DURANCE

a *phase Ib/II study to assess the safety and activity of DURvalumab (MEDI4736) in combination with S-488210/S-488211 vAccine in Non-muscle invasive bladder CancEr*

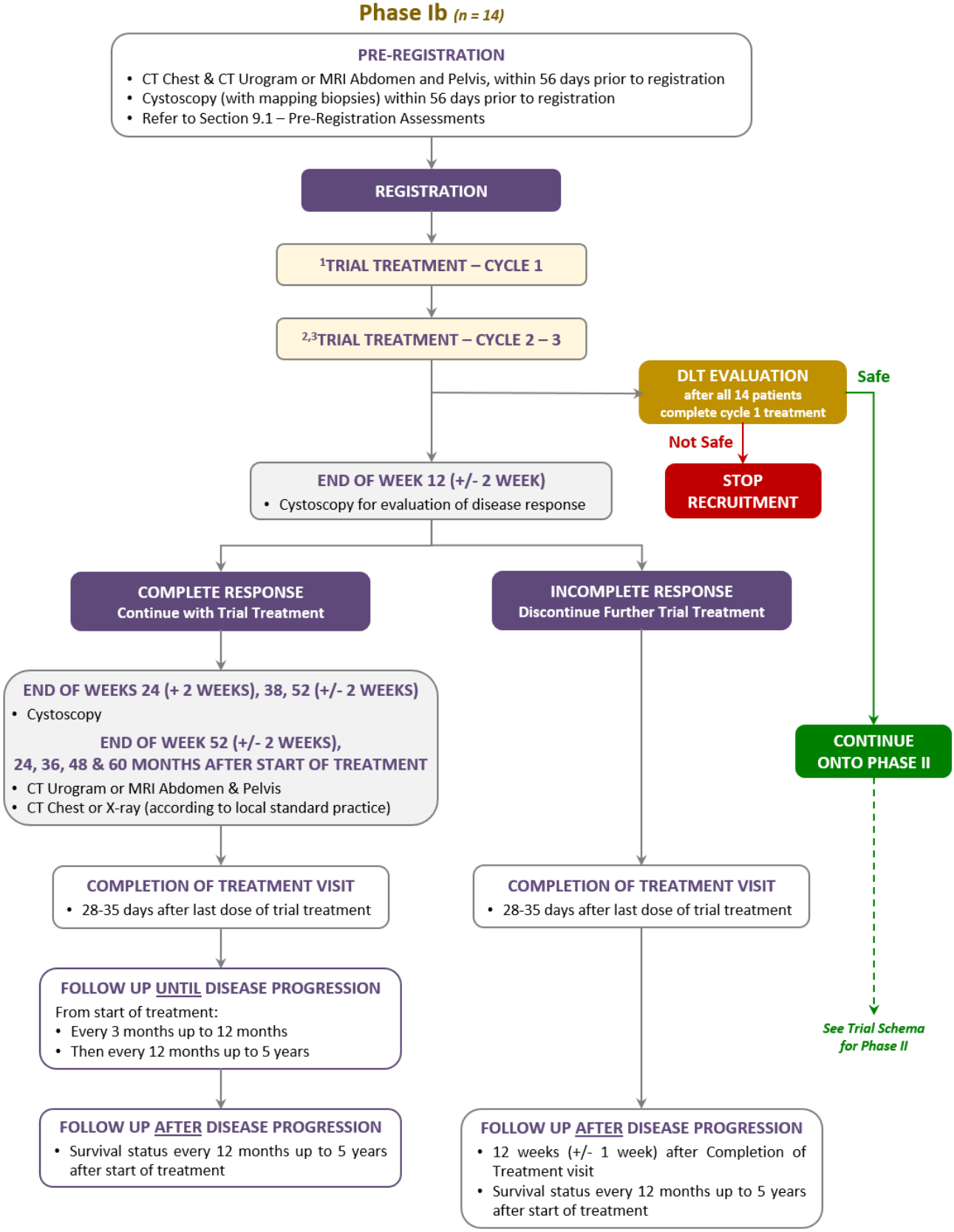
1. SUMMARY OF TRIAL DESIGN

Title:	A phase Ib/II study to assess the safety and activity of Durvalumab (MEDI4736) in combination with S-488210/S-488211 vaccine in non-muscle invasive bladder cancer (NMIBC).
Short title/acronym:	DURANCE
EudraCT no.:	2019-002312-50
Sponsor name:	University College London (UCL/121881)
Funders names & reference:	AstraZeneca & Shionogi
Clinicaltrials.gov no:	NCT04106115
Design:	This is a two part, phase Ib/II, multi-centre study to establish the safety and preliminary activity of S-488210/S-488211 in combination with durvalumab (MEDI4736).
Overall aim:	To establish the safety and clinical activity of combination durvalumab and S-488210/S-488211 peptide vaccine immunotherapy in NMIBC. To correlate an understanding of the tumour immunogenomic landscape with clinical outcomes in this patient group.
Primary endpoint:	• The safety and tolerability of durvalumab in combination with S-488210/S-488211 (assessed using CTCAE v5.0) • 1 year pathological disease free survival rate (1y DFSR) from cystoscopy and mapping biopsies
Secondary endpoints:	• 1y DFSR stratified by HLA-A*02:01 • 5y Overall Survival (OS) rate • Quality of Life (EORTC QLQ-C30 + QLQ-NMIBC24 and EQ-5D-5L)
Exploratory endpoints:	• 1y DFSR stratified by PD-L1 status • 1y DFSR stratified by baseline TIL status • 5y OS rate stratified by PD-L1 status and baseline TIL status • Correlation of plasma cytokine levels with 1y DFSR
Exploratory Biological Studies:	• To understand the mode of action of S-488210/S-488211 in combination with durvalumab • To evaluated the relationship between PD-L1/PD1 expression and DFSR (primary endpoint) • To identify and characterise the immune and genomic landscape of disease resistance to S-488210/S-488211 in combination with durvalumab
Target accrual:	64 patients *(phase Ib – 14, phase II – 50)*
Subjects:	Patients with non-muscle invasive bladder cancer (NMIBC) that have failed or are intolerant of bacillus Calmette-Guerin (BCG) therapy and who cannot have or are refusing cystectomy.
Main eligibility criteria for study:	**Inclusion criteria:** • Histologically proven high-risk NMIBC: — **High-risk tumours:** include any of the following features: T1 lesions, high-grade disease, tumours larger than 3 cm, multiple or recurrent lesions, and CIS • Adequate archival (baseline) tissue sample available for histological assessment (preferable acquired ≤6 months prior to planned start of treatment) • ≥18 years old

	• BCG unresponsive disease or intolerable to BCG therapy • Refused or deemed clinically inappropriate for radical cystectomy • Body weight >30 kg • WHO performance status 0-1 • Adequate bone marrow and organ function • Willing and able to give informed consent • Willing and able to comply with study procedures and schedule • Females must not be pregnant. Females of child bearing age and men must use highly effective form of contraception until 90 days after the last treatment dose administration **Exclusion criteria:** • Any history of autoimmune disease, with the exceptions of thyroid disease on stable treatment and chronic skin disease not requiring systemic corticosteroids • Patients with prior allogeneic stem cell or solid organ transplantation • Patients who have had prior treatment with anti- PD-1, PD-L1 or CTLA-4 monoclonal antibody or other novel immune-oncology agent(s) • Active invasive malignancy in the previous 2 years excluding non-melanoma skin cancer • History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan (history of radiation pneumonitis in the radiation field is permitted) • Patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity • QTcF value of >470 ms. If prolonged, this should be confirmed by 2 further ECGs each separated by at least 5 minutes • Patients with any of the following risk factors for bowel perforation: — History of acute diverticulitis or intra-abdominal abscess in the last 3 years — History of mechanical GI obstruction or abdominal carcinomatosis • Any unresolved grade ≥2 toxicity from any prior anti-cancer therapy (excluding alopecia, vitiligo, and laboratory test results of bone marrow and organ function defined in inclusion criteria) • Treatment with any experimental drug within 30 days or 5 half-lives (whichever is longer) of the first dose of trial treatment • Any evidence of severe or uncontrolled systemic diseases or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial • Receiving therapeutic oral antibiotics that cannot be discontinued at least 14 days prior to starting treatment or received intravenous (IV) antibiotics within 14 days prior to registration (patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or COPD) are eligible) • Any psychiatric or other disorder (e.g. brain metastases) that impacts the patients ability to give informed consent or comply with trial treatment and activities • Patients must not have had systemic corticosteroid therapy (>10 mg daily prednisolone equivalent) within 14 days prior to registration, or concomitant use of other immunosuppressive medications. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids

	(i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed • Administration of a live, attenuated vaccine within 4 weeks prior to planned start of treatment or anticipation that such a live, attenuated vaccine will be required during the study • Evidence of significant uncontrolled concomitant disease that could substantially increase the risk of incurring AEs, affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis), uncontrolled hypertension, serious chronic gastrointestinal conditions associated with diarrhoea and uncontrolled major seizure disorder • Major surgical procedure within 28 days prior to the first dose of trial treatment, excluding rigid cystoscopy and biopsy • Significant cardiovascular disease, such as: — New York Heart Association cardiac disease (Class II or greater) — Myocardial infarction within 3 months prior to registration — Unstable arrhythmias or unstable angina • Patients with uncontrolled Type 1 diabetes mellitus. Patients controlled on a stable insulin regimen are eligible • Patients with uncontrolled adrenal insufficiency • Patients with active hepatitis infection (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. • Known uncontrolled human immunodeficiency virus (HIV) (detectable viral load) or acquired immunodeficiency syndrome (AIDS)-related illness
Number of sites:	~10
Treatment summary:	Patients will receive treatment for up to 24 weeks: • Durvalumab (MEDI4736) is given as 1500 mg IV infusion every 4 weeks for up to 7 doses • S-488210/S-488211 is given as two subcutaneous injections, of S-488210/Montanide and S-488211/Montanide, starting the day after the first dose administration of durvalumab, then weekly for 6 doses and then every 2 weeks for a further 9 doses (up to a maximum of 16 doses)
Investigational products:	**Durvalumab (MEDI4736)** will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. **S-488210/S-488211** are freeze-dried injectable formulations. • S-488210 contains active peptide ingredients S-488201, S-488202 and S-488203 • S-488211 contains active peptide ingredients S-488204 and S-488205 Participants will receive subcutaneous (SC) injections of both S-488210/Montanide (1 mL) and S-488211/Montanide emulsion (1 mL) per administration.
Duration of recruitment:	24 months
Duration of follow up:	Patients will be followed up every 3 months for the first year and then every 12 months for up to a total of 5 years from the first dose of trial treatment.
Definition of end of trial:	For regulatory purposes the end of trial will be 5 years after the last patient is administered their first dose of trial treatment.

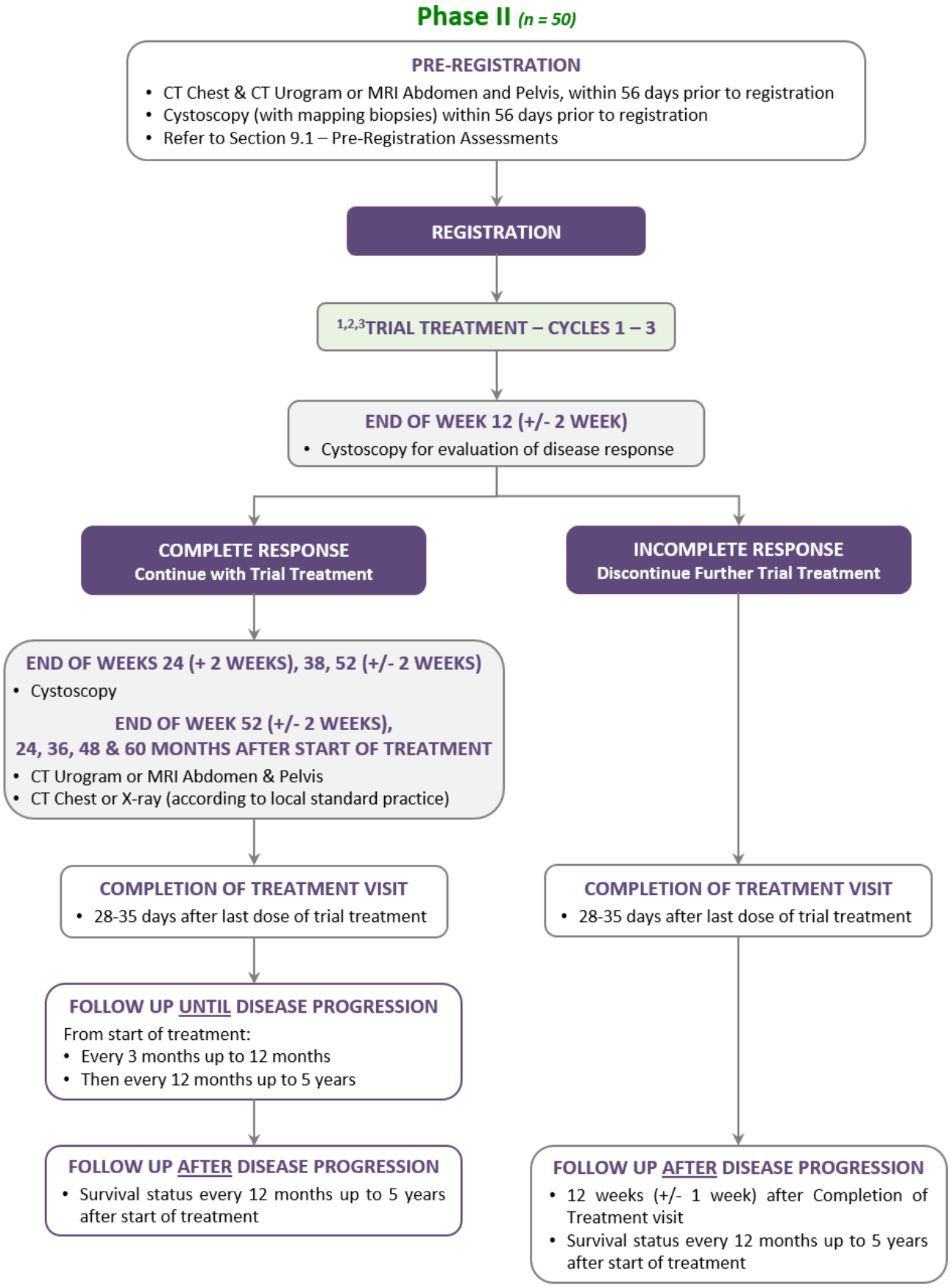
2. TRIAL SCHEMA



[1]***Cycle 1*** *= Durvalumab, 1500 mg IV infusion alone on day 1; S-488210/S-488211, two 1 mL subcutaneous injections on day 2 (day after the first durvalumab dose), then weekly for 3 weeks (up to 4 doses during cycle 1)*

[2]***Cycle 2*** *= Durvalumab, 1500 mg IV infusion and S-488210/S-488211, two 1 mL subcutaneous injections on day 1, followed by weekly doses of S-488210/S-488211 for 2 weeks*

[3]***Cycles 3 – 7*** *= Durvalumab, 1500 mg IV infusion and S-488210/S-488211, two 1 mL subcutaneous injections on day 1 of each cycle, followed by S-488210/S-488211 every 2 weeks*



[1]***Cycle 1*** *= Durvalumab, 1500 mg IV infusion alone on day 1; S-488210/S-488211, two 1 mL subcutaneous injections on day 2 (day after the first durvalumab dose), then weekly for 3 weeks (up to 4 doses during cycle 1)*

[2]***Cycle 2*** *= Durvalumab, 1500 mg IV infusion and S-488210/S-488211, two 1 mL subcutaneous injections on day 1, followed by weekly doses of S-488210/S-488211 for 2 weeks*

[3]***Cycles 3 – 7*** *= Durvalumab, 1500 mg IV infusion and S-488210/S-488211, two 1 mL subcutaneous injections on day 1 of each cycle, followed by S-488210/S-488211 every 2 weeks*