Clinical Trial Protocol

A phase II study of durvalumab in patients with mismatch repair deficient or *POLE* mutated metastatic colorectal cancer

DNA 복구 유전자 결핍 또는 POLE 유전자 돌연변이가 있는 전이성 대장암에서 durvalumab의 효능을 평가하는 2상 연구

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Version History

Version Number	Version date	Summary/Reason for changes
1.11	27Oct2017	Appendix C (Add POLE mutation method)
1.12	08Feb2018	Add sites
1.13	14Mar2018	Delete KCSG, contraception period modification Amended Appendix A
1.2	14Jun2018	IC #3 & EC #24, Study period
1.3	21May2019	Amended section 9.4.2 ,change sites & investigators.
1.4	01Dec2020	Amended Appendix A
1.5	11Nov2021	Amended Appendix A (TMG amendment)
1.6	12Apr2022	Added the maximum number of Durvalumab administrations allowed
1.7	12Dec2022	Amended Table 1.Highly effective methods of contraception Added section 9.4.1 to 9.4.4 (Other events requiring reporting; Timeline, Medication error, Drug Abuse, Drug misuse) Amended Appendix A (TMG amendment)

Protocol Synopsis	
Title	A phase II study of durvalumab in patients with mismatch repair deficient or *POLE* mutated metastatic colorectal cancer
Duration	IRB approval ~ Dec 2023
Investigators	Principal Investigator: Tae Won Kim, Department of Oncology, Asan Medical Center
Objectives	✓ Primary Objective • Objective response rates (RECIST 1.1) ✓ Secondary Objectives • Response rates by irRECIST • Disease control rates • Progression-free survival • Overall survival • Safety and toxicity assessments • Exploratory biomarker studies - Opal Multiplex Tissue Staining with Opal™ including PD-1 and PD-L1
Design	Prospective, open-label, multicenter phase II study
Background	Later-line therapies after failure of standard treatments for metastatic colorectal cancer patients are limited; regorafenib and TAS-102 have shown clinical activity for these patients, however, efficacy outcomes seemed not to be sufficient although there have been rather higher frequencies of adverse events. Mismatch repair (MMR) deficiency or microsatellite instability-high (MSI-H) played a role of negative predictive factor for adjuvant fluorouracil-based chemotherapy in patients with resected colorectal cancer. In the metastatic setting, deficient MMR or MSI-H represented poor prognosis; however, their predictive role has been documented after the pembrolizumab trial was reported. The results of the pembrolizumab trial demonstrated that the PD-1 blockade with pembrolizumab monotherapy showed 40% of confirmed immune-related objective response rates in patients with MMR deficient metastatic colorectal cancers; hence there was no objective response in those with MMR proficient tumors. The progression-free rates at 20 weeks were 78% versus 11%, respectively, also favouring those with MMR deficient tumors. However, the MMR deficiency of MSI-H is found in only about 5% in patients with metastatic colorectal cancer, which is too small to expand potential candidate of immunotherapy. One of the proposed mechanism of promising efficacy from pembrolizumab for MMR deficient colorectal cancer is that MMR deficient or MSI-H colorectal cancers harbour higher somatic mutation loads than MMR proficient colorectal cancer (a

	mean of 1782 somatic mutations per tumor in the MMR deficient tumors versus 73 in the MMR proficient tumors in the results of pembrolizumab trial); somatic mutations have the potential to encode non-self immunogenic antigens; therefore, immunotherapy enhancing immune surveillance produced promising treatment efficacy in the MMR deficient tumors. The *POLE* gene encodes the catalytic subunit of DNA polymerase epsilon, and it involves DNA repair and chromosomal replication. The *POLE* mutations are located in the exonuclease domain, and their presence has already been reported in the various cancers including colorectal and endometrial cancer. The *POLE* mutations represent high somatic mutation loads in patients with colorectal cancer, especially in those with MMR proficient or MSS, therefore, tumors harbouring *POLE* mutations might be susceptible to immune checkpoint blockade. Based on these reasons, we planned a phase II study of durvalumab monotherapy in patients with previously treated, metastatic, MMR deficient (MSI-H) or *POLE* mutated colorectal cancer.
Patients number	The primary endpoint is objective response rate of durvalumab in mismatch repair deficient (microsatellite instable) or *POLE* mutated metastatic colorectal cancer patients who have progressed after standard therapies. Assuming the target of response rate was set to 30% and a rate of 10% or below was considered futile. A 2-stage optimal design, as proposed by Simon, was used to allow early termination of any ineffective treatment early in the study. With a 1-sided, type I error of 5% and power of 0.8, the planned study was to proceed in 2 steps. In the first step, 10 patients were required, and if complete or partial response was observed in 2 or more patients, the study was to proceed to the second step with 19 additional patients (29 patients as a total). If this condition was not met, the study would be stopped for futility. In the second step, if complete or partial response was observed in 6 or more patients, the treatment will be considered effective. Assuming a dropout rate of 10%, 33 patients were required.
Inclusion criteria	1. Histologically or cytologically confirmed adenocarcinoma of the colon or the rectum. 2. Mismatch repair deficient or microsatellite instable (defined below), or *POLE* mutated tumors A. Mismatch repair deficient: loss of expression by immunohistochemical stains ≥ 1 out of 4 markers (MLH1, MSH2, MSH6, PMS2) B. Microsatellite instable: loss of stability ≥2 out of 5 gene panels (*BAT-25, BAT-26, D2S123, D5S346, D17S250*) C. POLE gene: P286R mutation or other mutation 3. Refractory to at least one agent of prior treatments(fluoropyrimidines, irinotecan or oxaliplatin) Progressed after at least first-line systemic chemotherapy for

	metastatic setting (progressed within 6 months after completion of adjuvant chemotherapy is also considered as first-line failure) 4. ≥ 1 measurable lesion(s) by RECIST 1.1. 5. Unresectable advanced or metastatic disease. 6. Age over 20 years old. 7. ECOG performance status of 0-1 or lower. 8. Adequate organ functions. A. Bone marrow function: Hemoglobin ≥ 9.0 g/dL, ANC ≥ 1,500/mm^3, platelet ≥ 100,000/mm^3 B. Hepatic functions: bilirubin ≤ 1.5 X ULN, AST/ALT ≤ 2.5 X ULN (≤ 5 X ULN in cases of liver metastasis) C. Renal functions: serum Cr ≤ 1.5 X ULN or calculated CCr (Cockroft) > 40 ml/min 9. Be willing and able to comply with the protocol for the duration of the study. 10. Give written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw the study at any time, without prejudice. 11. Female subjects must either be of non-reproductive potential (≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause, or history of hysterectomy, or history of bilateral tubal ligation, or history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry. 12. Women of childbearing potential and men must agree to use adequate contraception since signing of the IC form until at least 90days after the last study drug administration.
Exclusion criteria	1. Any prior treatment with PD-1 or PD-L1 inhibitor, including durvalumab. 2. Involvement in the planning and/or conduct of the study. 3. Receipt of the last dose of chemotherapy ≤ 28 days prior to the first dose of study drugs. 4. Mean QT interval corrected for heart rate (QTc) ≥ 470 msec calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction. 5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria 6. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. 7. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician. 8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer

	treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. 9. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses, which are not to exceed 10 mg/day of prednisolone, or an equivalent corticosteroid. 10. Concurrent or previous history of another primary cancer within 3 years prior to randomisation except for curatively treated cervical cancer in situ, non-melanomatous skin cancer, superficial bladder cancer (pTis and pT1) and curatively treated thyroid cancer of any stage. Concurrent, histologically confirmed, unresected thyroid cancer without distant metastasis could be allowed with the agreement of the chief principal investigator. 11. Uncontrolled CNS metastases; permitted if asymptomatic or neurologically stable. 12. Prior radiation therapy would be permitted, but non-radiated evaluable lesions should be present at study entry. 13. Radiation therapy during study treatment is not permitted, but if the local investigator decides that radiation therapy should be given during study treatments, he should be convinced that there is no evidence of disease progression with agreement of the chief principal investigator. 14. Congestive heart failure ≥ New York Heart Association (NYHA) class 2. 15. Unstable angina, new-onset angina within 3 months, or history of myocardial infarction within 6 months before the study entry. 16. Active or prior documented autoimmune disease within the past 2 years; subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded. 17. Active or prior documented inflammatory bowel disease. 18. History of prior immunodeficiency. 19. History of allogeneic organ transplantation. 20. History of hypersensitivity to durvalumab or any excipient. 21. Clinical diagnosis of active tuberculosis. 22. Receipt of live attenuated vaccination within 30 days prior to study entry. 23. Known history of testing positive for HIV 24. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive) Except, resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or Chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Subjects with chronic HBV

	infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy. 25. Major surgery or significant traumatic injury within 28 days prior to study treatment. 26. Non-healing wound, ulcer, or bone fracture. 27. Current evidence of significant gastrointestinal bleeding or (impending) obstruction. 28. Concomitant participation in another interventional clinical trial. 29. Pregnant of breast-feeding subjects. Women of child-bearing potential must have pregnancy test within 7 days and a negative result must be documented before start of study treatment. 30. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.
Treatment plan	The mismatch repair deficient or microsatellite instable, or *POLE* mutated metastatic colorectal cancer patients who were refractory to fluoropyrimidines, irinotecan and oxaliplatin with or without targeted agents will be accrued. After checking the eligibility for the study entry, patients will be entered into the study treatment with durvalumab monotherapy. Study treatment consists of durvalumab 1500 mg Q4W for patients > 30 kg, and will be repeated every 4 weeks. For patients ≤ 30 kg, weight based dosing of 20 mg/kg durvalumab Q4W will be used. Response evaluation will be performed every 8 weeks (± 1-week window period). Treatment will be continued until disease progression, unacceptable adverse events or the patient's refusal. Treatment through progression is at the investigator's discretion, and the investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicity that indicate that continuing treatment will not further benefit the patient. The Investigator should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study.
Statistical consideration	All patients who entered into the study will be included for response rates and survival estimation and who received at least 1 cycle of study treatment will be considered as eligible for safety assessment. Descriptive statistics were reported as proportions and medians. Progression-free survival (PFS) and overall survival (OS) were assessed by the Kaplan-Meier method and the 95% confidence interval (95% CI) for the median time to event was computed.

Evaluation	**Evaluation before study entry** (within 2 weeks) 1. Complete medical history. 2. Physical examination including ECOG performance status. 3. Radiologic assessments using RECIST 1.1. (permitted to be assessed within 28 days from the study treatment) 4. CBC with differentials. 5. Serum chemistry: calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes. 6. Routine urinalysis 7. Serum CEA 8. Serum TSH, free T4, T3 9. Serum amylase/lipase 10. EKG (3 consecutive EKG for eligibility check) 11. Chest X-rays 12. Urine β-hCG will be performed in women with child-bearing potential. 13. Other tests (i.e. bone scans) if clinically indicated. **Evaluation during study treatment (every cycle)** 1. Physical examination including ECOG performance status and drug-related side effects. 2. CBC with differentials. 3. Serum chemistry: calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes. 4. Serum amylase/lipase. 5. Toxicity assessments (NCI-CTC version 4.0) **Response evaluation (every 8 weeks ± 1 week window period)** 1. Serum CEA, TSH, T3 and free T4 2. CT (or MRI) scans of evaluable/measurable lesions by RECIST 1.1. 3. Other test (i.e. bone scans) if clinically indicated 4. Response evaluation will be performed every 8 weeks without regard to the schedules of study treatment. **Post-treatment follow-up (every 3 months)** 1. Subsequent treatments (chemotherapy, immunotherapy or radiotherapy) and their responses

	2. Survival information on subject 3. Status of disease and date of progression (in patients who stopped study treatment without documentation of disease progression) 4. Date and cause of death

연구 계획 요약	
연구 제목	DNA 복구 유전자 결핍 또는 *POLE* 유전자 돌연변이가 있는 전이성 대장암에서 durvalumab의 효능을 평가하는 2상 연구
연구 기간	IRB 심의일 ~ 2023년 12월
연구자	책임연구자: 김태원, 서울아산병원 종양내과
연구 목표	✓ 일차 목표 • 종양 반응율 (RECIST 1.1 기준) ✓ 이차 목표 • irRECIST 에 의한 종양 반응율 • 종양 조절율 (disease control rates) • 무진행 생존 기간 (progression-free survival) • 전체 생존 기간 (overall survival) • 안전성 및 독성 평가 • 탐색적 생체 표지자 연구 - Opal Multiplex Tissue Staining with Opal™ including PD-1 and PD-L1
연구 설계	전향적, 공개, 다기관 2상 연구
연구 배경	표준 치료에 진행한 전이성 대장암의 후기 치료는 제한되어 있다. 후기 치료로 regorafenib과 TAS-102 임상연구 결과가 일부 생존 기간 향상에 도움이 되는 것으로 보고되었으나 그 효과는 아직 불충분하고 일부 심한 독성도 보고되고 있다. DNA 복구 유전자 결핍 (mismatch repair deficiency, dMMR) 또는 현미부수체불안정 (microsatellite instability-high, MSI-H)는 수술적 절제가 시행된 대장암에서 플루오로피리미딘 기반 화학요법의 효과가 없는 음성 예측인자로 알려져 있으며, 전이성 대장암에서는 그 자체가 나쁜 예후를 반영하는 것으로 되어 있다. 그러나 최근 전이성 대장암에서 dMMR 또는 MSI-H가 pembrolizumab의 치료 예측인자로써 역할을 하는 연구 결과가 발표되었다. dMMR/MSI-H 전이성 대장암에서 pembrolizumab을 이용하여 PD-1을 억제하였을 때 종양 반응율이 40%에 달하였다. 반면 DNA 복구 유전자가 정상적으로 발현되는 경우 (mismatch repair proficiency, pMMR)에는 종양 반응율이 0% 였다. 20주 째에 종양이 진행하지 않은 환자의 비율도 78% 대 11%로 dMMR/MSI-H 대장암에서 높았다. dMMR/MSI-H 전이성 대장암이 pembrolizumab 등 면역치료에 반응하는 이론적인 근거 중 하나는, dMMR/MSI-H 전이성 대장암에서 종양 유전자 돌연변이가 매우 많이 발생한다는 것이다. 유전자 돌연변이가 많은 경우 항원에 대한 노출이 많아지기 때문에 면역치료의 역할이 커진다는 이론이다. 실제로 pembrolizumab에 반응하였던 dMMR/MSI-H 대장암 환자의 유전자 돌연변이 개수를 보았을 때 평균 1782개의 종양 유전자 돌연변이가 발견되었다. *POLE* 유전자 역시 DNA 복구와 염색체 복제 과정에 관여하는 유전자로 알려져 있으며, *POLE* 유전자 돌연변이가 있는 경우 다른 종양 유전체 돌연변이가 많이

	발생하는 것으로 보고되어 있다. 즉, pMMR/MSS 대장암에서 *POLE* 유전자 돌연변이가 있는 경우 dMMR/MSI-H 대장암과 마찬가지로 종양 유전자 돌연변이가 많이 존재하는 것으로 간주할 수 있으며, 이 역시 면역치료의 좋은 대상이 될 수 있다. 위와 같은 배경으로 표준 치료에 진행한 전이성 대장암 중에서 dMMR/MSI-H 또는 *POLE* 유전자 돌연변이가 있는 환자에서 durvalumab 단독치료의 2상 연구를 계획하였다.
환자 수	본 연구의 일차 목표는 dMMR/MSI-H 또는 *POLE* 유전자 돌연변이가 있는 전이성 대장암 환자에서 durvalumab 단독 치료를 하였을 때의 종양 반응율이다. 목표 종양 반응율을 30%, 10% 미만의 반응율을 보이는 경우 실패하는 것으로 가정하였을 때, Simon 2-stage optimal design에 의하면 1단계에서 10명의 환자 등재 후 2명 이상에서 종양 반응을 보이는 경우 2단계로 진입하고, 2단계에서 추가적으로 19명의 환자를 등재하게 된다 (type I error 5%, power 0.8). 총 29명의 평가 가능 환자가 필요하고, 10%의 탈락율을 고려할 때 총 33명의 환자가 등재된다.
선정 기준	1. 조직학적/세포학적으로 증명된 대장의 선암 2. DNA 복구 유전자 결핍 (dMMR) 또는 현미부수체 불안정 (MSI-H) 또는 POLE 유전자 돌연변이가 있는 경우 A. dMMR: 면역조직화학염색 기법으로 MLH1, MSH2, MSH6, PMS2 중 1개 이상 면역단백표현이 없는 경우 (loss of expression) B. MSI-H: PCR 기법으로 5개 유전자 중 (*BAT-25, BAT-26, D2S123, D5S346, D17S250*) 2개 이상에서 불안정성이 보이는 경우 C. POLE gene: P286R mutation or other mutation 3. 플루오로피리미딘, 옥살리플라틴 또는이리노테칸 중 최소 1가지 이상의 약제에 내성. 전이성 대장암의 치료로 최소한 1차 요법 이상 시행하여 진행한 경우(보조화학요법 종료 후 6개월 이내 임상적 또는 영상학적으로 진행한 경우에도 1차요법 이상에 실패한 것으로 간주) 4. RECIST 1.1. 기준에 따른 계측 가능 (measurable) 병변의 존재. 5. 수술적인 치료가 불가능한 경우 6. 만 20세 이상 7. ECOG 활동도 0-1 8. 적절한 장기 기능 A. 골수기능: 혈색소 (Hb) ≥ 9.0 g/dL, 호중구 (ANC) ≥ 1,500/mm^3, 혈소판 (PLT) ≥ 100,000/mm^3 B. 간기능: bilirubin ≤ 정상 상한치의 1.5배, AST/ALT ≤ 정상 상한치의 2.5배 (간 전이가 있는 경우 ≤ 정상 상한치의 5배) C. 신기능: 혈청 크레아티닌 ≤ 정상 상한치의 1.5배 또는 calculated CCr (Cockroft) > 40 ml/min 9. 연구 기간 동안 연구 계획서에 순응하고 치료 계획에 준수할 의지가 있는 환자. 10. 연구 동의서에 자발적으로 서명하고, 자발적으로 연구에 참여하고 언제든지 참여를 철회할 수 있음을 이해하는 환자.

	11. 대상자가 여성인 경우 임신 가능성이 없어야 함 (60세 이상이면서 1년 이상 생리가 없었던 경우 또는 자궁적출술 또는 양측난소절제수술을 시행한 경우). 그 외 임신 가능성이 있다면 연구 참여 전에 임신 반응 검사를 시행하여 임신이 아님을 증명하여야 한다. 12. 가임기의 남녀 환자의 경우, 연구약 투여 기간 동안과 최종 투여 후 최소한 90일까지 적절한 피임법을 준수할 수 있는 환자.
제외 기준	1. 이전에 durvalumab을 포함한 PD-1 또는 PD-L1 억제제를 사용한 적이 있는 경우. 2. 연구 계획 또는 수행에 관계된 종사자 3. 마지막 화학요법 시행 후 28일이 지나지 않은 경우 4. QTc ≥ 470 msec 이상인 경우 (3회의 EKG 시행 후 평균 값, Frediricia's Correction) 5. 이전 항암요법으로부터 해결되지 않은 CTCAE 2등급 이상인 독성 (탈모, 백반증, 선정기준에 적합하지 않은 실험실검사 결과 제외) 6. 2등급 이상의 신경병증 환자의 경우 대상자 질환에 대한 평가는 연구자의 의학적 자문 이후 진행한다. 7. 비가역성 독성 환자에서 durvalumab 치료가 증상을 더 악화하지 않을 경우에는 연구자의 의학적 판단을 기준으로 한다. 8. 항암 치료를 위해 화학요법, 시험약, 생물학적 제제, 또는 호르몬 요법을 현재 사용하는 환자. 암과 무관한 상태에 대한 호르몬 요법의 동시 사용(예: 호르몬 대체 요법)은 허용된다. 9. 14일 이내의 면역 억제제 사용, 단 흡입성 스테로이드나 생리적 용량의 스테로이드는 허용한다 (10 mg/day of prednisolone 또는 equivalent dose의 다른 스테로이드 제제). 10. 3년 이내에 다른 원발암의 병력이 있는 경우, 단 수술적으로 완치된 표재성 자궁경부암, 표재성 피부암 (흑색종 제외), 표재성 방광암 (pTis, pT1)과 4기를 제외한 갑상샘암은 허용된다. 갑상샘암의 경우 수술적인 제거가 되지 않았더라도 연구자의 판단 하에, 전이성 대장암의 치료 경과와 예후에 영향을 주지 않는다는 연구자의 판단이 있다면, 총 책임 연구자와 상의 후 환자를 연구에 참여시킬 수 있다. 11. 조절되지 않은 중추신경계 전이. 12. 이전의 방사선 치료 병력은 허용된다. 그러나 방사선 조사 범위에 들어가지 않는 평가 가능 병변의 존재가 있어야 한다. 13. 원칙적으로 연구 치료 기간 동안의 방사선 치료는 허용되지 않는다. 그러나 연구자가 질병진행의 증거가 없는 치료병변 외의 부위에 방사선 치료가 필요하다고 판단되는 경우 총 책임연구자와 상의 후 진행 할 수 있다. 14. New York Heart Association (NYHA) class 2 이상의 심부전. 15. 3개월 이내의 불안정성 협심증 병력, 또는 최근의 새로 생긴 심근 허혈 증상, 또는 6개월 이내의 심근 경색 병력이 있는 경우. 16. 2년 이내의 활동성 자가면역질환, 단 전신 치료가 필요하지 않는 vitiligo, 그레이브스씨 병, 건선은 허용된다.

	17. 염증성 장질환의 병력 18. 면역억제의 병력 19. 장기 이식 환자 20. Durvalumab 또는 비슷한 약제에 대한 과민반응 21. 연구 참여 시 활동성 결핵이 있는 경우 22. 생백신 (live attenuated vaccine) 투여 후 30일 이내 23. HIV 감염 병력 또는 알려진 면역결핍 신드롬. 24. 스크리닝 단계에서 활동성HBV/HCV 감염(HBV 표면항원양성 또는 HCV RNA 양성). 단, 회복된B형간염(anti HBs 와 anti HBc가확인되고, HBsAg, HBV DNA가 검출되지 않는 경우) 또는 HBsAg, HBV DNA로 확인된 만성 B형 간염의 경우 제외. 만성 B형 간염의 경우 항바이러스제 치료 중이며, HBV DNA <100IU/mL 임을 반드시 확인해야 한다. 25. 연구 시작 28일 이내의 주요 수술 또는 심각한 외상 병력. 26. 치유되지 않은 창상, 궤양 또는 골절. 27. 위장관 출혈이 지속되거나, 장 폐색이 의심되는 경우. 28. 현재 다른 약물이 투여되는 임상 연구에 참여 중인 경우. 29. 임산부 또는 모유 수유 중인 환자. 가임기의 여성은 연구 참여 7일 이내에 임신 반응 검사를 시행하여야 하며 음성임이 확인되어야 한다. 30. 연구 참여와 연구 결과 해석에 지장을 줄 수 있다고 판단되는 약물 남용자, 내과적/정신과적/사회적 질환을 가진 자.
치료 계획	이전의 표준 치료 (플루오로피리미딘, 옥살리플라틴, 이리노테칸)에 불응하며, DNA 복구 유전자 결핍 (mismatch repair deficiency) 또는 현미부수체불안정 (microsatellite instability) 또는 POLE 유전자 돌연변이가 있는 전이성 대장암 환자를 대상으로 한다. 선정/제외 기준에 만족하는 경우만 연구에 참여할 수 있으며, durvalumab은 1500 mg의 용량으로 매 4주 마다 반복한다. 반응 평가는 매 8주 마다 (± 1주) 시행되며, 질병의 진행, 감내할 수 없는 독성 또는 동의 철회가 있을 때 중지한다. 반응 평가는 연구 치료의 주기와 상관 없이 매 8주 마다 시행한다. 질병의 진행 이후에도 연구자의 판단 하에 durvalumab을 지속할 수 있으며, 이때는 감내할 만한 부작용이 없는지, 환자에게 이득이 되는지, 그리고 그 시점에서의 환자 상태가 선정/제외 기준에 부합하는지 평가 후 진행하여야 한다.
통계학적 고려	연구에 참여한 모든 환자는 유효성 (반응율) 분석에 포함될 것이며, 안전성 평가에는 1차 이상 연구 약제를 투여 받은 환자가 포함될 것이다. 통계 기술은 %와 중간값으로 기술되며, 생존 기간 (PFS, OS)은 Kaplan-Meier 기법을 이용하여 분석/비교될 것이다.
연구 절차	**연구 참여 전 절차** (연구 치료 시작 2주 이내)

	1. 병력 확인. 2. ECOG 활동도를 포함한 신체 검진. 3. RECIST 1.1 기준에 따른 계측 가능 병변 확인 4. 일반혈액검사 (CBC) 5. 혈청 일반화학검사 (Chemistry): calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes. 6. 요검사 7. 혈중 CEA 8. 갑상선 기능 검사 (TSH, T3, free T4) 9. 혈중 amylase/lipase 10. 심전도 (3회 시행) 11. 흉부 X-선 검사 12. 가임기 여성의 경우 임신 반응 검사 (소변 beta-hCG) 13. CT, MRI 등의 영상학적 검사 외에 연구자가 반응 평가에 필요하다고 판단하는 다른 검사 **<u>연구 치료 기간 동안의 절차 (매 연구 치료 시작 전)</u>** 1. 신체 검진, ECOG 활동도 검사, 약제 복용 확인 2. 일반혈액검사 (CBC). 3. 혈청 일반화학검사 (Chemistry): calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes. 4. 혈중 amylase/lipase 5. 독성 및 안전성 평가 (NCI-CTC version 4.0) **<u>반응 평가 (매 8주 마다 ± 1 week window period)</u>** 1. 혈중 CEA, 갑상선 기능 검사 (TSH, T3, free T4), 2. 영상의학적 검사를 통한 종양 계측/반응 평가 (RECIST 1.1) 3. 그 외 연구자가 반응 평가를 위해 필요하다고 판단하는 검사 4. 반응 평가는, 연구 치료의 주기와 상관없이 매 8주 (± 1주)마다 시행되어야 한다. **<u>치료 종료 후 절차 (매 3개월 마다)</u>** 1. 이후 치료에 대한 정보 (항암화학요법, 면역요법, 방사선치료): 기간, 반응, 약제 종류 등 2. 생존에 대한 정보 3. 질병의 확인 없이 연구 치료가 종료된 경우, 질병의 진행을 확인할 수 있는

	정보 4. 사망한 경우, 사망일과 사망 원인

1. TITLE OF THE STUDY

A phase II study of durvalumab (MEDI4736) in patients with mismatch repair deficient or *POLE* mutated metastatic colorectal cancer

2. PARTICIPATING CENTERS AND INVESTIGATORS

Chief Principal Investigator:

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Jiyeon Baek	National Cancer Center
Myoung-joo Kang	Inje University Haeundae Paik Hospital

3. INTRODUCTION AND STUDY RATIONALE

3.1. INTRODUCTION

Recent advances have made survival advances of patients with metastatic colorectal cancer (mCRC) upto median 30 months after upfront targeted agents plus doublet chemotherapy (Figure 1).[1,2]

Figure 1. Survival advances of metastatic colorectal cancer patients after optimized first-line systemic chemotherapy.

	Overall survival		Progression-free survival	
	Bevacizumab + chemotherapy	Cetuximab + chemotherapy	Bevacizumab + chemotherapy	Cetuximab + chemotherapy
FIRE-3	25.0	28.7	10.3	10.0
	HR 0.77, $p = 0.017$		HR 1.06, $p = 0.547$	
CALGB 80405	29.0	29.9	10.8	10.4
	HR 0.925, $p = 0.34$		HR 1.04, $p = 0.55$	

Later-line treatments after failure to standard treatments, however, are limited; regorafenib and TAS-102 showed mild improvement of survival without significant response rates although those agents had rather higher frequencies of significant adverse events (Figure 2).[3-5]

Figure 2. Limited survival advantages in the later-line setting; roughly 2 months of overall survival benefit with higher cost and higher frequencies of adverse events.

	OS primary endpoint		PFS	
	Experimental	Placebo	Experimental	Placebo
CORRECT Regorafenib	**6.4**	5.0	1.9	1.7
	HR 0.77, $p = 0.0052$		HR 0.49, $p < 0.0001$	
CONCUR Regorafenib in ASIAN	**8.8**	6.3	3.2	1.7
	HR 0.55, $p = 0.00016$		HR 0.31, $p < 0.0001$	
RECOURSE TAS-102	**7.1**	5.3	2.0	1.7
	HR 0.68, $p < 0.001$		HR 0.48, $p < 0.001$	

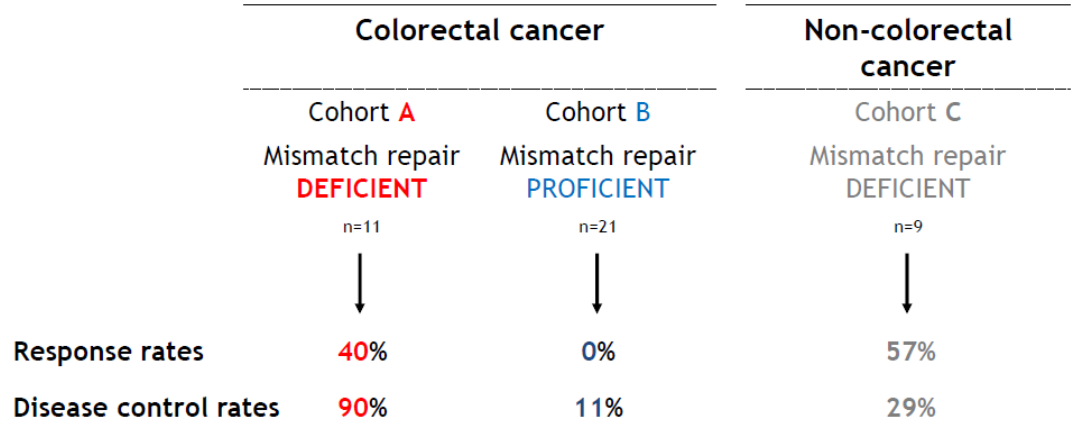
Mismatch repair (MMR) deficiency or microsatellite instability-high (MSI-H) itself is better prognostic factor in the resected stage II or III colorectal cancer; however, they played a

role of negative predictive factor for adjuvant fluorouracil-based chemotherapy in patients with resected colorectal cancer.[6-8] In the adjuvant setting, fluoropyrimidine based adjuvant chemotherapy did not benefit or did even harm for patient with resected stage II colorectal cancer with MSI-H or MMR deficiency. Adjuvant fluoropyrimidines even did not any benefit in those with resected stage III colorectal cancer with MSI-H or MMR deficiency.

In the metastatic setting, MMR deficiency or MSI-H represented poor prognosis and predictive of poor treatment responses from systemic treatments.[9] However, their positive predictive role has been documented from the results of the KEYNOTE-016 trial.[10]

The KEYNOTE-016 trial studied pembrolizumab monotherapy in the 3 parallel groups; MMR deficient mCRC, MMR proficient mCRC, and MMR deficient non-colorectal cancers. The study results were very promising; pembrolizumab monotherapy showed 40% of confirmed immune-related objective response rates in patients with MMR deficient mCRC; hence there was no objective response in those with MMR proficient tumors (Figure 3).[10] The progression-free rates at 20 weeks were 78% versus 11%, respectively, also favouring those with MMR deficient tumors. We can say that the KEYNOTE-016 trial has opened the new era of immunotherapy for colorectal cancer treatment, and also has an impact on finding novel positive predictive factor for better response in this field. However, the MMR deficiency of MSI-H is found in only about 5% in patients with metastatic colorectal cancer, which is too small to expand potential candidate of immunotherapy. On the bases of these results, the confirmatory phase II study of pembrolizumab monotherapy in the second- or third-line setting (KEYNOTE-164, NCT02460198) and a phase III study of pembrolizumab versus standard therapies (KEYNOTE-177, NCT02563002) for MSI-H mCRC patients are ongoing.

Figure 3. Promising activity of pembrolizumab monotherapy in MMR deficient or MSI-H mCRC patients.



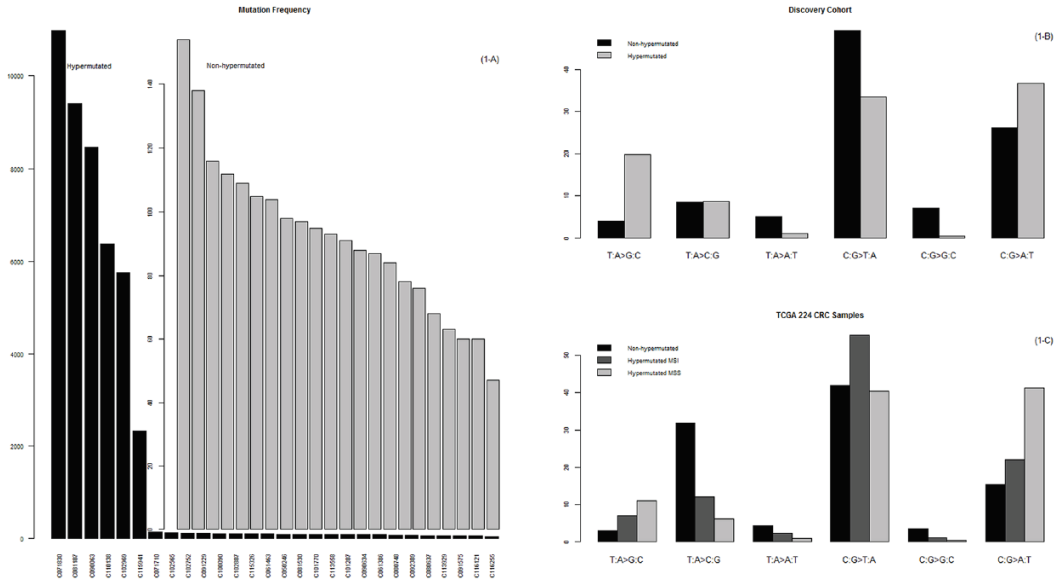
One of the proposed mechanism of promising efficacy from pembrolizumab for MMR

deficient colorectal cancer is that MMR deficient or MSI-H colorectal cancers harbour higher somatic mutation loads than MMR proficient colorectal cancer (a mean of 1,782 somatic mutations per tumor in the MMR deficient tumors versus 73 in the MMR proficient tumors in the results of KEYNOTE-016 trial); somatic mutations have the potential to encode non-self immunogenic antigens; therefore, immunotherapy enhancing immune surveillance produced promising treatment efficacy in the MMR deficient tumors.

CheckMate 142 is evaluating nivolumab (3 mg/kg) with and without ipilimumab (Yervoy; 1 mg/ kg) in patients with metastatic MMR-deficient/MSI-H colorectal cancer. The objective response rate was 31.1%, and 68.9% of patients demonstrated disease control for at least 12 weeks. Responses occurred early, at a median of 2.8 months, and the median duration of response has not been reached.[11]

The *POLE* gene encodes the catalytic subunit of DNA polymerase epsilon, and it involves DNA repair and chromosomal replication. The *POLE* mutations are located in the exonuclease domain, and their presence has already been reported in the various cancers including colorectal and endometrial cancer; however, its role as a prognostic or predictive factor has not been studied yet..[12-14] Our recent study demonstrated that the *POLE* mutations were found in 6 out of 28 colorectal cancer patients, characterized as younger age (< 40 years) and mismatch repair proficient (or MSS) tumors. More interestingly, 6 patients harbouring *POLE* mutations had higher somatic mutation loads in their tumors (ranged 2000 to 12,000) by whole-exom sequencing, compared to 50 to 150 mutation loads in those without *POLE* mutations (Figure 4).[15]

Figure 4. POLE mutation represents higher somatic mutation loads (recent published internal data).



The *POLE* mutations represent high somatic mutation loads in patients with colorectal cancer, especially in those with MMR proficient or MSS (microsatellite stable), therefore, tumors harbouring *POLE* mutations might be susceptible to immune checkpoint blockade.

3.2. DURVALUMAB (MEDI4736)

Durvalumab is a selective, high-affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 but does not bind to PD-L2, avoiding potential immune-related toxic effects due to PD-L2 inhibition, which has been noted in susceptible animal models.

Recent studies demonstrated that durvalumab is safe and active in patients with non-small cell lung cancer and bladder cancer.

For non-small cell lung cancer patients, 102 patients were enrolled into the dose-escalation phase and received durvalumab plus tremelimumab. The maximum tolerated dose was exceeded in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg. The most frequent treatment-related grade 3 and 4 adverse events were diarrhoea (11%), colitis (9%), and increased lipase (8%). Evidence of clinical activity was noted both in patients with PD-L1-positive tumours and in those with PD-L1-negative tumours. Investigator-reported confirmed objective responses were achieved by six (23%, 95% CI 9-44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising two (22%, 95% CI 3-60) of nine patients with PD-L1-positive tumours and four (29%, 95% CI 8-58) of 14 patients with PD-L1-negative tumours, including those with no PD-L1

staining (four [40%, 95% CI 12-74] of ten patients).[16]

For bladder cancer patients, durvalumab 10 mg/kg every 2 weeks was administered intravenously for up to 12 months. The most common treatment-related adverse events (AEs) of any grade were fatigue (13.1%), diarrhea (9.8%), and decreased appetite (8.2%). Grade 3 treatment-related AEs occurred in three patients (4.9%); there were no treatment-related grade 4 or 5 AEs. The objective response rate was 31.0% (95% CI, 17.6 to 47.1) in 42 response-evaluable patients, 46.4% (95% CI, 27.5 to 66.1) in the PD-L1-positive subgroup, and 0% (95% CI, 0.0 to 23.2) in the PD-L1-negative subgroup. Durvalumab demonstrated a manageable safety profile and evidence of meaningful clinical activity in PD-L1-positive patients with bladder cancer, many of whom were heavily pretreated.[17]

At present, studies of durvalumab with or without other agents for various tumor types are still ongoing.[18-22] Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus (which may present with diabetic ketoacidosis), and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, subcutaneous injection site reaction, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).
For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.
In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of participants discontinued the drug due to an AE.
Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

3.3. FIXED DOSING

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and

fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others.[24-27] Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.[25] In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters.[26]

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (Appendix B).

3.4. RATIONALE OF THE STUDY

PD-1 blockade (pembrolizumab) demonstrated promising efficacy outcomes in patients with MMR deficient or MSI-H mCRC.[10] Another immune check point blockade, targeting PD-L1 in these patients also demonstrated promising activity (nivolumab for MSI-H mCRC, CHECKMATE-142, NCT02060188); the confirmed response rate was 27% (9/33) without any significant adverse event.[28]

Immunotherapy for this population is worthy of further investigation and in unmet needs both in terms of finding adequate agents and selecting adequate population. On the bases of these results, we planned this study of durvalumab monotherapy, another PD-L1 blockade, for MMR deficient or MSI-H or *POLE* mutated mCRC patients to evaluate the efficacy and safety.

4. STUDY OBJECTIVES

The objective of this study is to investigate the efficacy and safety of durvalumab in patients with mismatch repair deficient or microsatellite instable or *POLE* mutated metastatic colorectal cancer refractory to irinotecan, oxaliplatin and fluoropyrimidines.

4.1. PRIMARY OBJECTIVE

- Objective response rates (RECIST 1.1)

4.2. SECONDARY OBJECTIVES

- Response rates by irRECIST
- Disease control rates
- Progression-free survival
- Overall survival
- Safety and toxicity assessments
- Exploratory biomarker analysis
    - Opal Multiplex Tissue Staining with Opal™ including PD-1 and PD-L1

5. STUDY DESIGN

5.1. DESIGN OVERVIEW

This is a prospective, open-label, multicenter phase II study to investigate the efficacy and safety of durvalumab monotherapy.

A total of 33 patients who meet the eligible criteria will be accrued (17 for mismatch repair deficient or microsatellite instable colorectal cancer and 16 for *POLE* mutated colorectal cancer).

Study treatment will be continued until at least one of the following occurs;

- Progressive disease as defined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. or clinical progression by the decision of investigators; Treatment through progression is at the investigator's discretion, and the investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. The Investigator

should ensure that patients still meet all of the inclusion criteria and none of the exclusion criteria for this study.

- Death.
- Unacceptable adverse events.
- Withdrawal of consent or lost to follow-up.
- Adverse events that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Treating physician determines discontinuation of treatment is in the subject's best interest.
- Non-compliance to the study protocol.
- Pregnancy or intent to become pregnant.

5.2. JUSTIFICATION OF THE DESIGN

As described previously, limited drugs are available in patients with metastatic colorectal cancer who have failed after standard therapies. Later-line treatments of currents showed limited antitumor activity in this setting. Mismatch repair deficiency (microsatellite instability) and *POLE* mutation is proved to be a reasonable target for immunotherapy for colorectal cancer patients; therefore, durvalumab monotherapy in this setting could be a valid option.

6. STUDY POPULATION

6.1. ELIGIBILITY

6.1.1. INCLUSION CRITERIA

1. Histologically or cytologically confirmed adenocarcinoma of the colon or the rectum.
2. Mismatch repair deficient or microsatellite instable (defined below), or POLE mutated tumors
   A. Mismatch repair deficient: loss of expression by immunohistochemical stains ≥ 1 out of 4 markers (MLH1, MSH2, MSH6, PMS2)
   B. Microsatellite instable: loss of stability ≥2 out of 5 gene panels (BAT-25, BAT-26, D2S123, D5S346, D17S250)
   C. POLE gene: P286R mutation or other mutation

3. Refractory to prior fluoropyrimidines, irinotecan and oxaliplatin (progressed during or within 6 months of those agents).
4. ≥ 1 measurable lesion(s) by RECIST 1.1.
5. Unresectable advanced or metastatic disease.
6. Age over 20 years old.
7. ECOG performance status of 0-1 or lower.
8. Adequate organ functions.
   A. Bone marrow function: Hemoglobin ≥ 9.0 g/dL, ANC ≥ 1,500/mm3, platelet ≥ 100,000/mm3
   B. Hepatic functions: bilirubin ≤ 1.5 X ULN, AST/ALT ≤ 2.5 X ULN (≤ 5 X ULN in cases of liver metastasis)
   C. Renal functions: serum Cr ≤ 1.5 X ULN or calculated CCr (Cockroft) > 40 ml/min
9. Be willing and able to comply with the protocol for the duration of the study.
10. Give written informed consent prior to study-specific screening procedures, with the understanding that the patient has the right to withdraw the study at any time, without prejudice.
11. Female subjects must either be of non-reproductive potential (≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause, or history of hysterectomy, or history of bilateral tubal ligation, or history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
12. Women of childbearing potential and men must agree to use adequate contraception since signing of the IC form until at least 90days after the last study drug administration.

6.1.2. EXCLUSION CRITERIA

All of the following exclusion criteria should be checked at the time of screening procedure.

1. Any prior treatment with PD-1 or PD-L1 inhibitor, including durvalumab.
2. Involvement in the planning and/or conduct of the study.
3. Receipt of the last dose of chemotherapy ≤ 28 days prior to the first dose of study drugs.
4. Mean QT interval corrected for heart rate (QTc) ≥ 470 msec calculated from 3 electrocardiograms (ECGs) using Frediricia's Correction.
5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
6. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

7. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
9. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses, which are not to exceed 10 mg/day of prednisolone, or an equivalent corticosteroid.
10. Concurrent or previous history of another primary cancer within 3 years prior to randomisation except for curatively treated cervical cancer in situ, non-melanomatous skin cancer, superficial bladder cancer (pTis and pT1) and curatively treated thyroid cancer of any stage. Concurrent, histologically confirmed, unresected thyroid cancer without distant metastasis could be allowed with the agreement of the chief principal investigator.
11. Uncontrolled CNS metastases; permitted if asymptomatic or neurologically stable.
12. Prior radiation therapy would be permitted, but non-radiated evaluable lesions should be present at study entry.
13. Radiation therapy during study treatment is not permitted, but if the local investigator decides that radiation therapy should be given during study treatments, he should be convinced that there is no evidence of disease progression with agreement of the chief principal investigator.
14. Congestive heart failure ≥ New York Heart Association (NYHA) class 2.
15. Unstable angina, new-onset angina within 3 months, or history of myocardial infarction within 6 months before the study entry.
16. Active or prior documented autoimmune disease within the past 2 years; subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
17. Active or prior documented inflammatory bowel disease.
18. History of prior immunodeficiency.
19. History of allogeneic organ transplantation.
20. History of hypersensitivity to durvalumab or any excipient.
21. Clinical diagnosis of active tuberculosis.
22. Receipt of live attenuated vaccination within 30 days prior to study entry.
23. Known history of testing positive for HIV
24. Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
    Except, resolved HBV infection (as evidenced by detectable HBV surface antibody,

detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or Chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Subjects with chronic HBV infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy.

25. Major surgery or significant traumatic injury within 28 days prior to study treatment.
26. Non-healing wound, ulcer, or bone fracture.
27. Current evidence of significant gastrointestinal bleeding or (impending) obstruction.
28. Concomitant participation in another interventional clinical trial.
29. Pregnant of breast-feeding subjects. Women of child-bearing potential must have pregnancy test within 7 days and a negative result must be documented before start of study treatment.
30. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

6.2. WITHDRAWAL OF SUBJECTS

Subjects should be withdrawn from the study treatment for the any of the following reasons;

- At their own or legally acceptable representative request.
- At any time of subject's decision not to participate further.
- In case of investigator's decision that the continuation of study treatment would be harmful to the subject.
- Use of other substances or herbal medicines that may affect the treatment and the results of this study.
- Development of more beneficial treatment, by investigator's judgment, for the subject in the treatment continuum.
- Disease progression or unacceptable adverse events.
- Development of a secondary malignancy.
- Lost to follow-up.
- Interruption of study drug due to drug related adverse events is longer than 4 consecutive weeks.

6.3. REPLACEMENT

A subject withdrawn from the study treatment will not be replaced.

7. STUDY TREATMENT

7.1. DURVALUMAB

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL of durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46 °F) and must not be frozen.

The dose of durvalumab for administration must be prepared by aseptic technique. Total in-use storage time from needle puncture of durvalumab vial to the start of administration should not exceed:

- 4 hours at room temperature
- 24 hours at 2°C to 8°C (36°F to 46°F).

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

Preparation of durvalumab doses for administration with an IV bag

A dose of 1500 mg (for patients > 30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22μm in-line filter. Add 30.0 mL (1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is between 1 and 20 mg/ml. Mix the bag by gentle inversion to ensure homogeneity of the dose in the bag.

Weight-based dosing (for patients ≤ 30 kg) will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-μm in-line filter. Appendix B includes an example of a weight-based dose calculation.

Standard infusion time is 60 minutes (± 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and

document if the line was not flushed.

In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.
No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.
In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Appendix A.**
As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.2. DOSE AND TREATMENT REGIMEN

Patients (> 30 kg in weight) will receive 1500 mg of durvalumab via intravenous infusion every 4 weeks. Patients (≤ 30 kg in weight) will receive weight based dosing of 20 mg/kg durvalumab via intravenous infusion every 4 weeks.

Durvalumab treatment can be continued up to the 36-cycle dosing. After 36 cycles of treatment, durvalumab should be discontinued.

7.3. DOSE MODIFICATION AND DELAYS

7.3.1. GENERAL RULES FOR DOSE MODIFICATION AND DELAYS

- Dose modification (reduction or escalation) is not allowed.
- Dose delays in case of clinically meaningful events are permitted; however, study treatment should be discontinued in case of 4 weeks delays.
- All the response evaluation procedures including CT scans should be performed as planned in patients with treatment delay without regard to the cycles of study treatment. Dose delays, reasons for treatment delay, actions to be taken and outcome will be recorded in patient chart and CRF.
- Regarding the adverse events, dose delays could be made under investigators' discretion.
- When the study treatment is restarted, the investigator should ensure that AE is recovered ≤ grade 1 or there is no safety risk for the patients.
- Prophylactic use of G-CSF (or GM-CSF) or erythropoietin is not allowed.

7.4. LABELING

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.
Labels will be provided as either a single panel label or as multi-language booklet labels.

7.5. STORAGE

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

7.6. COMPLIANCE

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the eCRF. Treatment compliance will be assured by site reconciliation of medication dispensed and returned.

7.7. CONCOMITANT THERAPY

7.7.1. PROHIBITED CONCOMITANT MEDICATIONS

- Any investigational anticancer therapy other than those under investigation in this study.
- Any concurrent chemotherapy, immunotherapy or biologic or hormonal therapy for cancer treatment.
- Any concurrent radiotherapy is not permitted; however, if the local investigator decides that radiation therapy should be given during study treatments, he should be convinced that there is no evidence of disease progression and there is no target lesion(s) included in the field of radiotherapy with agreement of the chief principal investigator.
- Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.
- Live attenuated vaccines are not permitted; inactivated vaccines (i.e. influenza vaccines) are permitted.
- Drugs with laxative properties and herbal or natural remedies for constipation.
- Prophylactic administration of G-CSF (or GM-CSF) or erythropoietin.
- All traditional medicines with an intention to control the tumor without regard to their truth

7.7.2. PERMITTED CONCOMITANT MEDICATIONS

- Standard therapies for treatment of concurrent medical conditions and complications or symptomatic therapy of adverse events are permitted.
- Blood transfusion.
- G-CSF (or GM-CSF) for febrile neutropenia or infection with neutropenia; however, the prophylactic use of these agents are not permitted even for 2nd occurrence without evidence of fever or infection.
- Antiemetics: as for acute nausea/vomiting, intravenous administration of 5-HT3 antagonist can be considered, but not recommended routinely. Metoclopramide, lorazepam or corticosteroid might be used.
- Antidiarrheals: in general, loperamide is recommended as the standard treatment. Because any agents having purgative activity might aggravate diarrhea, its use should be avoided. Make patients contact with investigators about the use of a purgative.
- Antibiotics, analgesics, analgesic antipyretics, steroidal agents, opioids including morphine, fentanyl patches, etc.

7.8. RESTRICTIONS

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

7.8.1. FEMALE PATIENT OF CHILD-BEARING POTENTIAL

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

7.8.2. MALE PATIENT WITH A FEMALE PARTNER OF CHILDBEARING POTENTIAL

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
  Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1). N.B Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

  - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

  - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 1. Note that some contraception methods are not considered highly effective (eg. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 1. Highly effective methods of contraception (<1% failure rate)

Nonhormonal methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion: Intrauterine device (provided coils are copper-banded)	• Implants: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®) • Intravaginal device: Ethinylestradiol/ etonogestrel-releasing intravaginal devices (e.g. NuvaRing®) • Injection: Medroxyprogesterone injection (e.g. Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (e.g. OrthoEvra®) • Mini pill: Progestrone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone- based based • Levonorgestrel-releasing intrauterine system (e.g. Mirena®)

7.8.3. BLOOD DONATION

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab

7.9. POST-STUDY TREATMENT

All subjects will enter the follow-up period upon discontinuation of either randomized

study treatment. Regardless of the reason for discontinuation, all subjects will be followed for survival until death is documented, except for those who specifically withdraw consent to follow-up. Subjects who withdraw consent from study drug treatment may enter the Follow-up Period. Assessment of survival status will be performed approximately every 3 months. In addition, for subjects who discontinue study treatment and have not experienced PD, available tumor assessments will be recorded in the CRF until PD is documented. Additionally, the administration of any anti-cancer drugs must be recorded in the CRF.

8. STUDY PROCEDURE AND SCHEDULE

8.1. TABULATED OVERVIEW

Study Period	**Screening**	**Study Treatment (-/+ 1 week)**			**Post Treatment (-/+ 2 weeks)**
Study Procedures: Study Day:	**D-14 to -1**	**Every cycle**	**Every 8 weeks**	**End of Treatment**	**Every 3 months**
Informed consent	O				
Inclusion/Exclusion criteria review	O				
Demographics; medical history	O				
Complete physical examination	O	O		O	
Vital Signs	O	O		O	
ECOG performance status	O	O		O	
Electrocardiography [1)]	O			O	
Concomitant medication	O	O		O	
Chest X-ray	O		O	O	
Tumor Assessment (CT or MRI)	O		O	O	
Other imaging procedure if needed	O		O	O	
Assessment of response			O	O	
Toxicity assessment (CTCAE version 4.0)		O		O	
Survival					O
Subsequent treatment					O
CBC	O	O		O	
Chemistry [2)], Amylase/Lipase	O	O		O	
CEA	O		O	O	
Thyroid function test (TSH, T3, free	O		O		

T4)					
Routine urinalysis	O				
Urine β-hCG pregnancy test [3)]	O				
Height (screening only)/Weight	O	O		O	
Biomarker assessment [4)]	O				

1) In patients without prior history of cardiovascular disease and showed normal electrocardiography, further examinations such as MUGA scan and echocardiography are not mandatory; however, patients with prior history of cardiac disease or those showed abnormal electrocardiography results, they would be checked with further examinations either with MUGA scan or echocardiography by the investigator's decision.
2) Chemistry labs include calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes(Na, K, Cl, Mg).
3) Urine β-hCG should be performed in women with child-bearing potential.
4) Perform tests for pertinent tumor markers if informative in the investigator's opinion and document at screening or as clinically indicated.

8.2. EVALUATION BEFORE STUDY TREATMENT (WITHIN 2 WEEKS)

- Complete medical history.
- Physical examination including ECOG performance status.
- Radiologic assessments using RECIST 1.1. (permitted to be assessed within 28 days from the study treatment)
- CBC with differentials.
- Serum chemistry: calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes.
- Routine urinalysis
- Serum CEA
- Serum TSH, T3 and free T4
- Serum amylase/lipase
- EKG (3 consecutive EKG for eligibility check)
- Chest X-rays
- Urine β-hCG will be performed in women with child-bearing potential.
- Other tests (i.e. bone scans) if clinically indicated
- Exploratory biomarker assessments:
    - Opal Multiplex Tissue Staining with Opal™ including PD-1 and PD-L1
- Biological samples will be obtained for biomarker evaluation from all eligible patients at the screening visit.

8.3. EVALUATION DURING STUDY TREATMENT (EVERY CYCLES OF STUDY TREATMENT)

- Physical examination including ECOG performance status and drug-related side effects.
- CBC with differentials.
- Serum chemistry: calcium, phosphorus, glucose, BUN, creatinine, total protein, albumin, AST/ALT, alkaline phosphatase, total bilirubin, uric acid and electrolytes.
- Serum amylase/lipase
- Toxicity assessments (NCI-CTCAE version 4.0)

8.4. RESPONSE EVALUATION (EVERY 8 WEEKS ± 1 WEEK WINDOW PERIOD)

- Serum CEA, TSH, T3 and free T4
- CT (or MRI) scans of evaluable/measurable lesions by RECIST 1.1.
- Other test (i.e. bone scans) if clinically indicated
- Response evaluation will be performed every 8 weeks without regard to the schedules of study treatment.

8.5. POST-TREATMENT FOLLOW-UP (EVERY 3 MONTHS)

- Subsequent treatments (chemotherapy, immunotherapy or radiotherapy) and their responses
- Survival information on subject
- Status of disease and date of progression (in patients who stopped study treatment without documentation of disease progression)
- Date and cause of death

Telephone follow-up is acceptable. Site staff must use caution when contacting the subject's family for this information, especially if they are no longer under the care of the investigator, so as to not inadvertently cause any distress to the family of a subject who is no longer alive. Additional phone contacts will be required for formal survival sweeps at the time of primary analysis.

9. ADVERSE EVENTS

9.1. DEFINITIONS

9.1.1. ADVERSE EVENT

The term **adverse event** covers any unfavorable and unintended sign, symptom, syndrome,

or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by safety parameters. However, if the outcome fulfills the definition of «serious adverse event», it must be recorded as such.

The adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors
- No causal relationship with the study medication or with the clinical study itself is implied by the use of the term «adverse event».
- Adverse events fall into the categories «non serious» and «serious».

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

9.1.2. SERIOUR ADVERSE EVENTS

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening [1]
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity [2]
- Is a congenital anomaly or birth defect
- Is an important medical event [3]

[1] «Life-threatening» means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] «Persistent or significant disability or incapacity» means that there is a substantial

disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the «Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form») should be used as guidance for adverse events that may be considered serious because they are medically important.

Clarification of the difference in meaning between «severe» and «serious»:
The term «severe» is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as «serious», which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.1.3. DEFINITION OF ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressant and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate,

should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician. AESIs observed with durvalumab include:

- Diarrhea/ Colitis and intestinal perforation
- Pneumonitis/ILD
- hepatitis / transaminase increase
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Myocarditis
- Myositis / Polymyositis
- Other inflammatory responses that are rare / less frequent with a potential im mune-mediated aetiology include, but are not limited to, pericarditis, sarcoido sis, uveitis and other events involving the eye, skin, haematological and rheu matological events, vasculitis, non-infectious meningitis and non-infectious encephalitis

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

9.1.4. RECORDING OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events will be recorded CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)

- The date <<and time>> when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (yes or no)
- Action taken with regard to durvalumab /comparator/combination agent
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to <<criteria>>
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

9.2. DOCUMENTATION AND REPORTING OF ADVERSE EVENTS BY INVESTIGATOR

All adverse events that occur during the observation period set in this protocol must be documented on the pages provided in the case report form in accordance with the instructions for the completion of adverse event reports in clinical studies. These instructions are provided in the case report form itself.

The following approach will be taken for documentation:

1) **All adverse events** (whether serious or non-serious) must be documented on the «Adverse Event» page of the case report form.
2) If the adverse event is suspected, serious, and unexpected, the investigator must complete, in addition to the «Adverse Event» page in the case report form, a «Serious Adverse Event/Expedited Report from a Clinical Trial» form at the time the serious adverse event is detected. When this form is completed, designated staff member of the Korean Cancer Study Group should be notified by e-mail within 1 working day and it also should be reported to IRBs according to their procedures.
3) When a «significant overdose» of the investigational product occurs without an adverse event, the investigator should only complete a «Serious Adverse Event/Expedited Report from a Clinical Trial» form. Instructions on where to send this form will be provided by

the the Korean Cancer Study Group. In this case, there is no need to complete the «Adverse Event» page in the case report form.

4) Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign or symptom should be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed by the end of study.

REPORTING OF SAEs

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

All SAEs should be reported to the Sponsor(PI): Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:
AEMailboxClinicalTrialTCS@astrazeneca.com

9.3. IMMEDIATE REPORTING BY INVESTIGATOR TO IRB AND MONITORING COMMITTEE

Serious, suspected, and unexpected adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance must be documented on a «Serious Adverse Event/Expedited Report from a Clinical Trial» form in accordance with the «Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial» form. This form must be completed and supplied to the sponsor within 1 working day. The «Serious Adverse

Event/Expedited Report from a Clinical Trial» form and the instructions are provided in the investigator's study file.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).
Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up «Serious Adverse Event/Expedited Report from a Clinical Trial» form.

The «Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial» form give more detailed guidance on the reporting of serious adverse events, adverse events that comply with alert terms, and adverse events initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the Chief Principal Investigator on a «Serious Adverse Event/Expedited Report from a Clinical Trial» form.

9.4. OTHER EVENTS REQUIRING REPORTING

9.4.1. Timeline

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca/MedImmune representatives within 1 day, ie, immediately but no later than 24 hours of when they become aware of it. The designated AstraZeneca/MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-threatening or follow-up Fatal/Life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the event of medication error, drug abuse, or drug misuse and within 30 days for all other events.

9.4.2. Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for study participants that either causes harm to the participant or has the potential to cause harm to the participant.

9.4.3. Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of study intervention or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

9.4.4. Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention for medicinal purposes outside of the authorised product information, or for unauthorised study intervention, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

9.4.5. HEPATIC FUNCTION ABNOMALITY

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 9.2 for contact information, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

9.4.6. PREGNANCY

- **Maternal exposure**

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the

patient was discontinued from the study.
If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.
The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.
The same timelines apply when outcome information is available.

- **Paternal exposure**

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.
Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.
Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

10. STATISTICAL CONSIDERATION

10.1. ANALYSIS SET

10.1.1. EFFICACY ANALYSIS SET

- **Intent-to-Treat Population**
  All patients who were screened and were eligible will be included in the intent-to-treat population.

- **Per-Protocol Population**
  The per-protocol population excludes patients who did not receive at least one dose study treatment, or who had a major violation of protocol inclusion or exclusion criteria.

10.1.2. SAFETY ANALYSIS SET

Safety analysis set comprises subjects who have been registered and took the study treatment at least once.

10.2. SAMPLE SIZE AND RATIONALE

The primary endpoint is objective response rate of durvalumab in mismatch repair deficient (microsatellite instable) or POLE mutated metastatic colorectal cancer patients who have progressed after standard therapies.
Assuming the target of response rate was set to 30% and a rate of 10% or below was considered futile. A 2-stage optimal design, as proposed by Simon, was used to allow early termination of any ineffective treatment early in the study. With a 1-sided, type I error of 5% and power of 0.8, the planned study was to proceed in 2 steps. In the first step, 10 patients were required, and if complete or partial response was observed in 2 or more patients, the study was to proceed to the second step with 19 additional patients (29 patients as a total). If this condition was not met, the study would be stopped for futility. In the second step, if complete or partial response was observed in 6 or more patients, the treatment will be considered effective. Assuming a dropout rate of 10%, 33 patients were required.

10.3. STATISTICAL PARAMETERS AND STATISTICAL ANALYSIS PLAN

Safety analysis will be conducted in the safety analysis set. Safety evaluation will include all patients who receive at least one dose of study drug. The safety analysis is based on the abnormality of laboratory test and clinical adverse events. Considering the percentage of laboratory abnormalities or clinical adverse events, descriptive statistics (or Fisher's exact test, Chi-square test for comparison between parameters) will be used. The primary endpoint, the objective response rates, will be described with percentage (%) and 95% confidence intervals. The survival outcomes, secondary endpoints, will be calculated using Kaplan-Meier method, compared using long-rank test and described with 95% confidence intervals. The disease-control rates will be described with percentage (%) and 95% confidence intervals, and compared using odds ratio and Chi-square tests. The Kaplan-Meier method will be used to estimate progression-free and overall survival curves, and the Cox proportional hazards regression model will be used for multivariate analysis of prognostic factors for survival outcomes.

10.4. FINAL ANALYSIS

Final analysis will be conducted in all patients for all endpoints at completion of follow-up.

11. ETHICAL AND LEGAL ASPECTS

11.1. GOOD CLINICAL PRACTICE (GCP)

This study is to be conducted according to globally accepted standards of good clinical practice (as defined in the Korean GCP), in agreement with the Declaration of Helsinki and in keeping with local regulations.

11.2. DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the study are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

11.3. SUBJECT INFORMATION AND INFORMED CONSENT

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the KGCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician. After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions. If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g., the subject's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date. A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator. The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. The investigator should inform the subject's

primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

11.4. CONFIDENTIALITY

All the information related to this study will be used only for research and all personal data will be handled in strictest confidence. Only the subject number and subject initials will be recorded in the case report form, and all personal information and/data will be handled as independent data to enable records to be identified with securing confidentiality. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor, institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with the Korean Medical Service Act.

11.5. PROTOCOL AMENDMENTS

Without investigators agreement this clinical study protocol will not be modified. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol. When contents of the analysis protocol are modified, the contents of all modifications will be described in the analysis protocol and final report of the study. Background for modification of the analysis protocol will be recorded.

11.6. APPROVAL OF THE CLINICAL STUDY PROTOCOLS AND AMMENDMENTS

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements must be met. The IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised. The investigator must keep a record of all communication with the IRB and, if applicable, between a coordinating investigator and the IRB. This also applies to any

communication between the investigator (or coordinating investigator, if applicable) and the authorities.

11.7. CLOSURE OF THE STUDY

The study must be closed at the site on completion. Furthermore, the sponsor or the investigator has the right to close this study site at any time. As far as possible, premature closure should occur after mutual consultation. Depending on local legislation, it may be necessary to inform IRB and the regulatory authorities when the study site is closed.

11.8. FINANCIAL DISCLOSURE

Not applicable to this study

12. Exploratory biomarker studies

Additional genetic tests will be performed in tumor tissues of patients participating in the study, and tests are performed to find predictive factors for treatment in patients with and without response. At least 10 slides from the paraffin block of the tumor tissue (primary or metastatic) will be prepared, therefore, in some patients with both primary and metastatic tumor tissues, a total of 20 (10) primary and metastatic sites can be prepared. The screening number and date of collection will be described and delivered to the Asan Medical Center, Seoul, Korea. The details of sample delivery, slide production, processing and delivery shall be as provided to each joint research institution. Providing slides for biomarker studies is not mandatory for participation in this study. However, because of the use of the stored tumor tissue, the patient is not burdened with any additional expense or procedure, and encourages active provision of the patient if there is no additional personal information or the risk of exposure of genetic information.

Biomarkers to be examined are as follows.

- Opal Multiplex Tissue Staining with OpalTM including PD-1 and PD-L1

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Appendix A.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –October 2022

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade $\leq$1, corticosteroid should be tapered over $\geq$28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids.

Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435

2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-1768.

3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2017;28(Suppl4):i119-i1142.

4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.

5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2022. Published February 28, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). – Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of	**For Grade 2** – Monitor symptoms daily and consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).

		steroid taper (≤10 mg prednisone or equivalent).	– Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider, discussing with Clinical Study Lead.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	in study protocol for defining the CTCAE grade/severity)		other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until re solution to Grade ≤1 • If toxicity improves to Grade ≤ 1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** • For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤ 1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). • For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy,</u>** **Permanently discontinue both durvalumab and tremelimumab for 1) Grade 3 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis.*** PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	• No dose modifications. • If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT ≥3 × ULN AND bilirubin ≥2 × ULN without initial	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

		findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug /study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV]) See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
	Isolated AST or ALT >ULN and ≤2.5× BLV,	– No dose modifications. – If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. – For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	ALT or AST > 2.5-≤ 5X BLV and ≤ 20xULN	• Hold study drug/study regimen dose until resolution to AST or ALT ≤ 2.5×BLV . • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

	or ALT ≤2.5×BLV , resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
ALT or AST >5-7X BLV and ⩽ 20X ULN OR concurrent 2.5 -5X BLV and ⩽ 20 XULN AND total bilirubin > 1.5 - < 2 x ULN	– Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤ 2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). − Consider Consulting a nephrologist. − Consider imaging studies to rule out any alternative etiology − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. − Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. − Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** − Consider including hydration, electrolyte replacement, and diuretics as clinically indicated − Follow urine protein/creatinine ratio every 3-7 days − Carefully monitor serum creatinine as clinically warranted.

			– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/ grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**

	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Stud

			y Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Consider consulting an endocrinologist for endocrine events. − Consider discussing with Clinical Study Lead, as needed. − Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. − Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though

			it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not
	Grade 1	No dose modifications.	

	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	indicated as long as there are no other signs or symptoms of pancreatic inflammation. − Assess for signs/symptoms of pancreatitis − Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) − If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase − If evidence of pancreatitis, manage according to pancreatitis recommendations
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology. − Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** − Consider IV hydration − Consider Gastroenterology referral
	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCA	**General Guidance**	**For Any Grade**

	E applicable version in study protocol for defining the CTCAE grade/severity)	– Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	– Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/stud y regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead.(Last bullet) – Consider hospitalization. – Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCA E applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/stud	**For Grade 2**

		y regimen.	– Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/stud y regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Transverse Myelitis	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain – Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, HIV, rapid plasma reagin (R PR), ANA, anti-Ro/La antibo dies, aquaporin-4 IgG, myeli n oligodendrocyte glycoprotei n (MOG) IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCA E applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes

			can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS – Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**

Guillain-Barré Syndrome (GBS)		General Guidance	− Recommend hospitalization − Obtain neurology consult − Obtain MRI of spine to rule out compression lesion − Obtain lumbar puncture − Antibody tests for GBS variants − Pulmonary function tests − Obtain electromyography (EMG) and nerve conduction studies − Frequently monitor pulmonary function tests and neurologic evaluations − Monitor for concurrent autonomic dysfunction − Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	− Obtain neurology consult − Recommend hospitalization − Obtain pulmonary function tests − Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies − Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis − Obtain electromyography (EMG) and nerve conduction studies − Consider MRI of brain/spine to rule out CNS involvement by disease − Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	− Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) − Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)

	Grade 3-4	Permanently discontinue	– Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement – Start plasmapheresis or IVIG – Consider rituximab if refractory to plasmapheresis or IVIG – Frequent PFT assessments – Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.

	Grade 2, 3 or 4	• If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation.

			– Consider, as necessary, discussing with the Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
	Grade 1	• No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the Clinical Study Lead.
	Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to

			3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3	**For Grade 3** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult

			– Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** − The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. − Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard or study protocol prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

APPENDIX B.

Durvalumab weight based dose calculation

For durvalumab dosing done depending on subject weight. Weight-based dosing should be utilized for patients ≤ 30 kg:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Cohort dose: 20 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

APPENDIX C.

POLE

After peer review (by a pathologist) of matched H&E slides for each of the FFPE tissues under the microscope, two to five 6 μm sections will be used for extraction of genomic DNA per FFPE tissue specimen, depending on tumor size and cellularity. After treatment with xylene and ethanol for de-paraffinization, genomic DNA will be isolated using the NEXprep FFPE Tissue Kit (#NexK-9000; Geneslabs, Gyeonggi, Korea) in accordance with the manufacturer's recommendations. The tissue pellet will be completely lysed overnight at 56°C by incubation with proteinase K in lysis buffer, followed by an additional incubation for 3 min with magnetic beads and solution A at room temperature. After incubation for 5 min on the magnetic stand, the supernatant is removed, and then washed with ethanol three times. After the beads are dried for 5 min, DNA is eluted in 50 μL DNase-/RNase-free water, followed by quantification using the Quant-iT™ PicoGreen dsDNA Assay kit (Invitrogen Life Technologies). Exon 9 will be amplified with the following primers: 5′-CTCCCTGTTGGTGATGAGGT-3′ (forward) and 5′-GGGTCCTTCTCCCAGCTCTA-3′ (reverse). The Sanger sequencing of all PCR products will be subsequently conducted on an ABI Prism 3730xl Genetic Analyzer (Life Technologies, Carlsbad, CA) for detecting POLE mutations. The representative hotspots for mutated POLE include P286R and V411L.