Abbreviated Title: Olaparib plus Durvalumab

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Title: Phase II Trial of Olaparib (LYNPARZA) plus Durvalumab (IMFINZI) in EGFR-Mutated Adenocarcinomas that Transform to Small Cell Lung Cancer (SCLC) and Other Neuroendocrine Tumors

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Commercial Agents:

Drug/Name:	Olaparib (Lynparza)	Durvalumab (Imfinzi)
IND Number:	IND Exempt	
Sponsor:	IND Exempt	
Manufacturer:	AstraZeneca	AstraZeneca
Supplier	AstraZeneca	AstraZeneca

PRÉCIS

Background:

- Targeted therapies designed for specific genetic alterations, known as cancer driver mutations, have changed the treatment paradigm in advanced non-small cell lung carcinoma (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective in NSCLC with activating mutation in the EGFR. Although most patients achieve robust responses to EGFR TKIs with tumor shrinkage and symptomatic relief, drug resistance eventually develops in the majority of patients.
- Small cell lung cancer (SCLC) transformation has been reported as one of the mechanisms of acquired resistance to EGFR TKIs.
- Several phase III trials showed durable response with poly (ADP-ribose) polymerase (PARP) inhibitors in the breast and ovarian cancer with BRCA mutation, a tumor suppressor gene involving homologous recombination repair (HRR) pathway, and several PARP inhibitors are now FDA approved for these cancers.
- Immune checkpoint blockade appears to be most effective against hypermutated tumors, suggesting that clinical responses correlate with an increased propensity to produce neoantigens.
- EGFR-mutated transformed SCLC is an aggressive cancer whose clinical course is similar to that of SCLC. There are no standard treatments for this disease and prospective studies have not been conducted to date. Immune checkpoint inhibitors alone are not effective for EGFR-mutated transformed SCLC. Analyses of EGFR transformed SCLC tumors suggest that these tumors are HRR deficient.

Objective:

- To assess the efficacy of a combination of durvalumab and olaparib with respect to best overall response (BOR) according to Response Evaluation Criteria (RECIST 1.1) in patients with EGFR-mutated non-small-cell lung carcinoma (NSCLC) that transform to SCLC and other neuroendocrine carcinomas.

Eligibility:

- Subjects with initial diagnosis of EGFR-mutated non-small-cell lung carcinoma (NSCLC) and histologically or cytologically confirmed transformation to small cell/neuroendocrine tumors following treatment with EGFR tyrosine kinase inhibitor.
- Subjects should have received platinum-based chemotherapy with or without immunotherapy for small cell/neuroendocrine transformation or refused such therapy.
- Age ≥18 years.
- Subjects must have measurable disease.
- ECOG performance status ≤ 2
- Adequate organ function

Design:

- This is an open label Phase II study evaluating the combination of durvalumab and olaparib in participants with EGFR-mutated non-small-cell lung carcinoma and histologically or cytologically confirmed transformation to small cell/neuroendocrine tumors following treatment with EGFR tyrosine kinase inhibitor.
- Patients will be treated with durvalumab (1,500 mg), IV, every 28 days and olaparib (300 mg BID for total daily dose of 600 mg) in a 28-day cycles.
- Patients will be evaluated for toxicity every 4 weeks by CTCAE v5.0, and for response every 8 (+/-1) weeks by RECIST 1.1
- Treatment will continue until disease progression or unacceptable toxicity.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objective

- To assess the efficacy of a combination of durvalumab and olaparib with respect to best overall response (BOR) according to Response Evaluation Criteria (RECIST 1.1) in patients with EGFR-mutated non-small-cell lung carcinoma (NSCLC) that transform to SCLC and other neuroendocrine carcinomas.

1.1.2 Secondary Objectives

- To determine the progression-free survival
- To evaluate safety and tolerability of a combination of durvalumab and olaparib
- To determine overall survival

1.1.3 Exploratory Objectives

- To study immune subsets and cytokine markers of response
- To evaluate circulating tumor cells and circulating tumor DNA (ctDNA)
- To study paraneoplastic autoantibodies
- To perform whole exome sequencing of normal (germline) DNA
- To perform molecular profiling of EGFR-mutated transformed small cell/neuroendocrine tumors by RNA sequencing and whole exome/genome sequencing of tumor tissue;
- To evaluate transcriptome and NanoString Pan Cancer Immune Panel genes in blood.

1.2 Background and Rationale

1.2.1 EGFR-Mutated Adenocarcinoma that Transformed to Small Lung Cell Carcinoma

Targeted therapies designed for specific genetic alterations, known as cancer driver mutations, have changed the treatment paradigm in advanced non-small cell lung carcinoma (NSCLC). Epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitors (TKIs) are effective in NSCLC harboring an activating mutation in the EGFR. Although most patients achieve robust responses to EGFR TKIs, with tumor shrinkage and symptomatic relief, acquired drug resistance eventually develops in the majority of patients. The most common mechanism of resistance is the EGFR Thr790Met gatekeeper mutation.

Small cell lung cancer (SCLC) transformation has been reported as one of the mechanisms of acquired resistance to EGFR TKIs. EGFR-mutated transformed SCLC was first described in 2006 in a 45-year-old woman with EGFR-mutant lung adenocarcinoma and treated with EGFR TKI erlotinib. The tumor responded for 18 months, and biopsy at the time of progression showed SCLC with the original EGFR exon 18 deletion mutation [1]. Since this first case, several other case series of EGFR-mutated adenocarcinoma transforming to SCLC have been reported. The reported incidence of SCLC transformation from EGFR-mutated lung adenocarcinoma varies from 2 to 14 % in different cohorts [2-5].

1.2.2 Molecular Mechanisms in EGFR-Mutated Transformed SCLC

Genomic sequencing of both the original tumor and the repeat biopsy samples at the time of resistance shows that transformed SCLC tumor samples retain the original EGFR mutation in most cases, which suggest that these are not de novo cancers, but a transformed phenotype as a mechanism of resistance to treatment [4]. EGFR-mutated transformed SCLC demonstrate many features of classical SCLC [6]. The transcriptional profiles of cell lines established from EGFR-mutated transformed SCLC mimic classical SCLC including neuroendocrine markers. The cell lines also show universal alterations of Rb1, the key tumor suppressor involving in de novo SCLC. Similar to de novo SCLC, EGFR expression is also lower in transformed SCLC cell lines.

A study by Lee et al. [7] using whole genome sequencing of nine tumors acquired at various time points from four patients with EGFR-mutated transformed SCLC showed complete inactivation of both Rb1 and TP53 in lung adenocarcinomas prior to transformation. They also found that inactivation of both Rb1 and p53 at the initial diagnosis of EGFR-mutated NSCLC was strikingly more frequent in the small-cell–transformed group than non-transformed lung adenocarcinoma group (82% vs 3%; odds ratio: 131; 95%CI: 19.9 – 859). Among patients registered in a predefined cohort (n = 65), an EGFR-mutated lung adenocarcinoma that harbored completely inactivated Rb1 and p53 had a 43 times greater risk of small cell transformation (relative risk: 42.8; 95% confidence interval [CI]: 5.88 – 311). Branch-specific mutational signature analysis revealed that apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC)-induced hypermutation was frequent in the branches with small-cell transformation.

Lin et al. [8] established two cell lines from EGFR-mutated transformed SCLC samples which also harbored inactivation of Rb1 and TP53. Interestingly, two distinct morphological phenotypes were observed in the two cell lines: a suspension of spheroid aggregates which expressed the neuroendocrine markers ("classical subtype SCLC cells") and an adherent monolayer which had characteristics of mesenchymal morphology and cell markers (non-neuroendocrine[non-NE] subtype SCLC cells). The cultured classical subtype SCLC cells had slower tumor growth rate than non-NE subtype SCLC cells. EGFR protein expression in classic SCLC and non-NE subtype SCLC cells were low and showed resistance to EGFR inhibitors, gefitinib and osimertinib.

Ogino et al. also established cell lines from EGFR-mutated transformed SCLC samples and showed classical and non-NE subtypes of SCLC among them as well as universal inactivation of TP 53 and Rb1 [9].

In a retrospective study of patients with EGFR-mutated transformed SCLC, the most common mutations in transformed SCLC were TP53 (38 [79%] of 48 patients), Rb1 (18 [58%] of 31 patients), and PIK3CA (14 [27%] of 52 patients) [10].

1.2.3 Clinical Course of EGFR-Mutated Transformed SCLC

There are no prospective studies that have been addressing the clinical course of EGFR-mutated transformed SCLC. Two retrospective studies are available.

Ferrer et al. [11] conducted a retrospective study of 48 patients with EGFR-mutated transformed SCLC and 13 patients with non-EGFR mutated transformed SCLC. Both groups had transformed from NSCLC. The median age of EGFR-mutated transformed SCLC group was 61 years, 33 (69%) were female, and 28 (62%) were never smoker. The majority of patients (36 of 48) had EGFR exon 19 mutation at initial NSCLC diagnosis. Molecular analyses were performed in 38 (79%) patients after transformation and 32 (84%) tumors retained the same mutation as the one observed

initially. One of thirty patients (3%) who harbored exon 19 EGFR mutation at initial diagnosis had L858R mutation and five (17%) lost their original EGFR mutation at transformation. One of seven (14%) tumors that initially had L858R EGFR mutation lost the original mutation at transformation. In 3 patients who initially had EGFR exon 19 mutation, the transformation was associated with PI3K mutation and c-MET amplification (one patient), ALK fusion alone (one patient), and ALK fusion and EGFR exon 21 and 10 mutations (one patient). The median time to SCLC transformation was shorter in EGFR-mutated group compared with non-EGFR mutated transformed SCLC group (16 vs. 26 months, P = 0.01). In EGFR-mutated SCLC group, 38 patients were treated with TKI and 10 patients were treated with platinum-based chemotherapy before transformation.

In the other retrospective study conducted by Marcoux et al. [10], 67 patients with EGFR-mutated transformed SCLC were included. Their median age was 56 years, 38 (57%) were female, 49 (73%) were never smokers. Nine (13%) patients had SCLC or mixed histology at initial diagnosis. Forty-five (67%) patients had EGFR exon 19 mutation initially. All the patients with EGFR-mutated NSCLC were treated with TKI before transformation and all of them retained their original mutations at transformation. Median time from NSCLC diagnosis to transformation was 17.8 months.

Of four NCI patients with EGFR-mutated transformed SCLC, two patients (CL0196, NCI0402) had EGFR exon 19 deletion at initial diagnosis of NSCLC and were treated with TKIs until transformation (**Table 1**).

Patient CL0083 was initially diagnosed as non-EGFR mutated NSCLC and treated with several systemic chemotherapies, and subsequently found to have EGFR exon 21 L858R mutation. The patient was started on erlotinib and was found to have exon 20 T790M mutation at resistance with erlotinib, and subsequently treated with osimertinib until SCLC transformation.

Patient #4 was initially diagnosed as EGFR exon 19 mutated stage IV NSCLC and treated with erlotinib. Resistance to erlotinib developed 16 months later with EGFR exon 20 T790M mutation. Subsequently patient started combination immunotherapy with nivolumab (PD-1 inhibitor), ipilimumab (CTLA4 inhibitor) and erlotinib but developed pneumonitis, and subsequently started osimertinib (3rd generation EGFR inhibitor). This patient was also treated with investigational personalized peptide vaccine, nivolumab and ipilimumab in addition to osimertinib. However, disease slowly progressed 21 months after starting osimertinib. Repeat biopsy with right supraclavicular lymph node showed transformation to high grade neuroendocrine lung cancer with small cell morphology.

At transformation, three tumors retained their original EGFR mutations (CL0083, NCI0402 and #4), whereas the other (CL0196) lost the original EGFR mutation. The time from initial diagnosis to transformation were 40.3, 14.5, 18.7 and 40 months, respectively.

1.2.4 Treatment for EGFR-Mutated Transformed SCLC

There are no standard treatments currently for patients with EGFR-mutated transformed SCLC and no prospective clinical trials have been conducted. In the retrospective study by Ferrer et al described above [11], 42 of 48 (88%) patients in EGFR-mutant SCLC group received at least one line of treatment after transformation, mostly platinum-based chemotherapy. Six patients received only supportive care at the time of transformation. The partial response rate and the median overall survival (OS) rates after diagnosis of NSCLC and transformation were similar between EGFR-

mutated and non-EGFR-mutated SCLC groups (partial response rate: 45% vs. 40%; median OS: 28 vs. 37 months after diagnosis of NSCLC and 9 vs. 10 months after transformation, respectively). In the other retrospective study by Marcoux et al [10], also, most patients (93%) were treated with platinum-based chemotherapy after transformation. Although clinical response rate was 54%, the median progression-free survival (PFS) was short at 3.4 months and median OS after transformation 10.9 months. These outcomes are similar to that of de novo SCLC.

In the Marcoux series, 17 of 67 patients were treated with immune checkpoint inhibitor such as single-agent programmed death-1 inhibitor (PD-1), programmed death-ligand 1 (PD-L1) inhibitor or combination with PD-1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitors. Interestingly, none of the 17 patients treated responded to the intervention. Among the four NCI patients described above, two (CL0083 and NCI0402) were treated with several systemic treatments including platinum-based chemotherapy, combination of osimertinib and chemotherapy or osimertinib and nivolumab, and phase 2 investigational treatment with no responses. These two patients died 13 and 4.6 months after SCLC transformation (**Table 1**). CL0196 was initially treated with platinum-based chemotherapy without any response but has an ongoing durable partial response to poly (ADP-ribose) polymerase (PARP) inhibitor olaparib and PD-L1 inhibitor durvalumab. Patient #4 remains on treatment with platinum-based chemotherapy (4.0 months after transformation).

Patient	Age	Sex	Race	Disease site at initial diagnosis	Egfr mutation at diagnosis	Treatment before transformation	Response	Time to transformation (months)	Egfr mutation at transformation	Treatment after transformation	Response	Survival from Diagnosis (months)	Survival from transformation (months)
CL0083	57	F	African American	diffuse pleural lesions in left chest left side pleural effusion diffuse bone lesions	exon 21 (L858R) exon 20 (T790M) (After erlotinib)	1. platinum + paclitaxel + bevacizumab followed by maintenance bevacizumab 2. pemetrexed + bevacizumab 3. topotecan 4. docetaxel 5. erlotinib 6. Osimertinib	1. SD 2. PD 3. SD 4. PD 5. SD 6. PR	40.3	exon 21 (L858R)	1. platinum +etoposide +osimertinib 2. nivolumab +osimertinib	1. PD 2. PD	53.2	13
CL0196	67	F	White	right upper lobe mass bilateral hilar and mediastinal lymphadenopathy left cervical lymphadenopathy bilateral supraclavicular lymphadenopathy	exon 19 deletion	1. pembrolizumab (until EGFR result came back) 2. Gefitinib	1. NA 2. PR	14.5	no EGFR mutation	1. platinum + etoposide 2. phase 2 investigational treatment	1. PD 2. PR	27.6+	13.1+
NCI0402	38	F	African American	Left lower lobe mass left lower lobe nodule left hilar lymphadenopathy left subcarinal lymphadenopathy right superior mediastinal lymphadenopathy brain lesions	exon 19 deletion (E746_A750del)	1. osimertinib	1. PR	18.7	exon 19 deletion (E746_A750del)	1. platinum + pemetrexed 2. phase 2 investigational treatment 3. platinum + etoposide	1. PD 2. PD 3. PD	23.3	4.6

Patient	Age	Sex	Race	Disease site at initial diagnosis	Egfr mutation at diagnosis	Treatment before transformation	Response	Time to transformation (months)	Egfr mutation at transformation	Treatment after transformation	Response	Survival from Diagnosis (months)	Survival from transformation (months)
#4	30	F	White	Bilateral lung nodules Mediastinal lymphadenopathy Supraclavicular lymphadenopathy Bone lesions Brain lesion	exon 19 (K745_A750del) exon 20 (T790M) (after erlotinib)	1. erlotinib 2. nivolumab + ipilimumab + erlotinib 3. osimertinib 4. investigational treatment 5. nivolumab + ipilimumab + osimertinib	?	40	exon 19 (K745_A750del)	1. platinum + etoposide	?	50.0+	4.0 +

Table 1 Clinical characteristics of patients with EGFR-mutated transformed SCLC

Best response was evaluated according to RECIST, F: female, PR: partial response, SD: stable disease, PD: progressive disease, NA: not assessed

1.2.5 Mutational Signatures in EGFR-Mutated Adenocarcinomas that Transform to Small-Cell Lung Cancer and Other Neuroendocrine Carcinomas

Alexandrov and colleagues derived 'mutational signature' from analysis of the genome [12], based on the principle that the type of nucleotide substitution and their context (i.e. the bases immediately before and after the substitution) may provide important information about the oncogenic process operative in the development and progression of cancer. By applying a mathematical algorithm to the aggregate of somatic mutations present in the individual cancers, 30 mutational signatures were identified initially, and later expanded to 49 signatures [13]. These include signatures that can be indicative of specific forms of DNA repair defects in cancer cells (e.g. homologous recombination repair [HRR] pathway defect [signature 3], DNA mismatch repair defect [signature 6, 15, 20, and 26], exposure to mutagenic/carcinogenic stimuli such as UV light [signature 7] and tobacco [signature 4 and 29]) [14, 15]. A study using ~1000 invasive breast cancer samples showed that biallelic inactivation of BRCA1/2 associates with mutational signature 3 [16]. A signature 3-based approach was superior to alternative approaches such as loss of heterogeneity and large-scale transition scores in classifying missense BRCA1 or BRCA2 variants known to impair HRR pathway.

To evaluate the HRR pathway defect in EGFR-mutated transformed SCLC, we analyzed the mutational signatures in 4 tumors of NCI patients with EGFR-mutated transformed SCLC described above (CL0083, CL0196, NCI0402) and 28 tumors from patients with de novo SCLC as control. As shown in **Figure 1**, the EGFR-mutated transformed SCLC group had a significantly higher proportion of signature 3 compared with de novo SCLC group (median [interquartile range]: 47 [34-49]% vs. 18 [14-27]%, p = 0.015 by Mann-Whitney test), suggesting that the former group may have an HRR pathway defect [14]. Signature 3 also inversely correlates with expression of genes involved in the HRR pathway such as RAD54B, RMI2, and UBE2T (**Figure 2 A-C**). Of 3 patients with EGFR-mutated SCLC, one patient (CL0196) has RAD51 mutation, which mediates pairing of homogenous DNA sequencing and strand invasion in HRR pathway [17] and another patient (CL0083) has DNA mismatch repair deficiency. As a confirmation, we also compared homologous recombination deficiency (HRD) score using whole exome sequencing data [18] in EGFR-mutated transformed SCLC (4 tumors) vs. de novo SCLC or extrapulmonary small cell cancers (37 tumors) of NCI Clinomics samples. The HRD score in EGFR-mutated transformed SCLC were significantly higher than de novo SCLC or extrapulmonary small cell cancers (P = 0.026 by Wilcoxon test, **Figure 3**)

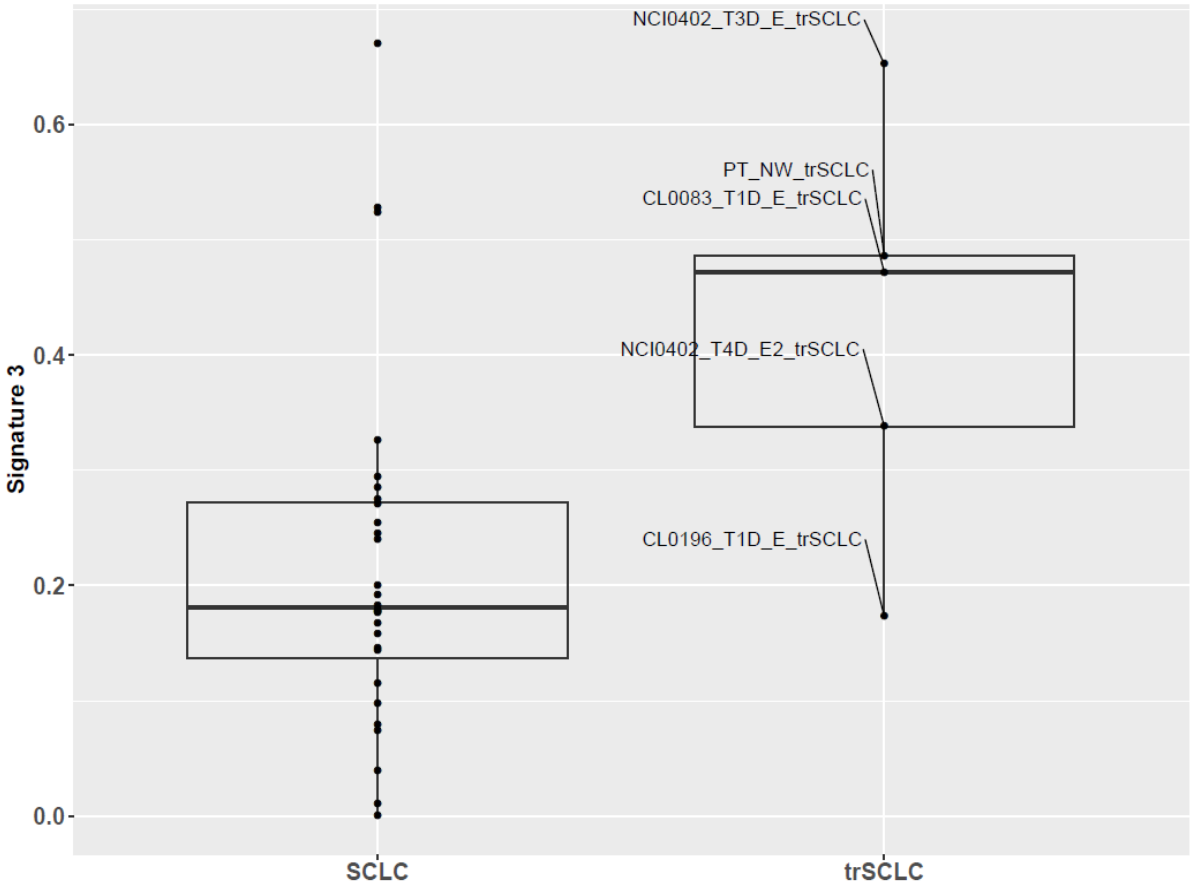
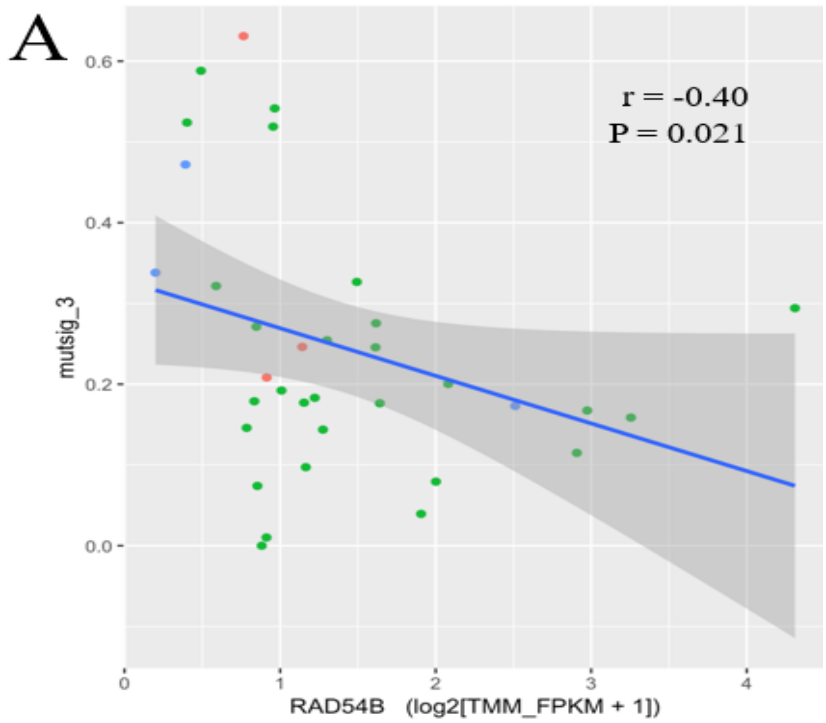
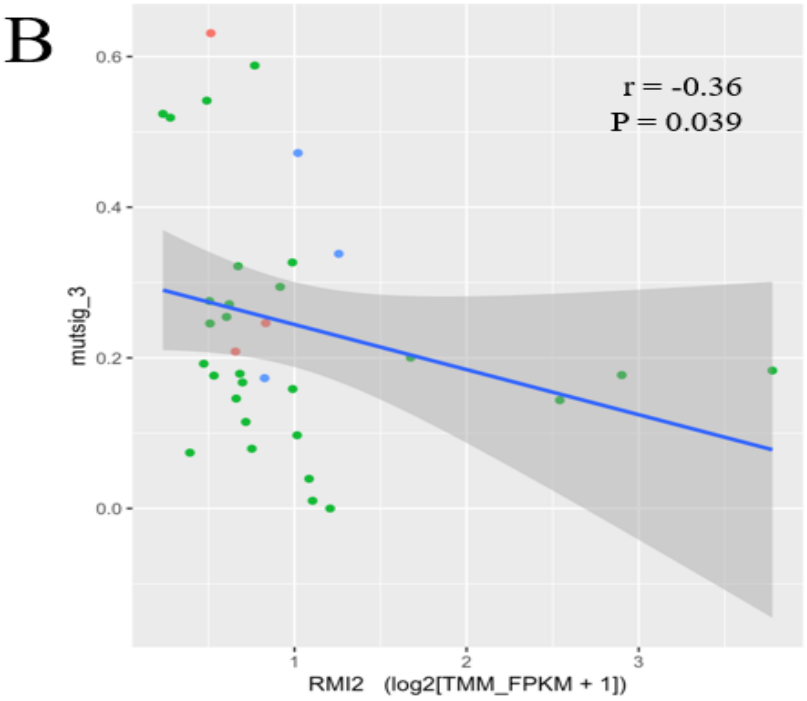


Figure 1. Proportion of signature 3 in patients with SCLC and EGFR transformed SCLC. Two samples were available from the patient NCI0402 at different time-points after transformation. trSCLC: EGFR-mutated transformed small cell lung carcinoma; PT_NW_trSCLC: patient #4.


A
r = -0.40
P = 0.021
mutsig_3
RAD54B (log2[TMM_FPKM + 1])


B
r = -0.36
P = 0.039
mutsig_3
RMI2 (log2[TMM_FPKM + 1])

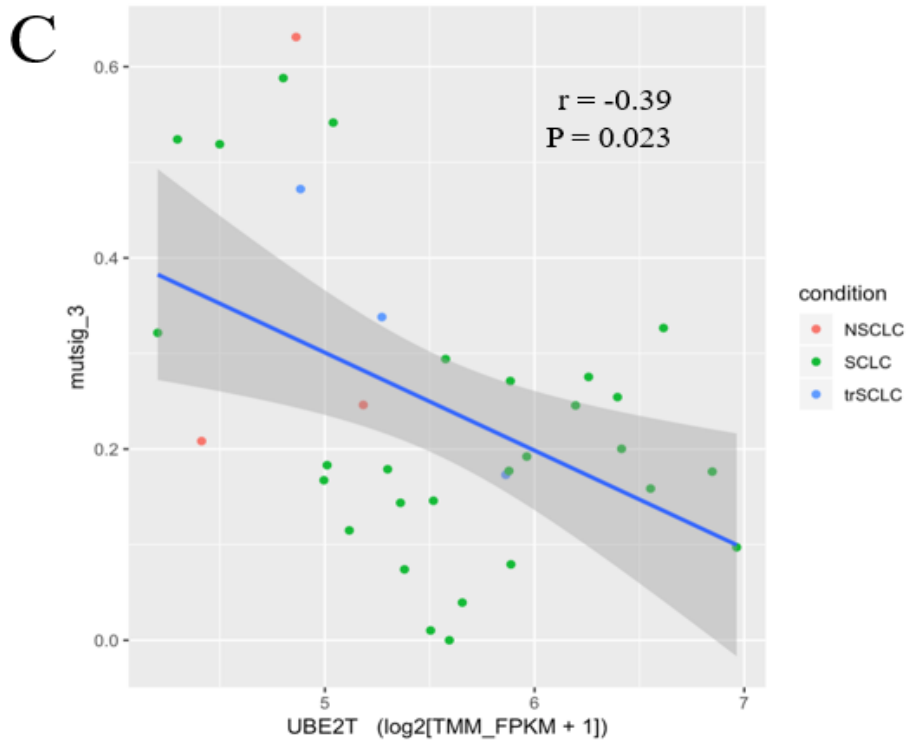


Figure 2: Correlation between the proportion of signature 3 and expression of RAD54B, RIM2, UBE2T. We used Spearman correlation test to evaluate the correlation. One sample from NCI0402 obtained before transformation was labeled as NSCLC. trSCLC: EGFR-mutated transformed small cell lung cancer; TMM: trimmed mean of M-value; FPKM: fragments per kilobase million

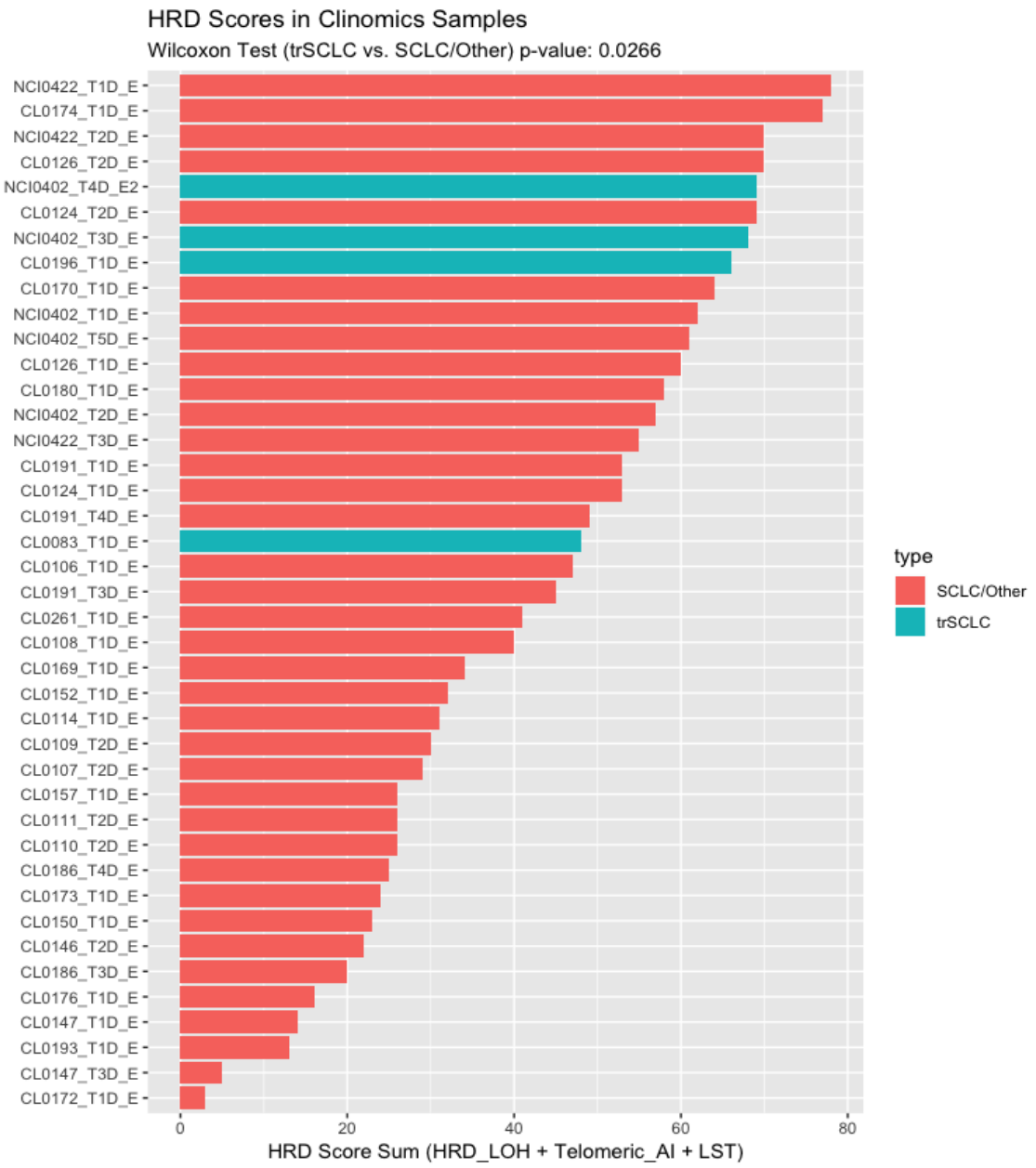


Figure 3: HRD score in EGFR-mutated transformed SCLC and de novo SCLC or extrapulmonary small cell cancers. We used Wilcoxon test to analyze statistical differences between EGFR-mutated transformed SCLC vs. others. HRD score was calculated as previously described [*18*]. HRD: homologous recombination deficiency; LOH; loss of heterozygosity; Telomeric AI; Telomeric allelic imbalance; LST; large-scale state transitions; SCLC: small cell lung cancer, trSCLC: EGFR-mutated transformed small cell lung cancer.

1.2.6 Poly (ADP-ribose) Polymerase (PARP)-1 Inhibitors in HRR Deficient Cancer

Proteomic profiling previously identified PARP-1 as a candidate drug target for SCLC [19]. PARP is recruited to DNA single-strand breaks (SSB) where it PARylates multiple substrates including histones to facilitate the relaxation of chromatin, as well as itself. PARP inhibitors stay bound within the PARP active site and the PARP protein is trapped on the DNA long enough to be

encountered by the replication machinery, and this results in a stalling of the replication fork, its collapse and the generation of DNA double strand breaks [20, 21]. Important consequence of this and the proposed basis of PARP inhibitor monotherapy activity is the generation of DNA double-strand breaks that would normally be repaired by the HRR pathway. In cancers with HRR deficiency, PARP trapping will result in significant genomic instability until it is no longer sustainable and tumor cell death results [22]. Several phase III trials showed durable response with PARP inhibitors in the breast and ovarian cancer with BRCA mutation, a tumor suppressor gene involving HRR pathway, and several PARP inhibitors are now FDA approved for these cancers [23-25].

Although PARP inhibitors are active in SCLC, the subsets of tumors that respond is not fully defined. In a phase I study, 23 patients with SCLC previously treated with ≥ 1 systemic therapy were treated with talazoparib [26]. Two (8%) patients had PR with duration response of 12.0 and 15.3 weeks, and further 4 patients (16%) has SD lasting at least 16 weeks. In a randomized phase II study of cisplatin and etoposide with veliparib or placebo in previously-untreated extensive-stage SCLC (N=128) [27], the median PFS and OS were not significantly different between two groups (median PFS: 6.1 months for veliparib vs. 5.5 months for placebo, P = 0.06; median OS: 10.3 vs. 8.9 months, P = 0.17). In a randomized, double-blind, phase II study of temozolomide in combination with veliparib or placebo in patients with refractory/relapsed SCLC (N=104) [28], no significant difference in 4-month PFS were noted between the two groups (36% for veliparib vs 27% for placebo, P = 0.19). The median OS was also not improved significantly (8.2 vs. 7.0 months, P = 0.50). In this study, significantly prolonged PFS (5.7 vs. 3.6 months, P = 0.009) and OS (12.2 vs. 7.5 months, P = 0.014) were observed in patients with SLFN11-positive tumors treated with temozolomide and veliparib. SLFN11 is a putative DNA/RNA helicase belonging to the Schlafen family of proteins which induces lethal S-phase arrest in response to DNA damage. Studies in patient-derived xenograft SCLC models have also demonstrated that SLFN11 expression measured by immunohistochemistry correlates with treatment responses to PARP inhibitors [29].

A recent preclinical report also showed that EGFR-mutated non-SCLC cells that acquired TKIs resistance exhibited PARP dependence for survival and PARP inhibitors sensitivity [30].

Authors demonstrated the 7 of 8 non-SCLC cell lines that acquired TKIs resistance with T790M mutation, MET amplification or epithelial to mesenchymal transition had lower half maximum inhibitory concentration, decreased colony survival, more tumor growth suppression efficacy, and increased gamma-H2AX foci (a biomarker for DNA double-strand breaks) with multiple PARP inhibitors compared with their TKI sensitive cell lines (**Figure 4)**. Interestingly, the PARP inhibitor sensitivity did not depend on PARP-trapping and DNA repair pathway, but NOX-dependent reactive oxygen species (ROS) though RAC1 (a small G-protein in the Rho family which is an activator of NOX-enzymes) PARPylation.

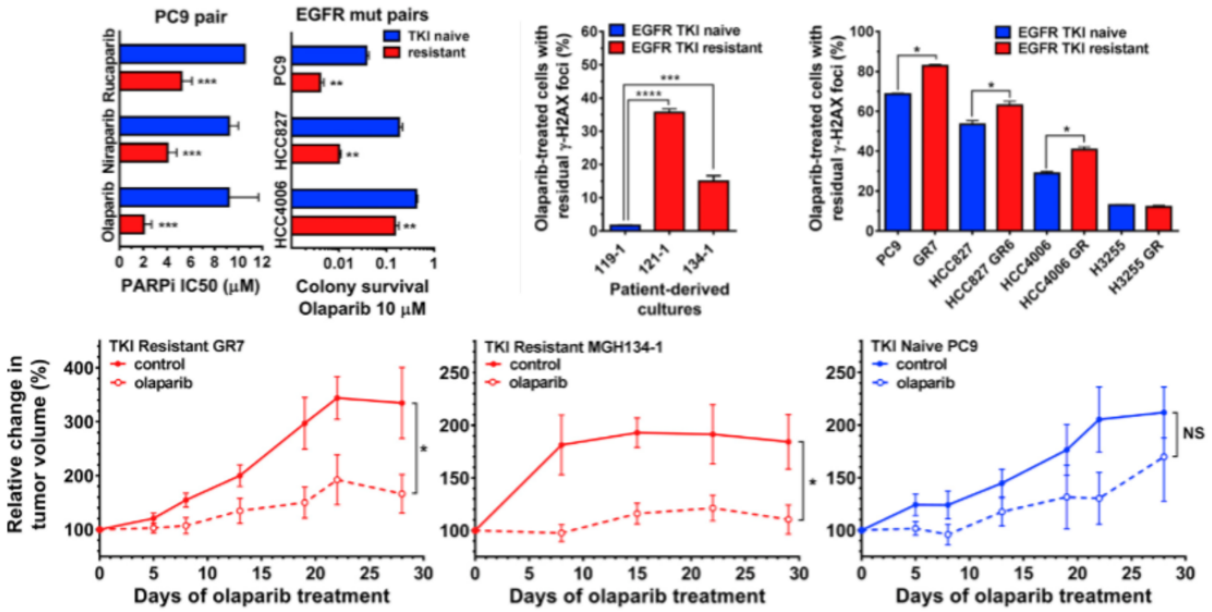


Figure 4. EGFR-mutated NSCLC lines are more sensitive to PARP inhibitors/inhibition. Several TKI-resistant EGFR-mutated non-SCLC cell lines had significant lower IC_{50} of rucaparib, niraparib, and olaparib compared with their TKI-naïve cell lines. Several TKI-resistant EGFR-mutated non-SCLC cell lines and heterotopic tumor xenograft from established and patient-delivered tumor cell lines were more sensitive to olaparib with significant higher levels of gamma-H2AX (a biomarker for DNA double-strand breaks) and tumor control. These data were published by Marcar L et al **[***30***]**

1.2.7 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumors with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

For full information, refer to investigator brochure.

1.2.7.1 Risks of Olaparib

1.2.7.1.1 Myelodysplastic Syndrome/Acute Myeloid Leukaemia (MDS/AML)

The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow up, was <1.5%, with higher incidence in patients with BRCAm PSR ovarian cancer who had received at least two prior lines of platinum chemotherapy

and were followed up for 5 years. The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from<6 months to >4 years. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA-damaging treatments. The majority of reports were in gBRCAm carriers and some of the patients had a history of more than one primary malignancy or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with olaparib, it is recommended that olaparib should be discontinued and the patient be treated appropriately.

1.2.7.1.2 Hematological Toxicity

Anaemia and other hematological toxicities were generally low grade (CTCAE Grade 1 or 2), however, there were reports of CTCAE Grade 3 and higher events. Anaemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies with first onset generally reported in the first 3 months of treatment. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with olaparib monotherapy, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in haemoglobin was 21%, absolute neutrophils 17%, platelets 5%, lymphocytes 26% and leucocytes 19% (all % approximate).The incidence of elevations in MCV from low or normal at baseline to above the ULN was approximately 68%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences. Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

1.2.7.1.3 Other Laboratory Findings

In clinical studies with olaparib the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 11%. Data from a double-blind placebo-controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline. The increase in blood creatinine level might be explained by inhibition of renal transporters such as OCT2, MATE1 and MATE2K by olaparib, as blood creatinine levels were found to return to baseline after treatment discontinuation.

1.2.7.1.4 Nausea and Vomiting

Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

1.2.7.1.5 Venous Thromboembolism

In clinical studies, the incidence of deep vein thrombosis and pulmonary embolism was 0.7% and 1.4%, respectively. Venous thromboembolism has been identified as an ADR associated with olaparib. A higher number of VTEs were noted in the olaparib arm of PROfound, PROpel, and PAOLA-1, and this imbalance appears to be associated with populations that have a higher risk of

VTEs, including an older male population with prostate cancer who also received continuous androgen deprivation treatment, and patients who received bevacizumab in combination with olaparib. Due to differences in follow-up time, patient selection, patient monitoring, and medical care, a direct comparison with the published literature data including published clinical trials, observational trials, and observational studies is challenging. However, the incidence of VTEs observed in PROfound, PROpel, and PAOLA-1 are consistent with the incidence reported in prostate cancer patients from the literature (Wong et al 2018, Deka et al 2019, Nguyen-Nielsen et al 2014, Sun et al 2016) and in the bevacizumab SmPC (described as a 'very common' ADR; Avastin SmPC 2022)

1.2.7.1.6 New Primary Malignancies Other Than MDS/AML

New primary malignancies have been reported in <1.0% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

For information on all identified and potential risks with olaparib always refer to the current version of the olaparib IB.

1.2.8 Efficacy of Immune Checkpoint Inhibitor in HRR Deficient Cancer

Immune checkpoint blockade appears to be most effective against hypermutated tumors, suggesting that clinical responses correlate with an increased propensity to produce neoantigens. BRCA1-mutated triple-negative breast cancer and high grade serous ovarian cancer exhibit an increased somatic mutational load and greater numbers of tumor-infiltrating lymphocytes, with increased expression of immunomodulatory genes including PD-1 and CTLA4, when compared BRCA1–wild-type tumors [31, 32]. In vivo studies also show that the combination of PD-1 and CTLA-4 inhibitors with cisplatin profoundly attenuate the growth of BRCA1-deficient breast tumors in vivo and improve overall survival [31, 33].

1.2.9 Durvalumab

Durvalumab (MEDI4736) is a selective, high-affinity human immunoglobulin G1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, thereby enhancing the function of tumor-directed T cells.

A population PK model was developed for durvalumab using monotherapy data from a Phase I 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 the 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 (5th, median and 95th 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 1,000 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-patient variability with fixed dosing regimen.

Similar findings have been reported by others [34-37]. 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 [35]. 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-patient variability in pharmacokinetic/pharmacodynamics parameters [36].

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 1,500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.2.9.1 Risks with durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus (which may present with diabetic ketoacidosis), diabetes insipidus, encephalitis, subcutaneous injection site reaction, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, enterocolitis, pancreatitis, proctitis, hepatic enzyme increased, other rare or less frequent inflammatory events including neurotoxicity, infusion-related reactions, hypersensitivity reactions, infections/serious infections, non-infective encephalitis, immune-mediated arthritis, uveitis and cytokine release syndrome.

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab investigator brochure.

In monotherapy clinical studies adverse events (AEs) (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 7% of patients experienced a serious adverse events (SAE) that was considered to be related to durvalumab by the study investigator. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated (**Appendix D**).

1.2.10 Combination Therapy with Durvalumab + Olaparib in SCLC and Transformed SCLC

We evaluated the efficacy of a combination of durvalumab, a PD-L1 inhibitor, and olaparib, a PARP inhibitor, in patients with relapsed SCLC in a phase II open-label, single-arm study [38]. In this study patients were treated with 1,500 mg every 28 days and olaparib 300 mg twice daily. After a median follow up of 11.1 months, one of 19 evaluable patients had confirmed CR and PR and four patients had SD. The median PFS was 1.8 months (95%CI: 0.9 – 2.4 months) and the median OS was 4.1 months (95%CI: 2.4 – 9.2 months). The study did not meet its primary endpoint and the objective response rate (ORR) of 10.5%. The confirmed ORR is similar to that of PD-1 inhibitor nivolumab alone in this setting [39]. The results of this study are in line with the findings from phase II basket study which administered olaparib as monotherapy for 4 weeks followed by combination with durvalumab in relapsed SCLC patients at least 12 weeks after platinum-based therapy [40]. Among 38 patients, 2 patients had responses (5%) and the 12-week disease control rate was 29%.

Interestingly, one of the cases with partial response in the NCI study had EGFR-mutated transformed SCLC (CL0196 described above; **Figure 5**). The patient was initially diagnosed as metastatic EFGR exon 19 deleted-lung adenocarcinoma and had received the PD-1 inhibitor pembrolizumab before the EGFR mutation results were available with no response, followed by a PR on gefitinib. Disease progression after one year of gefitinib was confirmed as transformed SCLC and did not respond to 2 cycles of carboplatin and etoposide. Subsequently the patient received olaparib plus durvalumab and had an 89% tumor shrinkage from baseline and remains on treatment at one year now. The patient's post-treatment biopsies displayed a dense T-cell infiltrate in clusters and aggregates extending deeply into the tumor with extensive tumor cell necrosis accompanied by increased PD-L1 expression on tumor and tumor-infiltrating immune cells suggesting a possible immune response driving the tumor response. In an international multicenter phase II basket study of olaparib and durvalumab, one instance of paired biopsy specimens obtained before and after olaparib run-in (that is, by olaparib alone) showed significant increase in PD-L1 expression and tumor infiltrating lymphocytes in a patient whose cancer responded to the combination [41].

Additionally, cell lines derived from patient #4 described above shows sensitivity to PARP inhibitors olaparib and rucaparib. The patient's tumor shows prominent proportion of signature 3 (approximately 80%)

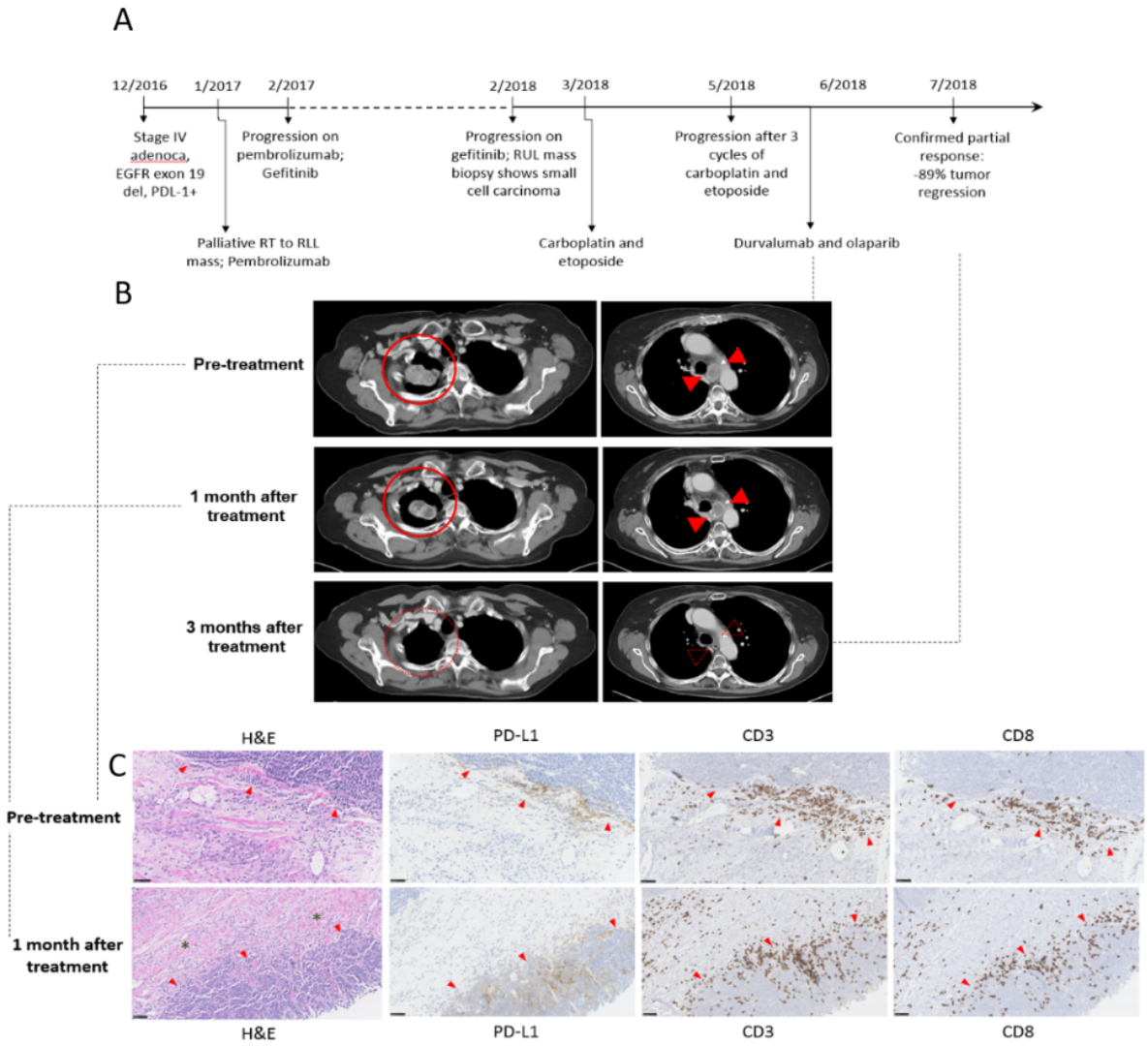


Figure 5. Clinical course and response with combination treatment with durvalumab and olaparib in a patient with EGFR-mutated transformed SCLC (CL0196). (A) timeline of treatment; (B) CT scan at pre-treatment, 1 months and 3 months after treatment. Red circles and arrows indicate right upper lobe mass and paraaortic lymph node, respectively; (C): Pre- and on-treatment biopsies stained immunohistochemically for the presence of PD-L1, CD3+ and CD8+ T cells (40X magnification)

1.2.11 Rationale for Combination Therapy with Durvalumab + Olaparib in EGFR Transformed SCLC

EGFR-mutated transformed SCLC is an aggressive cancer whose clinical course is similar to that of de novo SCLC. There are no standard treatments for this disease and prospective studies have not been conducted to date. Based on retrospective data reported by Marcoux et al, immune checkpoint inhibitors alone are not effective for EGFR-mutated transformed SCLC. Albeit in a limited number of patients, we have observed an enrichment of signature 3 indicative of defects in HRR pathways and a prevalence of mutations in DNA damage repair genes. We have also observed preclinical activity of PARP inhibitors in a patient derived cell line and durable ongoing partial response to olaparib and durvalumab in a patient with transformed SCLC. Taken together,

these provide rationale for a small pilot study testing combination of PARP inhibitor and immune checkpoint inhibitor in EGFR-mutated transformed SCLC.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

- Subjects with initial diagnosis of EGFR-mutated non-small-cell lung carcinoma (NSCLC) and histologically or cytologically confirmed transformation to small cell or neuroendocrine tumor following treatment with EGFR tyrosine kinase inhibitor.
- Subjects should have received platinum-based chemotherapy with or without immunotherapy for small cell/neuroendocrine transformation or refused such therapy.
- Age ≥18 years.
- Patients must have measurable disease per RECIST 1.1. See Section **6.3** for the evaluation of measurable disease.
- ECOG performance status ≤ 2 (**Appendix A**).
- Adequate hematological function within 28 days prior to enrollment as defined below:
  - white blood cell (WBC) count ≥ 3 × 10^9/L,
  - absolute neutrophil count (ANC) ≥ 1.0 ×10^9/L,
  - platelet count ≥75 × 10^9/L, and
  - Hgb ≥9 g/ dL if no blood transfusion within 4 weeks prior to enrollment OR >10 g/dL if no blood transfusion within 2 weeks prior to enrollment.
- Adequate hepatic function within 28 days prior to enrollment as defined by:
  - a total bilirubin level ≤ 1.5 × ULN; for subjects with documented/suspected Gilbert's disease, bilirubin ≤ 3 × ULN
  - an AST level ≤2.5×ULN, (≤ 5X ULN if liver metastasis)
  - an ALT level ≤2.5 ×ULN, (≤ 5X ULN if liver metastasis).
- Adequate renal function within 28 days prior to enrollment as defined by:

Creatinine OR Measured or calculated creatinine clearance (CrCl) (eGFR may also be used in place of CrCl) [A]	< 1.5x institution upper limit of normal OR ≥ 51 mL/min/1.73 m^2 for participant with creatinine levels ≥ 1.5 X institutional ULN
[A] Creatinine clearance (CrCl) or eGFR should be calculated per institutional standard.	

  - The effects of the study treatment on the developing human fetus are unknown; thus, women of childbearing potential must agree to use 1 highly effective form of contraception (see section **4.3.1.3**) and their partners must use a male condom, or they must totally/truly abstain from any form of sexual intercourse from the time of screening throughout the total duration of the protocol treatment and for at least 6 months after the last dose of the study drugs. Male participants and their partners must use a highly effective form of contraception (see section **4.3.1.3**) from the time of screening throughout the total duration of the protocol treatment and for 3 months after the last dose of study treatment.

- Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
  - Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of enrollment and confirmed prior to treatment on day 1. Postmenopausal is defined as: amenorrheic for 1 year (12 months in a row) or more following cessation of exogenous hormonal treatments; luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50, radiation-induced oophorectomy with last menses >1 year ago; chemotherapy-induced menopause with more than one-year interval since last menses; surgical sterilization for female participants (bilateral oophorectomy or hysterectomy) or male partners.
- Patients with symptomatic brain metastases will be excluded from trial secondary to poor prognosis. However, patients who have had treatment for their brain metastasis and whose brain disease is stable without steroid therapy for 2 weeks may be enrolled. Imaging to rule out brain metastases is not required for screening but should be performed prior to study enrollment if clinically indicated.
- Subjects must be able to understand and willing to sign a written informed consent document

2.1.2 Exclusion Criteria

- Patients who are receiving any other investigational agents. Patients may be on other clinical trials or treatment during screening to determine eligibility
- Systemic anti-cancer treatment or major surgery within 2 weeks prior to enrollment.
- Palliative radiation within 24 hours prior to enrollment.
- High-dose consolidative chest radiation within 2 weeks prior to enrollment.
- Major surgical procedure (as defined by the Investigator) within 28 days prior to enrollment. **Note:** local surgery of isolated lesions for palliative intent is acceptable.
- Patients receiving any medications or substances that are moderate and strong inhibitors or inducers of CYP3A4. A list of CYP3A4 inhibitors and inducers is provided in **Appendix B**. Note: dihydropyridine calcium - channel blockers are permitted for management of underling disease.
- History of auto-immune disease requiring steroid maintenance, or history of primary immunodeficiency.

- Current or prior use of immunosuppressive medication within 14 days before the enrollment, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone or an equivalent corticosteroid. In the case of short-term use of systemic corticosteroids (less than 24 hours within 28 days) of greater than 10 mg/day of prednisone or an equivalent corticosteroid, the required washout period prior to enrollment is 7 days.
- Patients with myelodysplastic syndrome/acute myeloid leukemia; or baseline clinical features suggestive of myelodysplastic syndrome or acute myelogenous leukemia.
- Persistent toxicities (≥ CTCAE grade 2) with the exception of alopecia, caused by previous cancer therapy.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition of olaparib or durvalumab.
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
- Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) and patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HBV or HCV RNA.
- HIV-positive patients on antiretroviral therapy are ineligible because of potential pharmacokinetic interactions with study drugs. However, patients with long-standing (>5 years) HIV on antiretroviral therapy > 1 month (undetectable HIV viral load and CD4 count > 150 cells/μL) may be eligible if the PI determines no anticipated clinically significant drug-drug interactions.
- History of allogenic organ transplantation, bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
- Uncontrolled intercurrent illness or medical condition including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia requiring medications ((except chronic atrial fibrillation/flutter with controlled vascular rate), or psychiatric illness/social situations that may impair the patient's tolerance of study treatments and, in the judgment of the investigator, would make the patient inappropriate for the study.
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication based on primary investigator decision.
- Pregnant women are excluded from this study because olaparib is a PARP inhibitor agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother

with durvalumab and olaparib, breastfeeding should be discontinued if the mother is treated with study drugs.

2.1.3 Recruitment Strategies

This study will be posted on the CCR website, www.clinicaltrials.gov, as well as on NIH websites and NIH social media forums. Outside providers and colleagues may directly refer patients for screening into this study.

2.2 Screening Evaluation

2.2.1 Screening Activities Performed Prior to Obtaining Informed Consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening Activities Performed after a Consent for Screening has been Signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. . Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Within 28 days prior to enrollment unless otherwise noted below:

- Complete medical history and physical examination, including height, weight, vital signs, and ECOG performance status.
- Three EKGs
- Laboratory Evaluation: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, glucose, albumin, calcium, magnesium, phosphorus, AST/ALT, total bilirubin, gamma glutamyl transferase, serum creatinine, PT/PTT, total protein, urine or serum HCG. Urinalysis: Hb/erythrocytes/blood, protein/albumin, glucose
- Activated partial thromboplastin time (APTT)
- International normalized ratio (INR)
- HIV (only for patients with long-standing (>5 years) HIV on antiretroviral therapy > 1 month), HBV and HCV viral load by PCR (only for participants with previous HBV or HCV infections)
- CD4 count (only for patients with long-standing (>5 years) HIV on antiretroviral therapy > 1 month)

- TB testing (if infection is suspected)
- CT of chest, abdomen and pelvis (or MRI of chest, abdomen and pelvis if clinically indicated)
- Tumor measurements
- Histologic or cytologic confirmation of small cell/neuroendocrine tumors transformation from any certified laboratory (at any time point prior to enrollment).
- Documentation of initial EGFR mutation status which was determined using standard assays such as PCR and NGS (at any time point prior to enrollment).
- Concomitant medication review
- Pregnancy test for women of child bearing potential

2.3 Participant Registration and Status Update Procedures

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Subjects with EGFR-mutated transformed small cell lung cancer or neuroendocrine tumors.

Arms

Number	Name	Description
1	Arm 1	Combination of durvalumab and olaparib.

Arm assignment

Subjects in Cohort 1 will be directly assigned to Arm 1.

2.3.2 Screen Failures

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

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a transient underlying condition not related to the condition under study may be rescreened once after the underlying condition has resolved.

2.4 Baseline Evaluation

Tests done at screening do not need to be repeated on baseline if performed in designated time frame prior to start of study treatment.

Within 14 days prior to first dose:

- CT of chest, abdomen and pelvis (if for clinical reason patient had MRI of chest, abdomen and pelvis at screening for evaluation of the disease, MRI will continue to be used for evaluation of disease during this trial)
- Tumor measurements
- Optional tumor research biopsy
- Baseline symptoms evaluation
- Amylase, lipase
- Collection of available unstained slides or a block from previous biopsies/surgeries for research
- Collection of research blood for paraneoplastic autoantibodies assays and whole exome/genome sequencing

3 STUDY IMPLEMENTATION

3.1 Study Design

The proposed study is an open label, single-arm phase II study of durvalumab in combination with olaparib, in patients with EGFR-mutated transformed small cell or neuroendocrine tumors.

Treatment with durvalumab and olaparib will be delivered in cycles consisting of 4 weeks (+/- 3 days) and start on cycle 1 day 1.

Durvalumab (1,500 mg) will be given IV every 28 days and olaparib (300 mg BID for total daily dose of 600 mg) will be administered orally on every day of every cycle.

Treatment will continue until off treatment criteria are met (see section **3.6.1**)

If one of the study drugs is permanently discontinued because of toxicity, the patient may continue the other study drug per PI discretion until off treatment criteria are met (section **3.6.1)**.

Patients will be monitored for disease status every 8 (+/- 1) weeks with imaging.

Patients may undergo optional biopsies for research purposes at the following time points: pretreatment, on cycle 1 day 15 (+/- 4 days) and at disease progression.

3.2 Drug Administration

3.2.1 Durvalumab

Durvalumab will be administered IV into a peripheral or central vein on Day 1 of every cycle at a flat dose of 1,500 mg.

The entire contents of the bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-μm in-line filter.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature (otherwise requires new infusion preparation).

The IV line will be flushed with a volume of 0.9% Sodium Chloride equal to the priming volume of the infusion set after the contents of the IV bag are fully administered

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab 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 (e.g., diphenhydramine) or equivalent medications may be administered at the discretion of the investigator. If the infusion related reaction is ≥ Grade 3 in severity, durvalumab will be discontinued.

As with any antibody, allergic reactions are possible. Therefore, 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.

3.2.2 Olaparib

Olaparib tablet will be administered at a total daily dose of 600 mg orally in two divided doses, approximately 12 hours apart. The dose should be taken at the same times each day with approximately 1 cup (240 mL) of water. Olaparib could be taken with or without regard to meals, with a light meal/snack (i.e. 2 pieces of toast or a couple of crackers).

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

Missing up to 15% of the doses for any given cycle is allowed.

Olaparib will be dispensed at the start of each cycle. Patients will be provided with a Medication Diary for olaparib (**Appendix C**), instructed in its use, and asked to bring the diary with them to each appointment.

If vomiting occurs shortly after the olaparib tablet is swallowed, the dose should only be replaced if the intact tablet can be seen. Should any patient miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time.

No routine prophylactic anti-emetic treatment is required at the start of study treatment. See Section **3.3.2.2** Management of nausea and vomiting. Patients will be provided with ondansetron and instructed to take 8 mg of ondansetron with small meal or snack to prevent nausea and vomiting approximately 30 minutes prior to each dose of olaparib if nausea or vomiting occurs and as required thereafter.

3.3 Dose Delay or Modifications

In case of unbearable toxicity definitely attributed to one of the study drugs, patient will be taken off this drug and per PI discretion may continue treatment with the other drug only.

For patients who are benefiting from combination therapy, since we don't know which agent is driving the response (i.e. either of the drugs alone or the combination), in the event that one drug

is causing toxicities and have to be discontinued, it is reasonable to continue the other drug to see if the patient might benefit from it.

When, at the beginning of a treatment cycle, treatment delay related to one of the drug is indicated, treatment with the other drug may continue without delay per PI discretion.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug, the dose of the other drug does not require modification.

3.3.1 Durvalumab

Guidelines for the management of immune-mediated adverse events (imAE), infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab Toxicity Management Guidelines (TMGs). Please see **Appendix D**.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in **Appendix D**. These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting investigator.

3.3.2 Olaparib

Summary of dose holding/interruptions and dose de-escalation recommendations for olaparib in case of olaparib-related adverse events (graded according to NCI-CTCAE v5.0).

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and treatment with olaparib should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors)

3.3.2.1 Management of Hematological Toxicity

3.3.2.1.1 Management of Anemia

Table 2 Management of anemia

Haemoglobin	**Action to be taken**
Hb < 10 but ≥ 8 g/dl (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) or interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl. **Subsequent occurrences:** If Hb**< 10** but **≥ 9 g/dl** investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) or dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb**< 9** but **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to grade 3 or worse anemia and/or development of blood transfusion dependence), refer to section **3.3.2.1.3**.

3.3.2.1.2 Management of Neutropenia, Leukopenia And Thrombocytopenia

Table 3 Management of Neutropenia, Leukopenia and Thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to section **3.3.2.1.3**.

3.3.2.1.3 Management of Prolonged Hematological Toxicities while on Study Treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2-week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50 x 10^9/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Olaparib treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption.

Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

3.3.2.2 Management of Non-Hematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study Sponsor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptom

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the investigator.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of crackers).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone.

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AZ.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

Table 4 Dose reductions for study treatment

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

3.3.2.3 Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (creatinine clearance calculated per institutional standard or based on a 24-hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change, or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

3.4 Study Calendar

	Screening[1]	Baseline[1]	All Cycles Cycle=28 (+/- 3) days		30 Days Safety FU[11, 13]	Long Term FU[12,13]
			Day 1[1]	Day 15[2]		
Durvalumab[3]			X			
Olaparib[4]			X[4]			
Medical History	X					
Height	X					
Histologic confirmation of the disease	X					
EKG	X[5]		X			
Physical exam, weight and ECOG	X		X	X	X	
Vital Signs	X		X	X	X	
Screening labs [6]	X					
Protocol labs [7]			X	X	X	
Amylase, lipase		X	X			
APTT	X		X[16]			
INR	X		X[16, 17]			
TB testing (if infection is suspected)	X					
HIV, HBV, HCV viral load by PCR (if history of HIV, HBV, HCV)	X					
CD4 count [15]	X					
Radiologic Evaluation[8]	X	X	X[8]			X
Tumor measurements[8]	X	X	X[8]			X
Serum or urine pregnancy test	X		X	X	X	
Concomitant medications	X		X	X		
Adverse event evaluation			X	X	X	
Baseline symptoms evaluation		X				
Bone marrow evaluation [18]			X			
Tumor biopsy[9]		X		X		

	Screening[1]	Baseline[1]	All Cycles Cycle=28 (+/- 3) days		30 Days Safety FU[11, 13]	Long Term FU[12,13]
			Day 1[1]	Day 15[2]		
Collection of available unstained slides or a block		X				
Research blood for Immune subsets[10]			X[10]	X		
Research blood for cytokine / chemokine [10]			X[10]	X		
Research blood for circulating tumor cells [10]			X[10]	X		
Research blood for circulating tumor DNA [14]			X	X		
Research blood for whole exome/genome sequencing		X				
Research blood for transcriptome [10]			X	X		
Assays for paraneoplastic autoantibodies		X				
Research blood for NanoString Pan Cancer Immune Panel [10]			X[10]	X[10]		
Phone call or e-mail for survival every 6 month						X

[1] Baseline and C1D1 evaluations do not need to be repeated if performed at screening or baseline in designated time frame. All evaluations will be done within 7 days before treatment initiation on Day 1 of every cycle. If treatment does not start within 28 days after enrollment, screening evaluations will be repeated.

[2] Day 15 (+/- 2 days) visit is only on Cycle 1

[3] Durvalumab via IV infusion on Day 1 of each cycle.

[4] Olaparib PO, BID every day of every cycle.

[5] Three EKGs during screening

[6] Laboratory Evaluation: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, glucose, albumin, calcium, magnesium, phosphorus, AST/ALT, total bilirubin, gamma glutamyl transferase, serum creatinine, PT/PTT, total protein, urine or serum HCG. Urinalysis: Hb/erythrocytes/blood, protein/albumin, glucose.

[7] Protocol labs: CBC with differential, Sodium, Potassium, Chloride, Bicarbonate, BUN, serum creatinine, glucose, albumin, calcium, magnesium, phosphorus, AST, ALT, alkaline phosphatase, total bilirubin, LDH, TSH, free T4, Urine protein to creatinine ratio (UPCR) or urinalysis, TBNK lymphocyte subsets, total protein. Urinalysis: Hb/erythrocytes/blood, protein/albumin, glucose

[8] CT/MRI of chest, abdomen and pelvis at screening/baseline and every 8 (+/-1) weeks after start of study therapy. If patient is taken off treatment for reason other than disease progression, imaging will continue during follow-up until disease progression.

[9] Optional tumor biopsies on baseline, cycle 1 day 15 (+/-4) days and at disease progression. Leftover sample from one of the biopsies may be used for disease confirmation.

[10] Pre-treatment on cycle 1 day 1, cycle 1 day 15 and cycle 3 day 1, and at disease progression.

[11] Follow up visit is planned to be performed at 30 (+/- 7) days after treatment discontinuation to evaluate patient's safety.

[12] After safety FU visit, subjects will be followed every 6 months (± 1 month) for survival by phone call or e-mail. Note: if patients are taken off treatment for reason other than disease progression, they will be invited for imaging studies every 8 (+/-1) weeks during follow up period until disease progression. Outside images are acceptable.

[13] If subjects are not willing to come to NIH for FU visits, they will be contacted by phone call or e-mail or any other approved NIH platform in compliance with local policies) for survival and adverse events.

[14] Research blood for circulating tumor DNA will be collected on cycle 1 day 1, cycle 1 day 15 and day 1 of subsequent cycles

[15] Patients with long-standing (>5 years) HIV on antiretroviral therapy > 1 month only

[16] If clinically indicated

[17] For patients taking warfarin it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

[18] Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample.

3.5 Cost and Compensation

3.5.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.5.2 Compensation

N/A

3.5.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.6 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, efforts must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.6.1 Criteria for Removal from Protocol Therapy

- Progressive disease
- Excessive toxicity (see section **3.3**)
- Patient request to be withdrawn from treatment
- PI discretion
- Positive pregnancy test
- Drugs become unavailable

3.6.2 Off -Study Criteria

- Death
- Patient request to be withdrawn from study
- PI discretion
- Lost to follow up
- PI decision to end the study
- Permanent loss of capacity to consent
- Screen failure

3.6.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visits and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (telephone calls and if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

All routine and appropriate supportive care (including blood products) will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the patient.

4.1 Prohibited Medications

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy (unless palliative), biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. (Note: Patients may continue the use of bisphosphonates or denosumab for bone disease.)

Live virus and live bacterial (including live attenuated) vaccines should not be administered while the patient is receiving study medication and during the 30-day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

4.2 Restricted Concomitant Medications (See Appendix B - Inhibitors and Inducers of CYP3A4 for more complete list of Inhibitors and Inducers of CYP3A4)

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it is allowed):**
Strong CYP3A inhibitors: itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir **Moderate CYP3A inhibitors**: ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.
Strong inducers: phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort **Moderate CYP3A inducers**: bosentan, efavirenz and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of olaparib

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it is allowed):**
• CYP3A4 substrates: hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine • CYP2B6 substrates: bupropion, efavirenz • OATP1B1substrates: bosentan, glibenclamide, repaglinide, statins and valsartan • OCT1, MATE1 and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Effect of olaparib on other drugs Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of 2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it is allowed):**
Administration of other anti-cancer agents	Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone.
Any natural/herbal products or other traditional remedies	The use should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with: • Reason for use • Dates of administration including start and end dates • Dosage information including dose and frequency

4.3 Methods of Contraception

4.3.1.1 Female Patient of Child-Bearing Potential

Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (see section **4.3.1.3**) from the time of screening throughout the total duration of the protocol treatment and the drug washout period (6 months after the last dose of protocol therapy). Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

Male partners of female patients (of childbearing potential) must also use a male condom plus spermicide or total/true abstinence throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if defined as: amenorrheic for 1 year or more following cessation of exogenous hormonal treatments; luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for women under 50, radiation-induced oophorectomy with last menses >1 year ago; chemotherapy-induced menopause with more than one-year interval since last menses; surgical sterilization (bilateral oophorectomy or hysterectomy).

4.3.1.2 Male Patients with a Female Partner of Childbearing Potential

Non-sterilized male patients who are not abstinent and intend to be sexually active with a pregnant woman or with a woman of childbearing potential must use a male condom plus spermicide or total/true abstinence from the time of screening throughout the total duration of the study treatment and at least 3 months after the last dose of study treatment). However, periodic 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 (see section **4.3.1.3**).

4.3.1.3 Effective Methods

Acceptable non-hormonal birth control methods:

- Total/true abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for at least 6 months (for female patients) or at least 3 months (for male patients) after the last dose of study treatment. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception.
- Vasectomised sexual partner PLUS male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
- Tubal occlusion PLUS male condom.
- Intrauterine device (provided coils are copper-banded) PLUS male condom.

Acceptable hormonal methods:

- Mini pill PLUS male condom: Progesterone-based oral contraceptive pill using desogestrel. Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone-based pill available.
- Combined pill PLUS male condom: Normal and low-dose combined oral pills.
- Injection PLUS male condom: Medroxyprogesterone injection (eg, Depo-Provera [Pfizer]).
- Implants PLUS male condom: Etonorgestrel-releasing implants (eg, Nexplanon [Merck Sharp & Dohme]).
- Patch PLUS male condom: Norelgestromin/ethinyl estradiol transdermal system (eg, Xulane).
- Intravaginal device (eg, ethinyl estradiol-/etonogestrel-releasing intravaginal devices such as NuvaRing [Merck Sharp & Dohme]) PLUS male condom.
- Levonorgestrel-releasing intrauterine system (eg, Mirena [Bayer]) PLUS male condom.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 Biospecimen Collection

The primary goal of the correlative studies is to identify potential predictive biomarkers of response to immune checkpoint inhibition with a PARP inhibitor. Although PD-L1 expression in tumor was highly predictive of response to a PD-1 inhibitor, nivolumab in treatment-naive lung cancer patients (50% in PD-L1–positive patients v. 0% in PD-L1–negative patients), this was not the case for pretreated patients (15% in PD-L1–positive vs 14% in PD-L1–negative). Pretreatment biopsy samples will provide important information on development of predictive biomarkers in cancer patients. Other correlative study aims include investigation of proof-of-concept biomarkers of immune checkpoint inhibition and DNA damage repair inhibition in recurrent cancer. These

will be performed in an exploratory fashion.

Test/assay	Sample volume (approx.)	Type of tube [a]	Collection point	Location of specimen analysis
Immune subsets	16 mL blood	2 x 8 mL CPT: blue and black top	Pre-treatment C1D1 C1D15 C3D1 disease progression	DTB Clinical Translational Unit
Comprehensive cytokine / chemokine	20 mL blood	2 x 10 mL EDTA tubes (lavender top)	Pre-treatment C1D1 C1D15 C3D1 disease progression	DTB Clinical Translational Unit
Enumeration of circulating tumor cells	20 mL blood	2 x 10 mL 10 ml CellSave	Pre-treatment C1D1 C1D15 C3D1 Disease progression	DTB Clinical Translational Unit
Assays for paraneoplastic autoantibodies	10 mL blood	10 mL red top tube	Baseline	DTB Clinical Translational Unit
RNA sequencing and whole exome/genome sequencing	NA	Tumor sample	Pre-treatment C1D1 C1D15	DTB Clinical Translational Unit /NCI COMPASS
Whole exome/genome sequencing	3 mL blood	1 x 3 ml light blue citrate tube	Baseline	DTB Clinical Translational Unit / NCI COMPASS
Transcriptome	2.5 mL blood	2.5 mL PAXgene RNA tube	Pre-treatment C1D1 C1D15 C3D1 Disease progression	DTB Clinical Translational Unit
Circulating tumor DNA Profiles	10 mL blood	Cell-free DNA BCT Streck tubes	C1D1 C1D15 Day 1 of subsequent cycles	DTB Clinical Translational Unit
NanoString Pan Cancer Immune Panel	2.5 mL blood	2.5 mL PAXgene RNA tube	Pre-treatment C1D1 C1D15 C3D1 Disease progression	DTB Clinical Translational Unit

Test/assay	Sample volume (approx.)	Type of tube [a]	Collection point	Location of specimen analysis
a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.				

5.2 Collection of Samples

5.2.1 Blood

Blood samples will be collected at time points indicated in the Study Calendar **3.4**. Blood samples will be sent to and processed by the DTB Clinical Translational Unit.

5.2.2 Tumor samples

Optional baseline and post-treatment biopsies will be performed at time points indicated in Study Calendar **3.4**. Frozen tumor samples will be procured by the DTB Clinical Translational Unit. Tissue for formalin fixation will be sent to the Laboratory of Pathology. Formalin-fixed samples will be analyzed for disease first, leftover will be used for research.

5.3 Correlative Studies for Research

5.3.1 Immune Subsets

PBMCs will be processed and stored at the DTB Clinical Translational Unit and will be assessed using multi-parameter flow cytometry for immune subsets including but not necessarily limited to Tregs, MDSC, effector and exhausted CD8+ T-cells. Assessment will include functional markers, i.e. PD-1, TIM3, CTLA-4 and/or CD40.

5.3.2 Comprehensive Cytokine / Chemokine

The cytokine analysis will be done at the DTB Clinical Translational Unit.

5.3.3 Enumeration and Gene Expression of Circulating Tumor Cells

Blood will be collected to correlate changes in circulating tumor cells (CTC) [42] enumeration with clinical response. CTC will be investigated using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers. Immune markers including but not limited to functional markers, i.e. PD-1 or PD-L1 in CTC will be studied

5.3.4 Assays for Paraneoplastic Autoantibodies

SCLC is the most frequent cancer histology associated with paraneoplastic syndromes. SCLC associated paraneoplastic syndromes are thought to be related to immune-mediated tissue destruction due to neural antigen expression from cancer cells and are associated with more favorable outcomes [43]. One red top tube (10 ml) will be collected and frozen at baseline for future evaluation of paraneoplastic autoantibodies. The antibodies of interest include Anti-Hu, Anti-Ri, Anti-amphiphysin, antineuronal antibodies Ma1 and Ma2 and antiYo or anti-Purkinje cell antibody. Since these antibodies are not truly paraneoplastic antibodies, as they can also occur in the non-paraneoplastic setting, but their baseline levels will be of use in the work-up of patients

who develop paraneoplastic syndromes on the trial. The analysis will be done at the DTB Clinical Translational Unit.

5.4 Samples for Genetic/Genomic Analysis

5.4.1 RNA sequencing and whole exome/genome sequencing on tumor tissue and blood

Emerging data suggest that tumor mutational loads and neo-antigens may correlate with clinical response to immune checkpoint inhibition[44] [45]. It has been reported that mutated peptides resulting from DNA mutations are recognized by CD8+ T-cells and CD4+ T-cells in a large fraction of melanoma patients, and these neo-antigen-specific T cell responses are likely to contribute to the clinical effects of cancer immunotherapy[44] [46] [47]. Patient samples will undergo whole exome sequencing of tumor and normal (germline) DNA and RNA sequencing to elucidate DNA damage repair genes, the mutational loads resulting from mutations in genes involved in DNA damage repair pathways and potential neo-antigens as an exploratory endpoint.

5.4.2 Transcriptome Blood

In order to address the exploratory goal of characterizing predictive biomarkers of response, genomic analysis including but not limited to RNAseq may be performed.

5.4.3 Circulating Tumor DNA (ctDNA) Profiles

Subclone architecture and genomic evolution of SCLC under treatment has not been well studied primarily due to lack of tumor specimens because of the aggressiveness of the disease, particularly longitudinal samples acquired during treatment. Recent findings showed high concordance of ctDNA and metastatic tumor whole-exome sequencing [48]. Mean variant allele frequency of clonal mutations from pre-treatment ctDNA is associated with PFS and OS [49]. SCLC is characterized by early hematogenous spread, which makes ctDNA sequencing a promising modality for genomic profiling. Plasma samples from patients with SCLC may be used to quantify somatic variants in ctDNA. The ctDNA can detect genomic alterations including single nucleotide variants, copy number alterations, and insertions or deletions in genes that are frequently mutated in SCLC, including TP53, RB1, and others. These liquid biopsies can potentially improve disease subclassification, improve monitoring of disease burden and depth of response to treatment, and provide early warning of disease relapse in patients with SCLC.

5.4.4 NanoString Pan Cancer Immune Panel

Peripheral blood will be analyzed for 730 immune genes and 40 control genes using the NanoString Pan Cancer Immune Panel.

5.4.5 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists. Subjects will be contacted at that time with a request to provide a sample to be sent to a CLIA certified laboratory.

For additional information on consenting, ordering and results for samples analyzed through the NCI COMPASS Program, refer to CCR SOP ADGC-5, Tumor/Normal Whole Exome

Sequencing: Consenting, Ordering, and Obtaining Results found at https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825#CCRPolicies/StandardOperatingProcedures(SOPs)-ADGC.

5.4.6 Genetic Counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense). This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis

5.5 Sample Storage, Tracking and Disposition

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements, if required.

5.5.1 Procedures for Storage of Patient Samples in the DTB Clinical Translational Unit

Contact the Lab by email (Min-Jung Lee: min-jung.lee@nih.gov; and Sunmin Lee: leesun@mail.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330. A lab member will come to pick up the blood. Please keep blood at ambient temperature. Members of the lab will enter the samples into a secure password protected patient's sample tracking database (Translational Pharmacodynamics Research Group Patient Sample Management System) and process the samples.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol. It is critical that the sample remains coded and linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate with these variables.

Blood samples will be stored initially in the DTB Clinical Translational Unit in the Magnuson Clinical Center. If, at any time, a subject withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested).

When a patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**

5.5.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly, and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO)

guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

5.5.3 NCI COMPASS Program

Participants may undergo genetic analysis through the NCI COMPASS program for tumor-normal exome and transcriptome. For additional information on consenting, ordering and results, refer to CCR SOP ADGC-5, Tumor/Normal Whole Exome Sequencing: Consenting, Ordering, and Obtaining Results found at https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

5.5.4 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be per the requirements of section **7.2**.

6 DATA COLLECTION AND EVALUATION

6.1 Data Collection

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 of Cycle 1 through 30 days after the study agent (s) was/were administered. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE only if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Adverse Events of grade 1 will not be collected.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Olaparib Adverse Events of Special Interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of Olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. Adverse Events of Special Interest for olaparib comprise the Important Identified Risk of MDS/AML, and the Important Potential Risks of new primary malignancy (other than MDS/AML) and pneumonitis.

6.2 Data Sharing Plans

6.2.1 Human Data Sharing Plan

The PI will share coded linked human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov and dbGaP
- in BTRIS
- in publication and/or public presentations
- with approved outside collaborators under appropriate agreements
- at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 Response Criteria

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (+/- 1 week).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [50, 51]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.3.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: >20 mm;
- By CT scan:
  - Scan slice thickness 5 mm or under as >10 mm
  - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: >10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound during the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when

biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.3.3 Response Criteria

6.3.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements

recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR

Non-Target Lesions	New Lesions	Overall Response
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.3.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.4 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP Office of Compliance and Training / IRB Reporting

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at:

https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

9 STATISTICAL CONSIDERATIONS

9.1 Study Objectives

9.1.1 Primary Objective

- To assess the efficacy of a combination of durvalumab and olaparib with respect to best overall response (BOR) according to Response Evaluation Criteria (RECIST 1.1) in patients with EGFR-mutated non-small-cell lung carcinoma that transform to SCLC and other neuroendocrine carcinomas.

9.1.2 Secondary Objectives

- To determine the progression-free survival (PFS)
- To evaluate safety and tolerability of a combination of durvalumab and olaparib
- To determine overall survival (OS)

9.1.3 Exploratory Objectives

- To study immune subsets and cytokine markers of response
- To evaluate circulating tumor cells and circulating tumor DNA (ctDNA)
- To study paraneoplastic autoantibodies
- To perform whole exome sequencing of normal (germline) DNA
- To perform molecular profiling of EGFR-mutated transformed small cell/neuroendocrine tumors by RNA sequencing and whole exome/genome sequencing of tumor tissue;
- To evaluate transcriptome and NanoString Pan Cancer Immune Panel genes in blood.

9.2 Sample Size Determination

In patients with EGFR-mutated transformed SCLC and other neuroendocrine tumors, it would be desirable if the fraction of patients who are able to achieve a response were consistent with 25% and more than 5%. In this small pilot cohort of 12 evaluable patients who receive durvalumab and olaparib, if there are 2 or more who exhibited a clinical response, the probability of this occurring is 11.8% if the true probability of response is 5%, and 84.2% if the true probability of response is 25%. In addition, the one-sided lower 90% confidence interval bound on 2/12 is 4.5% with 2/12 responses, thus demonstrating marginally improved results compared to 5%, and the upper one-sided 90% confidence interval bound on 2/12 is 38.6%, demonstrating consistency with 25%. Thus, if 2/12 (17%) or more of these patients achieve a response, this would be more consistent with 25% or more probability of this being the case than with 5% or less probability of this being the case, and thus would be considered an acceptable fraction.

It is expected that 12 evaluable patients can be accrued in 3 years. We will plan for a small number of inevaluable participants (2), intending to initiate intervention in up to 14 participants. Note: To allow for screen failures, a total of 25 will be set for the purposes of the NIH accrual ceiling.

9.3 Populations for Analyses

All patients who received at least one dose of both treatments and had at least one post-baseline tumor assessment will be evaluated for response. In addition, any treated patients who exhibited clinical progression before being evaluated for clinical response will be included in the analysis.

9.4 Statistical Analyses

9.4.1 General Approach

The clinical response rate of patients will be reported along with a confidence interval.

9.4.2 Analysis of the Primary Endpoints

The clinical response rate of evaluable patients will be reported along with a 95% confidence interval.

9.4.3 Analysis of the Secondary Endpoint

PFS and OS will be estimated by the Kaplan-Meier method. The median PFS and OS will be reported along with a 95% confidence interval.

9.4.4 Safety Analyses

Patients will be assessed for toxicity by reporting the grades of toxicity and the type of toxicity observed for all patients.

9.4.5 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported.

9.4.6 Planned Interim Analyses

None

9.4.7 Exploratory Analyses

Exploratory Objectives:

- To study immune subsets and cytokine markers of response
- To evaluate circulating tumor cells and circulating tumor DNA (ctDNA)
- To study paraneoplastic autoantibodies
- To perform whole exome sequencing of normal (germline) DNA
- To perform molecular profiling of EGFR-mutated transformed small cell/neuroendocrine tumors by RNA sequencing and whole exome/genome sequencing of tumor tissue;
- To evaluate transcriptome and NanoString Pan Cancer Immune Panel genes in blood.

Each these objectives will be evaluated in an exploratory fashion, with descriptive statistics obtained where appropriate. If any statistical tests are performed, the results will be reported without adjustment for multiple comparisons but may be reported in the context of the number of tests performed.

10 COLLABORATIVE AGREEMENT

10.1 Clinical Trial Agreement

A CTA has been executed between NCI, NIH and AstraZeneca (CTA 1165).

11 HUMAN SUBJECTS PROTECTIONS

11.1 Rationale for Subject Selection

No individual who meets the criteria for eligibility will be excluded from participation based on their race, ethnicity, gender, or socioeconomic status. Particular attention will be made to acquire a broad and diversified population.

11.2 Participation of Children

Children (younger than 18 years) will not be included in this protocol due to the limited data on study drugs in children and the different biology of childhood malignancy.

11.3 Risk/Benefit Assessment for All Participants

11.3.1 Known Potential Risks

11.3.1.1 Study Drug Risks

The primary risk to patients participating in this research study is from the toxicity of study drugs.

All care will be taken to minimize study treatment side effects, but they can be unpredictable in nature and severity. Patients will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of patients will be recorded in the patient's medical record.

For risk information, refer to investigator brochures.

11.3.1.2 Risk of Biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

Biopsies may be done under sedation. Potential side effects of sedation include headache, nausea and drowsiness. These side effects usually go away quickly.

11.3.1.3 Risks of Exposure to Ionizing Radiation

This research study has three optional CT guided biopsies and 6 CTs. The amount of radiation exposure from these procedures is equal to approximately 9 rem.

11.3.1.4 Risks from CT contrast

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain participants, such as those with impaired kidney function.

11.3.1.5 Risks from Electrocardiograms

Other than possibly experiencing some minor skin irritation from the electrodes, there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

11.3.1.6 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, low red blood cell count (anemia) can develop. Up to 106 mL of blood may be collected at each visit with a maximum of 414 mL in an 8-week period.

11.3.1.7 Urine Collection Risks

There are no risks associated with urine collection.

11.3.1.8 MRI and MRI Contrast Risks

Participants are at risk for injury from the MRI magnet if they have metal in their body. There is a possibility that participants may experience claustrophobia. There are risks of back discomfort related to lying in the scanner.

The most common side effects from MRI contrast (gadolinium) include injection site pain, nausea, itching, rash, headaches and dizziness. Serious but rare side effects such as gadolinium toxicity and nephrogenic systemic fibrosis, or NSF, are most often seen in individuals with severe kidney problems.

11.3.1.9 Other Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

11.3.1.10 Non-Physical Risks of Genetic Research

Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

11.3.2 Known Potential Benefits

The study drugs may help to control the disease. The results may help the investigators learn more about the disease and develop new treatments for patients with this disease.

11.3.3 Assessment of Potential Risks and Benefits

SCLC and other neuroendocrine tumors treatment need improved therapy options. Current studies suggest that combination of durvalumab and olaparib may have tremendous anti-tumor efficacy.

A number of clinically appropriate strategies to minimize risks to patients have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management

guidelines. Overall, the potential benefit of the combination of durvalumab and olaparib in subjects with solid tumors outweigh the risks associated with this drug.

The potential benefit to a patient that participates in this study is better control of their tumor growth and disease recurrence which may or may not have a favorable impact on symptoms and/or survival.

Potential adverse reactions attributable to the administration of the study drugs utilized in this trial are discussed in the package inserts. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity.

11.4 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, associate investigators and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

12.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have

a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

13.1 Durvalumab (IMFINZI)

For detailed information, refer to investigator brochure.

13.1.1 Source/Acquisition and Accountability

Commercial supplies of durvalumab (IMFINZI) will be supplied by AstraZeneca Inc. and delivered directly to the NIH Pharmacy. Individual IV bags will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. IV bags will be delivered from NIH Pharmacy to patient unit where drug will be infused to the patient.

13.1.2 Administration Procedures

Refer to section **3.2.1**.

13.2 Olaparib (LYNPARZA)

For detailed information, refer to investigator brochure.

13.2.1 Source/Acquisition and Accountability

Commercial supplies of olaparib (LYNPARZA) will be supplied by AstraZeneca and delivered directly to the NIH Pharmacy. Individual bottles with tablets will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. Patients will pick up bottles at NIH Pharmacy and will return bottles and not-used tablets after completion of every cycle together with Medication Diary to Study Coordinator. After review of leftover tablets and Medication Diary, unused tablets will be returned to pharmacy and disposed by pharmacy personnel.

13.2.2 Administration Procedures

See Section **3.2.2.**

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15 APPENDICES

15.1 Appendix A - Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

15.2 Appendix B - Inhibitors and Inducers of CYP3A4

CYP3A4 INDUCERS (PROHIBITED)

Armodafenil[1]	Modafinil[2]	Primidone[1]
Barbiturates[2]	Nafcillin[1]	Rifabutin
Bosentan[1]	Nevirapine	Rifampin
Carbamazepine	Oxcarbazepine	Rifapentine[1]
Dexamethasone[1]	Pentobarbital[1]	St. John's wort[2]
Efavirenz	Phenobarbital	Troglitazone[3]
Fosphenytoin[1]	Phenytoin	
Glucocorticoids[2] (see note)	Pioglitazone[2]	

Note: Topical steroids are permitted. Please contact overall PI if systemic steroids are clinically indicated while on trial.
1 Cited in [52]
2 Cited in Flockhart Table http://medicine.iupui.edu/clinpharm/ddis/table.asp.
3 Weak inhibitors per Lacy et al. May be used with caution.
Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 INHIBITORS

Strong Inhibitors (prohibited)	**Moderate Inhibitors** (use with caution, avoid if possible)	**Weak Inhibitors** (use with caution, avoid if possible)
Amprenavir[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Clarithromycin	Cimetidine[1]	Diethyldithiocarbamate[2]
Conivaptan[1]	Clotrimazole[1]	Fluvoxamine[2]
Delavirdine[1]	Cyclosporine[1]	Gestodene[2]
Fosamprenavir[1]	Desipramine[1]	Mibefradil[2]
Fospropofol[1]	Doxycycline[1]	Mifepristone
Imatinib[1]	Efavirenz[1]	Norfluoxetine[2]
Indinavir	Erythromycin	Star fruit[2]
Isoniazid[1]	Fluconazole	Troleandomycin[2]
Itraconazole	Fosaprepitant[1]	
Ketoconazole	Grapefruit juice	
Miconazole[1]	Haloperidol[1]	
Nefazodone	Lidocaine[1]	
Nelfinavir	Metronidazole[1]	
Nicardipine[1]	Norfloxacin[1]	
Posaconazole[1]	Sertraline[1]	
Propofol[1]	Tetracycline[1]	
Quinidine[1]	Verapamil	

Strong Inhibitors (prohibited)	**Moderate Inhibitors** (use with caution, avoid if possible)	**Weak Inhibitors** (use with caution, avoid if possible)
Ritonavir Saquinavir[2] Telithromycin	Voriconazole[1]	

1 Cited in [52]
2 Cited in Flockhart Table http://medicine.iupui.edu/clinpharm/ddis/table.asp.
Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Substrates (allowed – take note of possible interactions)

Alfentanil	Dexlansoprazole	Isradipine	Ranolazine
Alfuzosin	Dextromethorphan[2]	Itraconazole	Rifabutin
Alprazolam	Diazepam	Ixabepilone	Repaglinide
Ambrisentan	Dihydroergotamine	Ketamine	Risperidone[2]
Amiodarone	Diltiazem	Ketoconazole	Ritonavir
Amlodipine	Disopyramide	Lansoprazole	Salmeterol
Aprepitant	Docetaxel	Lapatinib	Saquinavir
Aripiprazole	Domperidone[2]	Lercanidipine[2]	Sibutramine
Armodafinil	Doxorubicin	Levonorgestrel	Sildenafil
Astemizole[2]	Eletriptan	Lidocaine	Simvastatin
Atazanavir	Efavirenz	Lovastatin[2]	Sirolimus
Atorvastatin	Eplerenone	Lopinavir	Solifenacin
Benzphetamine	Ergoloid mesylates	Maraviroc	Spiramycin
Bisoprolol	Ergonovine	Medroxyprogesterone	Sufentanil
Bortezomib	Ergotamine	Mefloquine	Sunitinib
Bosentan	Erlotinib	Mestranol	Tacrolimus
Bromazepam	Erythromycin	Methadone	Tadalafil
Bromocriptine	Escitalopram	Methylergonovine	Tamoxifen
Budesonide	Esomeprazole	Methylprednisolone	Tamsulosin
Buprenorphine	Estradiol	Miconazole	Temsirolimus
Buspirone	Estrogens conjugated	Midazolam	Telithromycin
Busulfan	synthetic	Mirtazapine	Teniposide
Cafergot[2]	Estrogens, conjugated	Modafinil	Terfenadine[2]
Caffeine[2]	equine	Montelukast	Testosterone[2]
Carbamazepine	Estrogens esterified	Nateglinide	Tetracycline
Cerivastatin[2]	Estropipate	Nefazodone	Theophylline
Chlordiazepoxide	Eszopiclone	Nelfinavir	Tiagabine
Chloroquine	Ethinyl estradiol	Nevirapine	Ticlopidine
Chlorpheniramine	Ethosuximide	Nicardipine	Tinidazole
Ciclesonide	Etoposide	Nifedipine	Tipranavir
Cilostazol	Exemestane	Nilotinib	Tolterodine
Cisapride	Felbamate	Nimodipine	Toremifene

CYP3A4 Substrates (allowed – take note of possible interactions)

Citalopram	Felodipine	Nitrendipine[2]	Tramadol
Clarithromycin	Fentanyl	Nisoldipine	Trazodone
Clobazam	Finasteride[2]	Norethindrone	Triazolam
Clonazepam	Flunisolide	Norgestrel	Trimethoprim
Clorazepate	Flurazepam	Omeprazole	Trimipramine
Cocaine	Flutamide	Ondansetron	Vardenafil
Codeine[2]	Fluticasone	Paclitaxel	Venlafaxine
Colchicine	Fosamprenavir	Paricalcitol	Verapamil
Conivaptan	Fosaprepitant	Pazopanib	Vinblastine
Cyclophosphamide	Gefitinib	Pimozide	Vincristine
Cyclosporine	Haloperidol	Primaquine	Vinorelbine
Dantrolene	Hydrocortisone[2]	Propranolol[2]	Zaleplon[2]
Dapsone	Ifosfamide	Progesterone	Ziprasidone[2]
Darifenacin	Imatinib	Quazepam	Zolpidem
Darunavir	Indinavir	Quetiapine	Zonisamide
Dasatinib	Irinotecan	Quinidine	Zopiclone
Delavirdine	Isosorbide dinitrate	Quinine	
Dexamethasone	Isosorbide mononitrate	Rabeprazole	

* Note: [52]
** Substrates cited in Flockhart Table http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011

15.3 Appendix C - Patient's Medication Diary _____

Cycle_____ Patient's ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment
2. You will take olaparib twice a day every day during 28-day cycle
3. Record the date and time you took the tablets and the number of tablets that you took.
4. If you have any comments or notice any side effects, please record them in the comments column.
5. Please bring this form and your bottles (even they are empty) when you come for your clinic visits.

Day	**Date**	**Oral olaparib (every 12 hours)**				**Comments**
		Time	**# of Tablets**	**Time**	**# of Tablets**	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						

Day	**Date**	**Oral olaparib (every 12 hours)**				**Comments**
		Time	**# of Tablets**	**Time**	**# of Tablets**	
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient's signature: _____

15.4 Appendix D - Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –September 2023

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 ≤ 1, corticosteroid should be tapered over ≥ 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. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2022;39:4073-4126.
3. Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2022;33 (12):1217-1238.

General Considerations Regarding Immune-Mediated Reactions

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 version1.2022. 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	**For Grade 2** – Monitor symptoms daily and consider hospitalization as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults.

		completion of steroid taper (≤10 mg prednisone or equivalent).	– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Consider HRCT or chest CT with contrast, Repeat imaging 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 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), 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 and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (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 prednisone equivalent, 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 investigator, in discussion with AstraZeneca Clinical Study Lead. • **For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:** A. Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade < 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent) B. **Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea colitis or 2) Any grade of intestinal perforation.** **Grade 4** Permanently discontinue study drug/study regimen.	**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. – **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.**	**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 findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until LFT elevations improve or resolve. – Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis). – 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.
	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. – Check CPK and aldolase (to rule out myositis). – 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 [d] **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.** **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])**	**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 liver function test: 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). – 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.

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 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**	
	Isolated AST or ALT >2.5 BLV and ≤5×BLV and ≤ 20 ULN	– 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 or ALT ≤2.5×BLV, resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis). – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – 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 ≤20XULN and total bilirubin > 1.5 - < 2 x ULN [d]	– 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. – Check CPK and aldolase (to rule out myositis) – 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 its 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 and 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.
Dermatologic Adverse Events **(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) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPHIGOID 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., emolient, 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 3** – Reconsult 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 Study 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	**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**

		regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**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 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
	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.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral

	defining the CTCAE grade/severity)		
	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 CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – 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	**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 antibiotic for bacterial coverage until cultures/panel results are back – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study 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. − 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 CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	− 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/study regimen.	**For Grade 2** − 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/study 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
Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**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, copper, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	**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 CTCAE 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 decompensation 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 at the discretion of the treating specialist consultant 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	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– 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, 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. – Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice. – 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 a TNF inhibitor (e.g., infliximab) IVIG or plasmapheresis, or other therapies based on the discretion of the 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 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 until resolution to Grade ≤1 or baseline	
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. – Consider steroids for patients who have previously experienced infusion reaction; use of steroid premedication may be permitted in these situations.
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."