopping
12	0 | 1	Early stopping
13	0 | 1	Early stopping
14	0 | 1	Early stopping

At the final analysis, the efficacy boundaries are the following:

Table 11-3 Boundaries for declaring efficacy

# Patients (inclusive)	# Responses (inclusive) are considered efficacious	Actions
15	4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15	Claim efficacy

At the final analysis, a homogeneity Fisher exact test with a significance level of 0.3 will be conducted in the non-futile cohorts showing a response rate of at least 15%. If the primary endpoint homogeneity assumption is confirmed, it will be reported in the pooled cohorts as the absolute and relative frequencies with a one-sided exact binomial confidence interval at an alpha level of 0.05. Otherwise, the confirmed ORR will be similarly reported in each cohort separately.

The efficacy of the futile cohorts and of the cohorts with a confirmed response rate lower than 15% will be reported separately.

ORR, BOR and DCR will be presented using contingency tables with absolute and relative frequencies. Time-to-response, DOR, PFS and OS medians and rates will be determined using the Kaplan-Meier method.

11.6.4.4. Safety

Safety analysis will be reported in the safety population

Dose limiting toxicities (Part A only)

The number and proportion of patients with DLTs will be presented overall and by dose and will be plotted vs. dose.

Treatment emergent adverse events

Frequencies of TEAEs including those leading to treatment discontinuation, as well as SAEs will be summarized by SOC and PT. AEs will also be tabulated by SOC and PT including maximum severity grade according to the NCI-CTCAE criteria version 5.0 and relationship to treatment.

Laboratory parameters

Safety laboratory parameters at each timepoint will be presented by dose as descriptive statistics. Shift tables based on the NCI-CTCAE version 5.0 toxicity grading will be presented for each laboratory parameter between pre-treatment and worst case on-treatment. The worst on-treatment assessment is determined by the value corresponding to the highest NCI-CTCAE version 5.0 toxicity grade. For parameters presenting both hyper- and hypo- NCI-CTCAE toxicities, both changes to lowest and highest on-treatment values will be presented as shift tables.

Scatter plots showing pre-treatment vs. lowest/highest on-treatment levels will be presented for each laboratory parameter. Clinically significant changes in laboratory values will be discussed on a case by case basis.

Vital signs

Vital signs at each timepoint will be presented as descriptive statistics. Shift tables from baseline to the worst on-treatment values will be provided by dose level using category defined below. The worst on-treatment value is defined as the most extreme change from baseline, i.e. the maximum absolute change from baseline. The limits for defining the three shift categories refer to the magnitude of the change from pre-treatment to worst case. For blood pressure (BP), the three categories are defined as: "Change to Low" (decrease from pre-treatment >20 mmHg), "No change" (change from pre-treatment within ± 20 mmHg) and "Change to High" (increase from pre-treatment >20 mmHg). The limit for pulse rate is set to 20 beats per minute (bpm). Scatter plots will be produced, presenting the highest and lowest on-treatment results in separate figures for each vital signs.

ECOG-PS

ECOG-PS will be presented as contingency tables by assessment timepoint.

ECG

Digital High-Quality ECG will be obtained by triplicate at pre-treatment, on-treatment, and change from pre-treatment to on-treatment will be analyzed centrally and will be presented as descriptive statistics, as appropriate. The number and percentage of patients with significant QTcF prolongation will be reported as contingency tables. Significant QTcF prolongation is defined as an interval >500 ms or an interval which increases by 60 ms over baseline. Several QTc prolongation analyses using different categories limits (>450, >480 and >500 ms, as well as increases from baseline of >30 ms and >60 ms) will be performed as per ICH-E14 guidelines.

11.6.4.5. Pharmacokinetics

PK concentrations will be presented by timepoint and by dose (Part A) and overall and by cohort (Part B) as descriptive statistics for Debio 1143 and Debio 1143-MET1.

Descriptive statistics will include the number of patients, arithmetic mean, standard deviation, minimum, median, maximum, CV%, geometric mean, standard deviation of the geometric mean, geometric CV%, and 90% CI of geometric mean.

Graphic displays of plasma concentration vs. time curves will be presented individually by patient and as arithmetic means ± arithmetic standard deviations using linear/linear scales and as geometric means ± geometric standard deviations using log10/linear scales.

PK parameters will be listed by patient and summarized as descriptive statistics.

PK data will be presented similarly for nivolumab, when applicable.

The relationship between PK disposition and clinical response, PDy, QTcF variations, safety and genetic variations in DMET genes will be analyzed by regression methods or association analyses.

11.6.4.6. Pharmacodynamics

Pharmacodynamics at baseline, at any scheduled visit, and the corresponding fold changes (log2) from baseline will be presented using descriptive statistics. The maximum increase on-treatment will be similarly presented, along with its fold change from baseline.

Graphics displaying PDy parameters absolute values and fold changes from baseline will be presented as individual curves and mean curves (±standard deviation) vs. time.

Exploratory data analyses will be conducted to investigate the relationship between PDy biomarkers and efficacy and safety parameters by using regression methods.

11.6.4.7. Pharmacogenetic factors and predictive biomarkers

Pharmacogenetic factors and predictive biomarkers assessments are exploratory. The relationship between efficacy, pharmacogenetic factors and predictive biomarkers will be analyzed by regression methods.

12. SPONSOR AND INVESTIGATOR OBLIGATIONS

12.1. Good Clinical Practice and Declaration of Helsinki

This trial will be conducted in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (and the ethical principles that have their origin in the Declaration of

Helsinki [see Appendix A in Section 14.1] and its subsequent amendments) as well as with all the applicable local regulations for clinical trials involving human subjects.

12.2. Institutional Review Board / Independent Ethics Committee

The study protocol, ICF, and any other relevant study documentation must be reviewed and approved by an appropriate IRB/IEC that conforms to local laws, prior to enrolment of patients into the study. It is the responsibility of the Investigator to assure that all aspects of the institutional review are conducted in accordance with local regulations and applicable ICH GCP. A letter documenting IRB/IEC approval (in which the protocol [title and protocol number] is specifically identified) and a list of IRB/IEC members and affiliations must be received by the Sponsor prior to initiation of the study. If applicable, the Investigator is responsible for submitting an Investigator Progress Report to the IRB/IEC in time for the IRB/IEC to carry out review prior to the expiration date of the current IRB/IEC approval. This is required as long as the study is ongoing.

The Investigator will inform the IRB/IEC of the completion or early termination of the study.

Every serious or unexpected AE that might affect patient safety must be brought to the attention of the IRB/IEC by the Investigator. Similarly, every report from the Sponsor concerning an AE must be brought to the attention of the IRB/IEC by the Investigator if applicable as per local guidelines.

12.3. Informed consent

The Investigator or designee will ensure that signed ICF in accordance with the Declaration of Helsinki, local laws, and all applicable regulatory requirements, is obtained from each potential patient prior to any study related procedure. The informed consent process will be documented.

Each patient will be given oral and written information in an easily understandable language describing the nature and duration of the study. This must take place under conditions where the patient has adequate time to consider the risks associated with study participation.

A least one original of the ICF will be signed by the patient (and/or legal authorized representative [guardian, next of kin, or other authorized individual] if applicable) and the Investigator or designee. One signed original or a copy of the original will be given to the patient and the original one will be kept in the Investigator file at the study site.

12.4. Patient confidentiality

The Investigator will ensure that patient reports and samples are identified only by a patient identifier to maintain patient confidentiality. All patient study records will be kept safely in an access-controlled area. Identification code lists linking the patient names to identifiers shall be stored separately from patient records. Clinical information will not be released without written permission from the patient, except for monitoring and/or audit by Regulatory Authorities or the study Sponsor.

12.5. Data reporting and electronic case report forms

The Investigator and/or designee will accurately, completely, and in a timely manner enter data resulting from execution of the protocol into eCRFs made available by the Sponsor via an EDC system, i.e. a web-based computerized system designed for the collection of clinical data in electronic format. One eCRF will be completed for each patient and must be electronically signed and dated by the principal Investigator or may be signed by the study Co-investigator on behalf of the principal Investigator. Corrections in eCRFs will be recorded in an audit trail. The data will be extracted from the eCRF database periodically after interim and final database locks. At the EOS, each site will be given a CD-ROM with all study data entered by EDC.

12.6. Retention of data

The Investigator will maintain adequate study records including the CD-ROM with electronically collected study data, medical records, laboratory reports, ICFs, drug disposition records, safety reports, information regarding participants who discontinued and other pertinent data, such as letters and administrative documents exchanged between the Sponsor and the center. Records can be in paper or electronic format.

All study records must be retained by the Investigator for the maximum period of time authorized by the hospital, institution or surgery but in no case for less than **15 years** after study completion.

To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records or if leaving the institution where the study was conducted. The Investigator will notify the Sponsor in the event of accidental loss or destruction of any study records.

12.7. Deviations from the protocol/protocol amendments

As per Sponsor's standard practice, in general, no waivers will be granted. In case of medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Sponsor and/or the CRO medical monitor and the IRB/IEC will be immediately notified of the type of emergency and course of action taken. Permanent changes to or deviations from the protocol will be formalized in an amendment to the protocol.

The amendment must be approved by the Sponsor, Health Authorities and the respective IRB/IEC prior to implementation. If the change implies a modification of treatment or of patient evaluation tests, a new version of the ICF must be prepared and submitted for approval to the IRB. The Sponsor will assume any responsibility or liability resulting from a change in the protocol, only if the change has been approved in writing by himself and the IRB/IEC.

The Sponsor will promptly notify the relevant Health Authorities, IRB/IEC and/or Investigators, as applicable, of any confirmed serious protocol deviations that may have an impact on subject safety or increase the risk/benefit ratio as a result for any participating subjects.

12.8. IMP accountability

The Investigator must maintain accurate records of the IMP(s) received from the Sponsor. These records will include receipt, preparation (for nivolumab), and dispensing dates, and dates of return and/or destruction of unused supplies.

At trial termination, clinical supplies must be accounted for and a written clarification provided in case of discrepancies. All unused supplies must be properly destroyed at the study site or returned promptly to the Sponsor; written authorization from the Sponsor must be obtained prior to destruction which must be documented.

When the above tasks are delegated to a pharmacist, the Investigator remains ultimately responsible for the maintenance of accurate drug dispensing records.

12.9. Study monitoring

At agreed times during the study and after the study has been completed, the Investigator will let Sponsor representatives periodically review the eCRF and corresponding office, hospital, and laboratory records (source documents) of each study patient. The eCRFs must be completed by the Investigator on a regular basis and prior to each monitoring visit.

Monitoring visits allow the Sponsor or a mandated CRO to evaluate study progress, verify accuracy and completeness of eCRFs, resolve any inconsistencies in the trial records, and ensure that all protocol requirements, applicable local laws, ICH guidelines, and Investigator obligations are fulfilled.

12.10. Sponsor audits

During the study or after the study has been completed, the Investigator will allow Sponsor representatives or external auditors to conduct an audit of the study. The purpose of the audit is to evaluate compliance with GCP guidelines, applicable regulations, the study protocol and the Sponsor's procedures, and to assess accuracy of the study data.

Before the audit, the Investigator will be contacted by the monitor to arrange a convenient time for the visit. Investigator and staff are expected to be present, co-operate with the auditors, and allow access to all patient records supporting the eCRFs, and other study-related documents.

12.11. Regulatory agency inspections

The Investigator may undergo a Regulatory Agency/IRB/IEC inspection during the study or after the study has been completed. The purpose of such an inspection is to conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial.

The Investigator and staff are expected to be available for the inspection and allow access to patient records supporting the eCRFs and other study-related documents. If given advance notice of this inspection, the Investigator must contact the Sponsor immediately.

12.12. Publications

A scientific communication/paper related to this study will be published as agreed between the Sponsor and the Investigator and after review of the final draft by the Sponsor.

The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.

12.13. Insurance policy

The Sponsor will subscribe a liability insurance covering his and the Investigator's responsibility as well as the responsibility of any person involved in the conduct of the study, provided there is proper adherence to the protocol. An insurance certificate will be provided by the Sponsor to the IRB/IEC if required.

12.14. Premature study termination

The trial may be prematurely terminated by the Sponsor, the Investigator, or the IRB/IEC at any time. If the study is prematurely terminated, the Investigator must promptly inform the study patients and ensure that they receive appropriate therapy and follow-up. All procedures and requirements pertaining to study closure as defined by the Sponsor will be carried out.

If the Investigator terminates the trial, he/she should promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation of the termination. If the Sponsor terminates the trial, the Investigator should promptly inform the IRB/IEC and provide a detailed written explanation of the termination. If the IRB/IEC terminates the trial or suspends its approval, the Investigator should promptly inform the Sponsor and provide a detailed written explanation of the termination.

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14. APPENDICES

14.1. Appendix A: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

RISKS, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in

writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative.These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informedconsent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethicscommittee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information -must also be disclosed to participants during the informed consent process.

RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be

made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

14.2. Appendix B: Prohibited medications and special warnings

Special drug warnings/recommendations and prohibited medications with Debio 1143 concomitant intake

The Trade names of this list are provided for sake of information. Trade names are based on "Dorosz" – Guide pratique des medicaments 2016 and "VIDAL – Le Dictionnaire" 2016 and are consequently mainly reflecting Trade names routinely used in France. For other countries, investigators should refer to the International Nonproprietary Name (INN)

A. Anesthetic and analgesic drugs

The drugs below present a high drug-drug interaction (DDI) risk with Debio 1143. Their starting dose should be carefully considered based on table footnotes. If their use is clinically indicated, they can be used but close clinical monitoring is strongly encouraged, particularly within one week from starting treatment or after any dose adjustment.

International Nonproprietary Name (INN)	TRADE NAME
Anesthetic drugs	
Alfentanil[1]	Rapifen
Analgesic drugs	
Fentanyl [1]	Abstra, Effentora, Instanyl, Pecfent, Durogesic, Matrifen, Fentanyl
Morphine[2]	Morphine Injectable, Actiskenan, Oramorph, Sevredol, Morphine Cooper, Moscontin Lp, Skenan Lp, Kapanol Lp

[1] Risk of DDI due to Debio 1143 inhibition of CYP 3A4. Clinical impact may result in an increase of exposure with higher clinical effects of alfentanil and fentanyl at standard doses. Clinical monitoring of effects is warranted.
[2] Risk of DDI: Concomitant use of Debio 1143 may increase the exposure (and consequently clinical effects) of morphine. Therefore, careful monitoring of patients for signs of respiratory and central nervous system depression is recommended.

B. Gastric mucosal protectants

Gastric mucosal protectants must be taken at least 2 hours before or 2 hours after Debio 1143 intake. Patients should be instructed accordingly.

International Nonproprietary Name (INN)	TRADE NAME
Actapulgite de Mormoiron	Actapulgite
Crospovidone	Bolinan
Carbolevure	Carbolevure
Charcoal, Activated, dimeticone, simeticone	Carbosylane
Charcoal, Activated	Charbon de Belloc
Macrogol	Forlax
Attapulgite de Mormoiron	Gastropulgite
Aluminum hydroxide and Magnesium trisilicate	Gaviscon
Aluminium hydroxide and magnesium hydroxide	Maalox

Dimeticone and Guaiazulene	Pepsane
Povidone	Poly-karaya
Dimeticone	Polysilane
Diosmectite	Smecta
Alginic acid	Topaal

C. Prohibited food and herbal preparations

- Grapefruit juice and grapefruit-containing products.
- St John's Wort (= millepertuis) and St John's Wort-containing products.

D. P-gp inhibitors/inducers prohibited

International Nonproprietary Name (INN)	TRADE NAME	SUGGESTION OF ALTERNATIVE DRUGS (IF APPLICABLE IN ANY CASE)
Amiodarone	CORDARONE	
Atorvastatine	TAHOR, BONTEFEL, CADUET, LIPTRUZET	Preferably Pravastatine or Fluvastatine. Eventually Rosuvastatine
Boceprevir	VICTRELIS	
Cannabidiol	SATIVEX	
Carbamazepine	CARBAMAZEPINE, TEGRETOL	
Clarithromicin	NAXY, ZECLAR, MONONAXY, MONOZECLAR	
Ciclosporine	NEORAL, SANDIMMUN	
Cobicistat	STRIBILD	
Daclatasvir	DACLINZA	
Diltiazem	TILDIEM, BI-TILDIEM, MONO-TILDIEM LP, DELTAZEN LP	
Dronedarone	MULTAQ	
Dipyridamole	CLERIDIUM, PERSANTINE	
Enzalutamide	XTANDI	
Erythromycin	ERY, EGERY, ABBOTICINE, ERYTHROCINE	
Fidaxomicin	DIFICLIR	
Hydroquinidine	SERECOR	
Itraconazole	SPORANOX	
Ivacaftor	KALYDECO, ORKAMBI	
Ketoconazole	KETOCONAZOLE	
Lansoprazole	LANZOR, OGAST, OGASTORO	Preferably Pantoprazole. Eventually Omeprazole or Esomeprazole
Ledipasvir	HARVONI	
Mirabegron	BETMIGA	
Propafenone	RYTHMOL	
Quinine, Quinidine	QUINIMAX, HEXAQUINE	
Ranolazine	RANEXA	
Retigabine	TROBALT	
Rifabutin	ANSATIPINE	
Rifampin	RIFADINE, RIMACTAN	
Rilpivirine	EDURANT, EVIPLERA	

International Nonproprietary Name (INN)	TRADE NAME	SUGGESTION OF ALTERNATIVE DRUGS (IF APPLICABLE IN ANY CASE)
Ritonavir	NORVIR	
Saquinavir	INVIRASE	
Simeprevir	OLYSIO	
Telaprevir	INCIVO	
Telithromycine	KETEK	
Ticagrelor	BRILIQUE	
Tipranavir	APTIVUS	
Tolvaptan	JINARC	
Ulipristal	ELLAONE, ESMYA	
Verapamil	ISOPTINE, TARKA	

Please note that this is not an exhaustive listing; refer to the label of potential comedications to verify whether or not they are strong inhibitors/inducers of P-gp.

E. P-gp substrates that <u>should be avoided, however;</u> If treatment with this medication is clinically indicated, an alternative treatment should be encouraged whenever is possible (examples are provided), otherwise the risk/benefit should be carefully assessed

International Nonproprietary Name (INN)	TRADE NAME	ALTERNATIVE DRUGS
Aliskiren	RASILEZ	
Apixaban	ELIQUIS	
Bilastine	BILASKA, INORIAL	
Colchicine	COLCHICINE, OPOCALCIUM, COLCHIMAX	
Dabigatran	PRADAXA	
Digoxin	DIGOXINE, HEMIGOXINE	
Fexofenadine	TELFAST	
Indacaterol	ONBREZ, BREEZHALER, OSLIF BREEZHALER	
Linagliptine	TRAJENTA	
Loperamide	IMODIUM, ALTOCEL, ARESTAL, IMODIUMLINGUAL, DIASTROLIB	Racécadotril (TIORFAN)
Ondansetron	ZOPHREN	Granisetron (KYTRIL) or Palonosetron (ALOXI)
Paliperidone	XEPLION	
Posaconazole	NOXAFIL	
Riociguat	ADEMPAS	
Saxagliptine	ONGLYZA	
Silodosine	UROREC, SILODYX	
Sitagliptine	JANUVIA, XELEVIA, JANUMET, VELMETIA	
Sofosbuvir	SOVALDI, HARVONI	

F. CYP 3A4 substrates <u>prohibited</u> as per SmPC recommendations

According to the SmPC labelling, concomitant administration of the drugs listed below with a strong CYP 3A4/5 inhibitor such as Debio 1143 is contraindicated (risk of clinically significant increased toxicity or decreased efficacy).

In agreement with the SmPC guidelines, their concomitant intake with Debio 1143 is not allowed by the Sponsor. Please note that this is not an exhaustive listing; refer to the label recommendations for other drugs that are low therapeutic index drugs or sensitive substrates of CYP 3A.

International Nonproprietary Name (INN)	TRADE NAME	ALTERNATIVE DRUGS
Alfuzosine	XATRAL, URION	
Apixaban	ELIQUIS	
Apoxetine	PRILIGY	
Artemether	RIAMET	
Atazanavir	REYATAZ	
Atorvastatin	TAHOR, BONTEFEL, CADUET, LIPTRUZET	Preferably Pravastatin or Fluvastatin. Eventually Rosuvastatin
Avanafil	SPEDRA	
Bosentan	TRACLEER	
Bromocriptine	PARLODEL	
Cinacalcet	MIMPARA	
Ergotamine Dihydrate	DIERGOSPRAY	
Dolutegravir	TIVICAY, TRIUMEQ	
Domperidone	BIPERIDYS	
Ebastine	KESTIN, KESTINLYO	Desloratadine (AERIUS)
Efavirenz	SUSTIVA	
Eletriptan	RELPAX	
Eplerenone	INSPRA	
Ergotamine	GYNERGENE CAFEINE	
Fesoterodine	TOVIAZ	
Fosamprenavir	TELZIR	
Halofantrine	HALFAN	
Indinavir	CRIXIVAN	
Ivabradine	PROCORALAN	
Lopinavir	KALETRA	
Lumefantrine	RIAMET	
Maraviroc	CELSENTRI	
Mizolastine	MIZOLLEN, MIZOCLER	
Manidipine	IPERTEN	
Nevirapine	VIRAMUNE	
Piperaquine	EURARTESIM	
Praziquantel	BILTRICIDE	
Quetiapine	XEROQUEL	
Repaglinide	NOVONORM	
Rivaroxaban	XARELTO	
Rupatadine	WYSTAMM	
Sildenafil	VIAGRA, VIZARSIN, REVATIO	
Simvastatine	LODALES, ZOCOR	
Sirolimus	RAPAMUNE	
Solifenacine	VESICARE	
Tacrolimus	PROGRAF, ADVAGRAF LP, MODIGRAF	

International Nonproprietary Name (INN)	TRADE NAME	ALTERNATIVE DRUGS
Tadalafil	CIALIS, ADCIRCA	
Tamsulosine	JOSIR, MECIR, OMEXEL, OMIX	
Tolterodine	DETRUSITOL	
Vardenafil	LEVITRA	
Voriconazole	VFEND	

G. CYP 3A4 substrates for which close medical monitoring is recommended considering carefully the patient need; narrow therapeutic range or sensitive substrates of CYP 2Cs (2C8, 2C9, 2C19), 2B6, or 1A2

International Nonproprietary Name (INN)	TRADE NAME
Clopidogrel	PLAVIX
Valproic Acid	DEPAKINE, DEPAKINE CHRONO, MICROPAKINE LP
Hydroxyzine	ATARAX

Drugs that are narrow therapeutic range or sensitive substrates of CYP 2Cs, 2B6 or 1A2 should be closely monitored. Some CYP 3A substrates (not prohibited as per paragraph F above) also require close monitoring. Their metabolism may be modified by Debio 1143 resulting in potential increased safety events or decreased efficacy. Please note that this is not an exhaustive listing; refer to the label recommendations for other drugs metabolized by CYP 3A, 2Cs, 2B6, 1A2, or transported by P-gP.

H. Drugs with a known risk of QTc prolongation

Considering that the potential of Debio 1143 to prolong the QTc interval has not yet been fully characterized, caution should be exercised when using Debio 1143 with drugs having a known risk of QTc prolongation (refer to product label or Arizona CERT database at website: http://www.crediblemeds.org). Monitoring of patients' electrolyte levels is strongly recommended.

14.3. Appendix C: Response to treatment criteria

1. **Time point response: patients with target (± non-target) disease as per RECIST criteria, version 1.1***

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR= complete response, PR= partial response, SD= stable disease, PD= progressive disease, and NE= inevaluable

*Reproduced from Eisenhauer et al, 2009 (38)

2. **GCIG CA-125 criteria[µ]**

GCIG-Rustin-modified Criteria for CA-125 Response
Patients will be scored as having attained a CA-125 response if they meet the GCIG-Rustin-modified criteria which require that there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment.

Definition of PFS and duration of response by CA-125
PFS based on CA-125 will be defined as the time from first study drug infusion until the GCIG-Rustin-modified criteria of progression are met, or until the date of death (with or without disease progression). Duration of CA-125 response will be defined as the time between when the CA-125 was first documented to have decreased by 50% in a patient who meets all the GCIG-Rustin-modified criteria for a CA-125 response, and the time the CA-125 is first documented to have risen to the point where the patient meets GCIG criteria of disease progression.

GCIG-Rustin-modified definition of progressive disease according to CA-125 criteria		
	Definition of progression	**Date of progression**
Patients with elevated CA-125 before treatment and normalization of CA-125 during treatment	CA-125 ≥ 2 X ULN documented on 2 occasions**	Date CA-125 is first elevated to ≥ 2 X ULN
Patients with elevated CA-125 pretreatment that never normalizes	CA-125 ≥ 2 X nadir value on 2 occasions**	Date CA-125 is first elevated to ≥ 2 X nadir value
Patients with CA-125 in normal range pretreatment	CA-125 ≥ 2 X ULN documented on 2 occasions**	Date CA-125 is first elevated to ≥ 2 X ULN
**Repeat CA-125 anytime but normally not less than 1 week after the first elevated CA-125 level. CA-125 levels in samples obtained after administration of mouse antibodies or within 4 weeks after surgery or paracentesis should not be taken into account.		

In patients for whom response to treatment is evaluated by both RECIST and CA-125 criteria, the date of response and progression will be the earliest date of the two methods.

[µ]Adapted from Rustin et al, 2004 (41)

3. Comparison of RECIST 1.1 and iRECIST[§]

	RECIST 1.1	**iRECIST**
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD

Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD“

“i” indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumors. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

§ Reproduced from Seymour et al, 2017 (40)

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