ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A171901

OLDER NON-SMALL CELL LUNG CANCER PATIENTS (>/= 70 YEARS OF AGE) TREATED WITH FIRST-LINE MK-3475 (PEMBROLIZUMAB) +/- CHEMOTHERAPY (ONCOLOGIST'S/PATIENT'S CHOICE)

Commercial agent: Pembrolizumab; IND: Exempt

ClinicalTrials.gov Identifier: NCT04533451

Study Chair
Cancer in the Older Adult Committee Chair
[redacted]

Study Co-chair
[redacted]

Community Oncology Co-chair
[redacted]

Correlative Study Co-chair
[redacted]

Pharmacogenomics and Population Pharmacology Co-chair
[redacted]

Respiratory Committee Chair
[redacted]

Cancer in the Older Adult Co-chair
[redacted]

Primary Statistician
[redacted]

Secondary Statistician
[redacted]

Data Manager
[redacted]

Protocol Coordinator
[redacted]

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Study Resources:

Expedited Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A171901 Nursing Contact

[redacted]

A171901 Pharmacy Contact

[redacted]

Biospecimens Accessioning and Processing (BAP)

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at [redacted] and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.

For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.

Older Non-Small Cell Lung Cancer Patients (>/= 70 Years of Age) Treated with First-Line MK-3475 (pembrolizumab) +/- Chemotherapy (Oncologist's/Patient's Choice)

Eligibility Criteria (see Section 3.2)

- Histologic or cytologic diagnosis of non-small cell lung cancer (adenocarcinoma). Stage IV or recurrent metastatic non-small cell lung cancer. (See §3.2.1.)
- Planning to begin MK-3475 (pembrolizumab) treatment within 14 days of registration, with or without combination chemotherapy. (See §3.2.2) Patients with autoimmune disorder, post-organ transplantation, or are receiving ongoing immunosuppression treatment are ineligible (See §3.2.3) .
- Prior adjuvant therapy is allowed and must have been completed at least 6 months prior to registration. (See §3.2.4)
- No planned radiation or other cancer treatment in the 3 months following registration (See §3.2.5)
- No untreated brain metastases. Patients must be off oral and IV corticosteroids and asymptomatic at registration. (See §3.2.6)
- Age ≥70 years of age. (See §3.2.7)
- Language: Patients must be able to read and comprehend English (See §3.2.9)

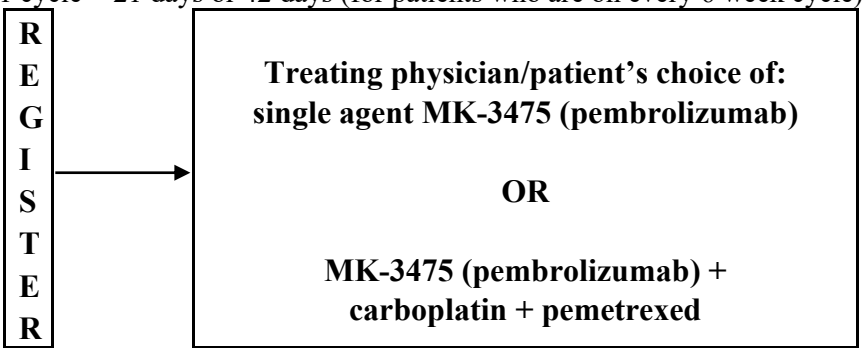
Required Initial Laboratory Values (See § 3.2.8)

ANC	≥ 1500/mm^3 (1.5 x 10^9/L
Platelet count:	≥ 100,000/mm^3 (100x 10^9/L)
Calculated creatinine clearance:	≥ 30 ml/min* for patients enrolled to pembrolizumab alone and > 45 ml/min for patients enrolled to chemotherapy + pembrolizumab
Total bilirubin	≤ 1.5 ULN (< 3 ULN if Gilbert's disease)
AST and/or ALT	≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present)
Alkaline phosphatase	≤ 2.5 x ULN (≤5 x ULN if bone or liver metastases present)

*Calculated using the Cockcroft-Gault formula

Schema

1 cycle = 21 days or 42 days (for patients who are on every 6 week cycle)



Pembrolizumab treatment is to continue until disease progression (treating physician's discretion) or unacceptable adverse event. Patients will be followed for survival for 5 years after registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Site staff who intend to administer the comprehensive geriatric assessment must complete the geriatric assessment training. (See Section 15.0)

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Table of Contents

1.0 BACKGROUND

There is a dearth of data on immunotherapy in older cancer patients. The number of older patients with cancer is increasing[1]. Yet, the optimal treatment for these patients remains understudied. With respect to immunotherapy, Marrone and Ford have commented, "Specific efficacy and safety data by age in the phase III trials leading to FDA approval of immune checkpoint inhibitors are limited" [2]. In 15 phase 3 studies that led to the approval of anti-PD-1 monotherapy, anti-CLA-4 monotherapy, or anti-PD-1/CTLA-4 monotherapy, the following observations underscore a lack of well-defined, age-based data: 1) the median age of patients enrolled was uniformly under 65 years; 2) nearly half of these trials failed to denote the percentage of patients 65 years or older; and 3) of those studies where an elderly sub-cohort was identified, that sub-cohort, as alluded to above, comprised only a small subset of the total cohort and hence was unrepresentative of older cancer patients at large. These observations point to the need to ascertain whether previous findings with immunotherapy are relevant to older cancer patients.

Further emphasizing this dearth of data and hence the need for prospectively-conducted clinical trials in older patients, Elias and others conducted a meta-analysis of PD-1 and PD-L1 inhibitors in older adults and reported comparable efficacy between patients who were 65 years of age and older and those younger [3]. However, among 53 trials, they noted that only 9 reported hazard ratios based on age, and, within this exceedingly small subgroup of trials, the percentage of patients who were 65 years of age or older was less than 50%. In contrast to what we propose here, this meta-analysis did not examine adverse events. Importantly, our group has shown that trials specifically designed for older patients are far more likely to enroll much older patients – the "oldest of the old," or patients in their 80's or 90's -- than those designed for a more general population of cancer patients [4, 5]. Thus, there is a clear need to conduct a trial such as the one described here.

1.1 Rationale and need for current trial

The trial proposed here is timely and important because checkpoint inhibitors now define the standard of care in non-small cell lung cancer therapeutics. Reck and others randomly assigned 305 previously-untreated non-small cell lung cancer patients to single agent pembrolizumab versus conventional chemotherapy in patients with PD-L1 expression ≥ 50% [6]. Pembrolizumab patients manifested a median progression-free survival of 10.3 months (95% confidence interval (CI): 6.7 to not reached) versus 6.0 months (95% CI, 4.2 to 6.2) (hazard ratio: 0.50; 95% CI, 0.37 to 0.68; P<0.001). Similarly, in a 123-patient randomized phase 2 trial, Langer and others showed that the objective tumor response rate was greater with pembrolizumab in combination with carboplatin and pemetrexed versus chemotherapy alone: 55% (95% CI: 42-68) versus 29% (CI: 18-41) [7]. More recently, in a 616-patient study, Gandhi and others randomly assigned patients in a 2:1 ratio to either pembrolizumab plus chemotherapy versus placebo plus chemotherapy[8]. The former was more beneficial; a median progression-free survival of 8.8 months (95% CI, 7.6 to 9.2) was observed in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group (hazard ratio for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001). Pembrolizumab is now often used in the first-line setting in patients with metastatic non-squamous non-small cell lung cancer, yet the safety profile of this agent in older patients has not been objectively evaluated.

1.2 Lack of Adverse event data in checkpoint inhibitors

Adverse event information on checkpoint inhibitors in older patients is growing but only incrementally. First, with pembrolizumab, data from 3991 patients with melanoma, non-small cell lung cancer, head and neck cancer, lymphoma, or urothelial cancer, show that only 16% of the cohort was 75 years of age or older [9]. Although subgroup analyses did not show major, age-based differences in adverse events, this conclusion might not be relevant to most older cancer patients, as clinical trials with new agents appear to select for more fit older patients. Thus, one

could convincingly argue that further data are necessary to gain greater reassurance of the safety of pembrolizumab in older cancer patients. Second, Betof and others recently reviewed retrospective data on 254 melanoma patients who were treated with anti-PD-1/PD-L1 [10]. Within this group, 57 (22%) were <50 years of age, 85 (34%) between 50-64 years of age, 65 (26%) between 65-74 years of age, and 47 (19%) ≥75 years old. One hundred and ten patients (43%) experienced adverse events from immunotherapy with colitis occurring in 25 (10%) and endocrine adverse events occurring in 26 (10%). Although this important study concluded that overall survival and rates of adverse events did not appear to differ based on age, its retrospective study design and relatively small number of older patients invite further investigation of age-based adverse events with immunotherapy within the context of a prospective study. Third, Grossi and others preliminarily evaluated 70 patients who were 75 years of age or older and all of whom participated in an Italian expanded access program for nivolumab, another checkpoint inhibitor [11]. These investigators observed that 8 (11%) patients discontinued therapy because of adverse events. However, this older cohort of patients with squamous cell carcinoma was relatively small and not representative of a US population [7]. Fourth, Freeman and Weber examined data from 148 patients, 52 of whom were older than 65 years of age [12].

These investigators observed no statistically significant, age-based differences in commonly observed adverse event rates such as diarrhea, rash, and vitiligo. Again, however, numbers were small. Finally, unpublished, pharmaceutical company data from Merck seem to show comparable adverse event profiles based on age (**Table 1**) [13]. However, these clinical trial data likely reflect bias, as only the most fit older patients were likely included; and these data are generated from a pharmaceutical company.

Table 1:

KN001, KN002, KN006 and KN010 melanoma and lung cancer subjects treated with pembrolizumab

Age	<65	65-74	75-84	≥85
Number of patients	1587	857	316	39
Drug-related AE (%)	73	73	77	79.5
Drug-related SAE (%)	9	11	13	10
Discontinued due to drug-related AE (%)	4	6	8.5	3

1.2.1 Limitations of previous studies

In summary, the above 5 studies provide some degree of reassurance of the safety of checkpoint inhibitors in older cancer patients. However, these conclusions appear to be tentative at best because they 1) are based on either relatively small cohorts or retrospective analyses, 2) rely on studies that have included older patients enrolled in age-unspecified trials which tend to capture a more fit group of older patients who are likely to generate a more acceptable adverse event profile, and 3) were often generated and reported under pharmaceutical company sponsorship. Such limitations underscore the importance of seeking robust, prospectively-collected data with no potential for bias in older cancer patients with the goal of better characterizing the adverse event profile of pembrolizumab in older patients.

1.3 MK-3475 (pembrolizumab) adverse events

With single agent pembrolizumab, < 20% of patients (age not specified) developed severe toxicity [14]. As per this drug's package insert, the following adverse events of all grades occurred in > 10% of patients, with numbers in parentheses indicative of the percentage from the entire cohort: **fatigue (25),** rash (24), vitiligo (13), diarrhea (26), nausea (21), pruritus (17), arthralgia (18), back pain (12), cough (17), dyspnea (11), decreased appetite (16), headache (14), hyperglycemia (45), hypertriglyceridemia (43), hyponatremia (28), increased AST (27), hypercholesterolemia (20), anemia (35), and lymphopenia (33). Grade 3+ adverse events occurred at the following rates: fatigue (0.9), rash (0.2), arthralgia (0.4), back pain (0.9), dyspnea (0.9), decreased appetite (0.5), headache (0.2), hyperglycemia (4.2), hypertriglyceridemia (2.6), hyponatremia (4.6), increased AST (2.6), hypercholesterolemia (1.2), anemia (3.8), and lymphopenia (7). In view of this diffuse but unusual adverse event profile, here we propose to report on these adverse events both in aggregate – in effect, grade 3 or worse -- as well as descriptively.

1.3.1 Might Older Patients Have Different Adverse Event Outcomes Than Younger Patients?

Although older cancer patients can benefit from cancer treatment, previous work from the Alliance for Cancer Clinical Trials in Oncology suggests that older patients manifest more frequent and severe adverse events. These studies that show different, age-based adverse event profiles often relied on re-analyses of prospectively-conducted, age-unspecified trials; therefore, to reiterate, because presumably more fit older patients were included, these analyses likely under-represent the adverse events that are seen in older patients treated in a non-study setting. First, Tallarico and others show that when examining non-conventional chemotherapy, or biologic therapies, such as rituximab, alemtuzumab, lenalidomide, and other similar agents, older patients with chronic lymphocytic leukemia suffered more treatment toxicity than younger patients with an odds ratio for grade 3 and 4 hematologic adverse events of 1.70 (95% CI= (1.57, 1.84); p=0.0089); and for non-hematologic adverse events 1.47 (95% CI (1.39,1.55); p=0.022) [15].

Second, similar conclusions were reached with conventional chemotherapy when studying older versus younger patients with gastroesophageal cancer or gastric cancer [16]. Studying 367 patients from 8 consecutive, first-line trials that included: i) etoposide + cisplatin; ii) 5-fluorourucil + leucovorin; iii) 5-fluorouracil + levamisole; iv) irinotecan; v) docetaxel + irinotecan; vi) oxaliplatin + capecitabine; vii) docetaxel + capecitabine; and viii) bortezomib + paclitaxel + carboplatin, our group reported that 154 patients(42%) were 65 years of age or older (range: 65-86 years of age),and 213 were younger (range: 20-64 years of age). Rates of grade 3 or worse adverse events across all chemotherapy cycles in univariate and multivariate analyses (adjusted for gender, performance score, and stratified by individual study) were significantly higher among older patients. Rates of neutropenia, fatigue, infection, and stomatitis in elderly versus younger patients were 31% versus 29% (p=0.02 by multivariate analyses), 15% versus 5% (p=0.01), 9% versus 4% (p=0.03), and 6% versus 1% (p=0.04), respectively, although duration of chemotherapy, overall survival, and progression-free survival were comparable.

Finally, disparities in adverse event rates in older patients are also relevant to those who receive radiation [17]. Our group analyzed data from a 263-patient phase III trial that examined etoposide and cisplatin plus either twice-daily radiotherapy or once-daily radiotherapy in patients with limited-stage small cell lung carcinoma. No difference in survival was observed between the 54 patients (21%) who were older than 70 years of age and the 209 (79%) younger patients. However, notably, grade 4 or worse pneumonitis

occurred in 6% of older patients but in none of the younger patients (P = 0.008). Similarly, death occurred in 3 of 54 (5.6%) older patients and in 1 of 209 (0.5%) younger patients (P = 0.03). All these findings underscore the point that older patients manifest worse toxicity profiles with cancer treatment and that focusing on adverse events in older cancer patients is important.

1.3.2 Comprehensive Geriatric Assessment

The comprehensive geriatric assessment (CGA) embraces the domains of functional status, comorbid medical conditions, cognition, nutritional assessment, psychosocial status, and social support; these domains are logically important in the care of older patients with cancer. Of note, the incorporation of the CGA into a multi-site cancer clinical trial is feasible, as Hurria and others have demonstrated [18,19,20,21]: the mean time to completion is 27 minutes (standard deviation = 10 minutes; range = 8 to 45 minutes) with most patients' (87%) completing the self-administered section independently. In a 15-site, 95-patient (85 were assessable), study, CALGB 360401 showed 100% of patients completed their portion of the GA, 87% completed it without assistance, the time to complete the testing was 15 minutes for patients, and 5 minutes for healthcare providers with 92% of patients being satisfied with the length of the questionnaire. Moreover, among older chemotherapy-treated cancer patients, the CGA was able to predict risk of toxicity. Such risk increased with an increasing risk score, as derived from the CGA: 36.7% low, 62.4% medium, 70.2% high risk; P < .001. These data point out the importance of incorporating the CGA as therapeutic decisions are made among older cancer patients who are potential candidates for chemotherapy. However and importantly, these data also underscore the fact that similar validated data are not available for older patients who are considered candidates for checkpoint inhibitors, such as pembrolizumab. Here we propose for the first time to begin to evaluate whether or not the CGA-based risk score developed for chemotherapy is also predictive of toxicities for older immunotherapy candidates. If the previously developed CGA-based risk score does not appear to predict toxicities in older patients treated with immunotherapy, we will use the CGA data collected here to develop a risk score for older immunotherapy candidates and will plan a future study to validate the newly developed risk score.

1.3.3 Identifying a Subset of Tumor-Reactive CD8+T Cells in Peripheral Blood, Their Relationship to Fatigue, and CX3CR1 Subsets as a Mechanism-Based Explanation of MK-3475 (pembrolizumab)-Induced Fatigue

Because fatigue is one of the most common adverse events with pembrolizumab (see above) and occurs in at least 25% of patients who receive this drug, we have chosen to further explore rates and mechanisms of this prevalent symptom in this proposal [22,23]. In an earlier publication within *Nature*, Dong and others from the Mayo Clinic described their discovery of PD-L1, the target for agents such as pembrolizumab. These investigators continue to characterize mechanisms of tumor resistance to checkpoint inhibitors as well as biomarkers that might serve as predictors of tumor response [24,25]. These investigators recently observed that a subset of tumor-reactive CD8+ effector T cells, which express CX3CR1, proliferate in patients who respond to pembrolizumab [24,25]. Surprisingly, these CX3CR1 effector CD8+ T cells are maintained – and at times even increased -- with the addition of chemotherapy. Interestingly, although Dong and others did not specifically focus on fatigue, their observations on this subset of CD8+ T cells correlate with the patterns of fatigue observed with pembrolizumab therapy, and, from a plausibility standpoint, the proliferation of CX3CR1 effector CD8+ T cells is an energy-consuming process.

Moreover, Pereira and others have shown that exercise appears to result in a decline in CX3CR1-expressing CD8+Tcells, a finding that adds credence to our hypothesis that fatigue might be immunologically-mediated in this group of patients [26]. Based on these observations and the clinical, correlative patterns of fatigue over time and with the addition of chemotherapy, we hypothesize -- in this highly exploratory aim -- that this proliferation of CX3CR1-expressing CD8+ effector T cell subset results in severe, clinical fatigue. To test this hypothesis, we will obtain peripheral blood and examine whether increasing numbers and percentages of CD8+ T cells that express CX3CR1are associated with worse fatigue scores at baseline and at 3 weeks for a total of 3 chemotherapy cycles (approximately 9 weeks). This approach could provide insight into mechanisms underlying pembrolizumab-induced fatigue and could hence potentially give rise to the testing of other interventions at a later date, perhaps exercise-based, to palliate this prevalent symptom.

1.4 Notable Aspects of the Proposed Trial Design

First, although this proposal focuses on first-line patients with metastatic non-small cell lung cancer, this work has broad implications for patients with various other cancer types and for those on other checkpoint inhibitors. Checkpoint inhibitors are currently being used widely, and their use is expected to expand further [27,28,29,30,31,32.] The current study will likely provide important information and precedent that goes well beyond one drug for one cancer indication. Second, as shown by Langer and others, in patients with non-small cell lung cancer, administering a combination of pembrolizumab and chemotherapy is a reasonable approach [7]. Therefore, in the current trial, we will allow patients to receive either single agent pembrolizumab or combination therapy with an anticipated 1:1 ratio, and we will report adverse events rates based on whether patients had received chemotherapy or not. We acknowledge that **in older cancer patients, pembrolizumab as a single agent might be perceived as a better option** because of its favorable adverse event profile and recognize the importance of enabling patients and oncologists to have the latitude of monotherapy versus combination pembrolizumab with chemotherapy [7,8].

This unrestricted study design element is considered a major advantage, as it enables us to acquire information on a particularly vulnerable group of older patients who are deemed poor candidates for chemotherapy by their oncologist. Third, using a pragmatic approach, we will allow oncologists latitude with respect to chemotherapy dose reductions at trial initiation and over time. This approach has clear precedent in other studies that have examined chemotherapy in older cancer patients [33]. Finally, we have incorporated into our trial design several measures to liberalize recruitment of older patients and thereby enroll a more population-based, representative group of older patients; these measures include 1) liberalization of dosing; 2) elimination of performance score in the eligibility. These measures are designed to allow for a truly representative group of older non-small cell lung cancer patients.

In summary, this trial addresses the adverse event profile of MK-3475 (pembrolizumab) in older lung cancer patients within the context of a non-pharmaceutical-sponsored study design. It also includes other study design elements – a trial design for older patients and the option of up front chemotherapy dose reductions, all of which are conducive to the enrollment of a group of patients who are more representative of those in the general non-small cell, older lung cancer population.

1.5 Impact on standard of care and future clinical trials

The information gleaned from the conduct of this trial will be essential as oncologists across the United States engage in informative discussions with older patients – in effect, the majority of those patients with lung cancer – as they together make decisions on whether or not to start

systemic cancer therapy. In essence, the information derived from this trial would have a direct clinical impact. Adverse event data obtained from this study would enable healthcare providers to counsel older patients appropriately and relevantly on what to expect when receiving these treatment regimens. In addition, were we to observe high rates of a specific and severe adverse event within an older group of patients, we would be well-positioned to consider the development of symptom intervention trials aimed at mitigating such drug-induced toxicity in older cancer patients.

2.0 OBJECTIVES

2.1 Primary objective

To estimate the adverse event profile of MK-3475 (pembrolizumab) over the first six months of treatment, in non-small cell lung cancer patients who are 70 years of age or older and who are treated with MK-3475 (pembrolizumab) +/- chemotherapy in a first-line setting.

2.2 Secondary objectives

2.2.1 To estimate overall survival.

2.2.2 To describe patient quality of life during the treatment using the Linear Analogue Self-Assessment (LASA) questionnaire.

2.2.3 To explore whether Comprehensive Geriatric Assessment (CGA) -derived risk score is able to predict rates of severe adverse events in older cancer patients who receive MK-3475 (pembrolizumab) or MK-3475 (pembrolizumab) + chemotherapy.

2.3 Exploratory objectives

2.3.1 To disaggregate the adverse events and identify potential causes of individual adverse events.

2.3.2 To describe patient fatigue level as measured with the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF); exercise level using the Godin Leisure Time Exercise Questionnaire (GLTE); and other symptoms and concerns using the LASA questionnaires.

2.3.3 To estimate time-to-treatment failure for single-agent MK-3475 (pembrolizumab) and MK-3475 (pembrolizumab) + chemotherapy in older patients.

2.4 Correlative science objectives

2.4.1 To evaluate whether older patients who experience fatigue or other adverse effects would be correlated with a change of PD-L1 therapy-responsive T cell subset (i.e. CX3CR1+ CD11ahighCD8+ T-cells) in their peripheral blood from baseline (prior to therapy) to post therapy. (See Sections 6.2 and 14.1)

2.4.2 To determine the extent to which MK-3475 (pembrolizumab) demonstrates time dependent decrease in clearance in older adult patients (aged ≥ 70 years) with non-small cell lung cancer being treated with pembrolizumab monotherapy or in combination with cytotoxic chemotherapy. (See Sections 6.2 and 14.2)

2.4.3 To determine the intrapatient and interpatient variability in clearance in older adult (≥ 70 years) patients with non-small cell lung cancer receiving pembrolizumab monotherapy and when combined with cytotoxic chemotherapy. (See Sections 6.2 and 14.2)

2.4.4 To preliminarily explore the correlation between pembrolizumab exposure (AUC) with observed immune related toxicities in this older adult (aged ≥70 years) patient population

receiving pembrolizumab monotherapy and when combined with cytotoxic chemotherapy. (See Sections 6.2 and 14.2)

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- No other concomitant medical or psychiatric condition that the treating oncologist believes would interfere with monitoring the patient while on study.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Documentation of Disease: Histologic or cytologic diagnosis of non-small cell lung cancer (adenocarcinoma). Stage IV or recurrent metastatic non-small cell lung cancer.** No planned initiation of definitive (potentially curative) concurrent chemo-radiation.

___ **3.2.2 Planning to begin MK-3475 (pembrolizumab) treatment within 14 days of registration, with or without combination chemotherapy.**

Treating physician considers pembrolizumab as appropriate and plans to proceed with one of the following treatment schedules:

(a) MK-3475 (pembrolizumab) 200 mg IV flat dose every 21 days or 400 mg IV flat dose every 42 days.

(b) MK-3475 (pembrolizumab) 200 mg IV/ 400 mg IV + carboplatin AUC=5 + pemetrexed 500 mg/m^2 (20% chemotherapy dose reduction is permitted per the discretion of the treating physician).

___ **3.2.3 Patients will be ineligible if they are post-organ transplantation or are receiving ongoing immunosuppression treatment. Patients will be ineligible if they have an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).**

Note: Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Patients who require inhaled corticosteroids would not be excluded from the study. Patients with vitiligo or resolved childhood asthma/atopy would not be excluded from the study. Patients who require local steroid injections (for example, a steroid injection to a joint) would not be excluded from the study.

___ **3.2.4 Prior adjuvant therapy is allowed and must have been completed at least 6 months prior to registration.**

___ **3.2.5 No planned radiation or other cancer treatment in the 3 months following registration.**

___ **3.2.6 No untreated brain metastases. Patients must be off oral and IV corticosteroids for this condition and asymptomatic at registration.**

___ **3.2.7 Age ≥ 70 years of age. (See next page, for additional eligibility criteria.)**

___ **3.2.8 Required Initial Laboratory Values:**

Absolute neutrophil count (ANC)	≥ 1500/mm^3 (1.5 x 10^9/L)
Platelet count:	≥ 100,000/mm^3 (100x 10^9/L)
Calculated creatinine clearance:	≥ 30 ml/min* for patients enrolled to pembrolizumab alone and > 45 ml/min for patients enrolled to chemotherapy + pembrolizumab
Total bilirubin	≤ 1.5 ULN (< 3 ULN if Gilbert's disease)
AST and/or ALT	≤ 3 x ULN (≤ 5.0 x ULN if liver metastases present)
Alkaline phosphatase	≤ 2.5 x ULN (≤5 x ULN if bone or liver metastases present)

* Calculated using the Cockcroft-Gault formula

___ **3.2.9 Language: Patients must be able to speak and comprehend English** in order to complete the mandatory patient-completed measures.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the **RCR Help Desk** by email [redacted]

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol specific requirements for A171901 site registration

Evidence of Geriatric Assessment Training, as described in Section 15.0. At least one site staff member must have completed the Geriatric Assessment Training for the site to be approved for the study.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A171901*.

Click on *Documents, Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration to* download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] in order to receive further instruction and support.

4.2.5 Checking site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.

- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

4.3.2 Patient-reported outcomes

This study includes the use of the mandatory patient completed measures. The measures are available in English. Participation in Alliance A171901 is restricted to patients who are able to speak, understand and read English.

Electronic patient reported outcomes (ePRO): This study includes the use of ePRO, (electronic patient-reported outcomes). After the patient is registered to the trial, the CRP will complete a second registration to the Patient Cloud. The CRP will create a unique patient registration code by accessing the Patient Cloud through iMedidata Rave. Patients (with assistance from CRPs) will need to download the Patient Cloud app on their own device and use the unique registration code given by the CRP to create an account. Once completed, the patient will be able to complete the submission of patient reported outcomes electronically.

Prior to registration, the patient should be asked about the availability of an electronic device and willingness to complete the patient-reported questionnaires on the device. See Appendix V for further instructions on setting up patient cloud.

If sites intend to use a shared institutional device, the CRP can assist the patient with access and registration to the Patient Cloud app, with the patient completing the electronic data submission independently. Detailed instructions are included in Appendix V. If patients will be using devices supplied by the institution, CRPs will need to help the patient log into the device.

Patient questionnaire booklets:

Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A171901 CTSU web site) and submitting the form through the CTSU regulatory portal. Samples of the booklets are found in Appendices I-IV, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

Booklets should be offered **only** to those patients who are not willing and/or are unable to use an electronic device for completion of questionnaires. The patient should be informed that the same method of completion, that is paper or electronic, should be used by the patient throughout the duration of the study for all time points, as much as possible.

Geriatric Assessment: Healthcare professional questionnaire:

This portion of the questionnaire is **not** included in the patient questionnaire booklets, and sites are required to print it from Appendix I and enter the responses in Medidata Rave after completion.

4.3.4 Protected Health Information

Samples collected for the pharmacokinetics sub-study A171901-PP1 will be sent directly to [redacted] Staff Scientist, Clinical Pharmacology Program at the National Cancer Institute at the following address:

[redacted]

These samples will be labeled with patient initials, patient study ID and collection date/time.

Protection of data shared with [redacted]

Once samples are received at the lab, any patient data received will be entered into a secure e-database that is encrypted and only accessible by [redacted] authorized designees trained in human subjects' research. Additionally, the sample tubes themselves will be barcoded to be read by a secure e-database, and this also serves to de-identify the sample tube itself.

4.4 Patient Enrollment (registration/randomization procedures (Step 1))

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).
- **Site staff have completed the Geriatric Assessment training described in Section 15.0**

Assurance of drug provision:

As MK-3475 (pembrolizumab) will be used on-label, patients and their treating physicians will secure their own supply of the drug. Arrangements with third party insurers, private or public, should be made prior to registration. The patient must be willing to pay for the balance of the drug's cost that is not covered by third party insurance.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted]

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There are 2 required sub studies within Alliance A171901. These substudies do not require separate IRB approval. The substudies included within Alliance A171901 are:

- Using Immune Markers to Track Fatigue in Older Patients who Receive Pembrolizumab on Alliance A171901, Alliance A171901-ST1 (Section 14.1)
- Pharmacokinetics and Population Pharmacokinetics of Pembrolizumab, Alliance A171901-PP1 (Section 14.2)

All patients should be registered to **Alliance A171901-ST1** and **A171901-PP1** at the same time they are registered to the treatment trial (A171901). Samples should be submitted per Section 6.2.

4.6 Stratification Factors and Treatment Assignments

None. Descriptive factors are listed in Section 13.9.

5.0 STUDY CALENDAR

Pre-Study Testing Intervals: The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical and baseline adverse event assessment.

To be completed ≤ 42 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

	Prior to Registration	Day 1 of each cycle of treatment (with or without chemotherapy)	End of Treatment€
Tests & Observations			
H&P, height, weight, PS*	X	X(1)	X
Adverse Event Assessment	X	X(1) (2)	X
Patient reported measures**			
CGA (Appendix I)		A	
MFSI-SF (Appendix II)		B	X
GLTE (Appendix III)		B	X
LASA (Appendix IV)		B	X
Laboratory Studies			
CBC w/ Differential, Platelets	X	X(1)	X
Serum Creatinine	X	X(1)	X
Albumin, glucose, AST, ALT, Alk. Phos., Bili	X	X(1)	X
TSH with reflex		X(1)	X
Staging			
CT/any other imaging modality	X	C	C
Mandatory Correlative studies for all patients (A171901-ST1 and A171901-PP1):			
Whole Blood and Serum	*See Section 6.2 for specimen submission instructions*		

* Height required at baseline only, not at every visit. Survival information is required annually until 5 years following registration. See also Section 12.0.

** To be completed using ePRO. See Section 4.3.2 and Appendix V for further instructions.

1 Need not be repeated if done ≤ 14 days prior to treatment, for Day 1 of Cycle 1 only. For subsequent cycles, may be done within 3 days prior to treatment.

2 Virtual visits will be allowed for all patients irrespective of treatment schedule. For patients who are on 6 week treatment cycles, AE assessments are to occur every 3 weeks by telephone or virtual visits.

€ Within 21 days of last day of treatment.

A Prior to treatment on Day 1 of Cycle 1 only, may be completed any time following consent and registration, prior to treatment

B Every 3 weeks for the first 9 weeks only, for all patients. To be completed prior to treatment on treatment visits.

C Scanning and its frequency is left to the discretion of the treating physician.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule:

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

6.1.2 Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information

on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the CTSU Help Desk at [redacted]

6.1.3 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis. Supporting documentation will include pathology and radiology reports and must be submitted at the following time points:

Baseline: Pathology and radiology reports and clinic notes

All supporting documentation should be de-identified according to institutional standards prior to upload into RAVE.

6.1.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Specimen collection and submission

For all patients registered to Alliance A171901: The submission of these blood samples for review is **required** for all patients registered to this study. Biomarker and pharmacokinetic studies will be performed. All patients who provide their consent to participate in the main study will have provided their consent to participate in **A171901-ST1 and A171901-PP1.**

Correlative Science Manual (CSM): The Alliance A171901 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be found on the study-specific webpage on the Alliance, BioMS, and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

Rationale and methods for the scientific components of these studies are described in Section 14.0. For all patients who consent to participate in the main study, blood samples will be collected at the following time points for these mandatory sub-studies:

	Day 1 of Cycles 1, 2 and 3€	**Day 1 of Cycle 6 and Cycle 9€**	**End of treatment¥**
Mandatory for <u>all</u> patients registered to A171901; submit the following for A171901-ST1 and A171901-PP1 (All samples (except end of treatment) to be collected <u>prior</u> to infusion)			
Number and volume of tubes to draw			
Whole Blood[1] (EDTA tube)	3x10 mL *		3x10 mL
Serum[2] (Red top Vacutainer)	1x5 mL	1x5 mL	1x5 mL

€ Day 1 samples for these cycles may be collected within 3 days prior to treatment, as long as the exact time and date of collection is recorded on the forms. The exact time and date of infusion start and stop (to assess duration of infusion) will be collected in Rave as well.
¥ Within 21 days of last day of treatment (the date of the last infusion). Not required for patients who are not scheduled for a visit during this window.
* Day 1 of Cycle 3 sample not required for patients receiving 400 mg pembrolizumab every 42 days.
1 Whole blood to be used for biomarker analyses described in Section 14.1.(A171901-ST1)
2 Serum from whole blood to be used for pharmacokinetic analyses described in Section 14.2. (A171901-PP1). Cycle 6 and Cycle 9 samples are required only for patients still receiving treatment. If collection of Cycle 9 sample is missed, samples may be collected on Day 1 of Cycle 12 instead. Effective with Update 1, serum samples are being sent to [redacted] at the National Cancer Institute (NCI). Serum samples for A171901-PP1 at end of treatment are only required for patients consented following Update 1 to the study.

6.3 Submission of Patient Completed Measures

It is strongly recommended that patients are offered the option of completing the measures using ePRO. Paper booklets should be offered only to those patients who are not willing and/or are unable to use an electronic device for completion of questionnaires.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3.2). Samples of questionnaire booklets are available in Appendices I-IV for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person and site staff will enter patient responses into Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

Submission of Completed Booklets: The data from the booklets are to be entered into Medidata Rave by site staff. Patients should be instructed to return the booklets by mail or to return the booklets at their regularly scheduled clinic visit. Institutions should provide patients with sufficient self-addressed stamped envelopes for this purpose.

Submission of measures completed in the patient cloud app: The data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation. See Appendix V.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for protocol treatment doses to be delivered within a +/- 3 day (business days) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Tuesday through the following Wednesday. In addition, patients are permitted to have a new cycle of chemotherapy/protocol treatment delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

This study will be an open label Phase II study and will allow for either single agent MK-3475(pembrolizumab) or the combination of MK-3475 (pembrolizumab) with carboplatin and pemetrexed (based on oncologists'/patient's choice) as first-line therapy for patients with advanced non-small cell lung cancer.

Treatment of single agent pembrolizumab versus combination therapy is based on treating physician's or patient's choice.

Agent	Starting Dose	Route of Administration	Frequency of Administration
MK-3475 (pembrolizumab)	200 mg Or 400 mg	IV	Once every 21 days Or Once every 42 days

OR

Agent*	Starting Dose	Route of Administration	Frequency of Administration
MK-3475 (pembrolizumab)	200 mg Or 400 mg	IV	Once every 21 days Or Once every 42 days
Pemetrexed**	500 mg/m^2	IV	Once every 21 days
Carboplatin**	AUC=5	IV	Once every 21 days

* For pemetrexed and carboplatin, oncologists are allowed to start and continue therapy with up to a 20% dose reduction based on their discretion (not more than a 20% reduction; for example, a 30% dose reduction is **not** permitted). Note that after the first cycle of chemotherapy, dose reductions are left to the discretion of the treating oncologist.

** Patients treated with pemetrexed require folic acid and vitamin B12 supplementation to reduce treatment related side effects. The timing of the initiation of folic acid and B12 administration is left to the discretion of the treating physician but should start no later than on the date of chemotherapy administration and is encouraged to start sooner.

Pembrolizumab treatment (with or without combination chemotherapy) will continue until disease progression (disease progression is defined as symptomatic, rapidly progressive disease that

requires urgent intervention or occurs with a decline in performance status or is confirmed at 4 to 6 weeks with repeat imaging) or unacceptable adverse event.

7.1 MK-3475 (pembrolizumab)

MK-3475 (pembrolizumab) will be given as 200 mg administered as an intravenous infusion over 30 minutes or according to institutional standards, on Day 1 of every 21 day cycle until disease progression or unacceptable toxicity or; 400 mg administered as an intravenous infusion over 30 minutes or according to institutional standards, on Day 1 of every 42 day cycle until disease progression or unacceptable toxicity.

It will be administered either as a single agent or with pemetrexed and carboplatin according to the treating physician's discretion. When administering pembrolizumab in combination with chemotherapy, it will be administered prior to chemotherapy.

7.2 Pemetrexed

Pemetrexed will be given as 500 mg/m^2 as an intravenous infusion over 10 minutes on Day 1 of every 21-day cycle.

7.3 Carboplatin

Carboplatin will be administered intravenously as per institutional guidelines on Day 1 of every 21-day cycle. The number of carboplatin cycles is left to the discretion of the treating oncologist. Based on KEYNOTE-189[34] , we recommend up to four cycles of carboplatin if tolerated.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary objective. As a general rule, simultaneous enrollment on any other treatment study, with or without investigational agents, is discouraged, although exceptions may be allowed in unusual circumstances by the study chair in collaboration with the executive officer and primary statistician.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered; except for hormones administered for non-disease-related conditions (e.g., insulin for diabetes).

8.1.4 Antiemetics may be used at the discretion of the attending physician.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Palliative radiation therapy may not be administered. Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF): Use of Filgrastim (G-CSF)/pegfilgrastim, tbo-filgrastim and sargramostim (GM-CSF) is permitted at the discretion of the treating physician.

8.1.8 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to drugs as per institutional standards.

8.2 Dose Modifications

Dose modifications for MK-3475 (pembrolizumab), pemetrexed and carboplatin will be according to the current package insert and treating physician's discretion.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Event Solicited Form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at **baseline** and **every 3 weeks until end of treatment.**

CTCAE v5.0 Term	**CTCAE v5.0 System Organ Class (SOC)**
Hypothyroidism	Endocrine Disorders
Abdominal Pain	Gastrointestinal disorders
Diarrhea*	Gastrointestinal disorders
Constipation	Gastrointestinal disorders
Nausea	Gastrointestinal disorders
Vomiting	Gastrointestinal disorders
Fatigue	General disorders and administration site conditions
Neutrophil count decreased	Blood and lymphatic system disorders
Anemia	Blood and lymphatic system disorders
Platelet count decreased	Investigations
Blood bilirubin increased	Investigations
Alanine aminotransferase increased	Investigations
Anorexia	Metabolism and nutrition disorders
Arthralgia	Musculoskeletal and connective tissue disorders

Cough	Respiratory, thoracic, and mediastinal disorders
Dyspnea	Respiratory, thoracic, and mediastinal disorders
Peripheral sensory neuropathy	Nervous system disorders
Confusion	Nervous system disorders
Acute kidney injury	Renal and urinary disorders

* Diarrhea will not be solicited at baseline, but number of stools per day will be collected, in order to assess diarrhea as a solicited adverse event during treatment.

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Baseline CRF and Adverse Events CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date.

b) Late Adverse Events CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting.

The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

≤ Grade 4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other adverse events that result in ≥24-hour hospitalization or prolongation of an existing hospitalization must be reported via CTEP-AERS.

New primary malignancies should be reported in Rave.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported

as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

Revised MK-3475 CAEPR – Version 2.6, July 15, 2021

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, July 15, 2021[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]	
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis) [2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[36]	Hepatobiliary disorders - Other (sclerosing cholangitis)	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease) [2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis) [2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation) [2]		
	Immune system disorders - Other (sarcoidosis) [2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis) [2]		
	Myalgia[2]		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome) [2]	
		Nervous system disorders - Other (neuromyopathy) [2]	
		Nervous system disorders - Other (non-infectious encephalitis) [2]	
		Nervous system disorders - Other (non-infectious meningitis) [2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy) [2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis) [2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (dermatitis) [2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

General considerations: All study agents are to be administered at the registering institution.

10.1 MK-3475 (pembrolizumab) (Keytruda®)

Background: Highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling. Anti-PD-1 antibodies reverse T-cell suppression and induce antitumor responses.

IND Exempt: Pembrolizumab is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for Pembrolizumab; this investigation will use an approved route of administration and dosage of Pembrolizumab and has no factors that increase the risk of the product; this investigation will be in compliance with 21CFR parts 56, 50, and 312.7; and neither the investigator nor sponsor will promote or represent that Pembrolizumab is safe or effective for the context that is under investigation in this study.

Formulation

Commercially available for injection 25mg/ml (4ml) [contains polysorbate 80] in a one-vial formulation.

Preparation, storage and administration

Follow institutional standards.

Pharmacokinetic information

Note: Clearance is ~20% lower at steady state than with the first dose. With weight-based dosing (2 mg/kg), pembrolizumab concentrations in pediatric patients are comparable to those of adults (at the same dose).

Distribution: V_{dss}: 6.1 L

Half-life elimination: 23 days

Potential Drug Interactions

There are no known significant drug interactions.

Known potential toxicities

Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:

Cardiovascular: Facial edema

Central nervous system: Fatigue

Dermatologic: Pruritus, skin rash

Endocrine & metabolic: Hyperglycemia, hyponatremia, hypoalbuminemia, hypertriglyceridemia, hypocalcemia, decreased serum bicarbonate

Gastrointestinal: Nausea, decreased appetite, constipation, diarrhea, vomiting, abdominal pain

Hematologic & oncologic: Anemia, lymphocytopenia

Hepatic: Increased serum AST, increased serum ALT, increased serum alkaline phosphatase

Neuromuscular & skeletal: Arthralgia Respiratory: Cough, dyspnea

Miscellaneous: Fever

Less common known potential toxicities, 1% - 10%:

Central nervous system: Confusion, peripheral neuropathy

Endocrine & metabolic: Hypothyroidism, hyperthyroidism

Gastrointestinal: Colitis

Immunologic: Antibody development

Neuromuscular & skeletal: Weakness, arthritis

Respiratory: Pneumonitis, pleural effusion, pneumonia, respiratory failure

Rare known potential toxicities, <1% (Limited to important or life-threatening)

Adrenocortical insufficiency (immune-mediated), bullous pemphigoid (immune-mediated), chronic inflammatory demyelinating polyradiculoneuropathy, diabetic ketoacidosis, exfoliative dermatitis (immune-mediated), Guillain-Barre syndrome (immune-mediated), hemolytic anemia (immune-mediated), hepatitis (including autoimmune hepatitis), hypophysitis, infusion-related reaction, interstitial nephritis (with renal failure), myasthenia gravis (immune mediated),myositis (immune-mediated), nephritis (autoimmune), pancreatitis (immune-mediated), partial epilepsy (immune-mediated; in a patient with inflammatory foci in brain parenchyma), thyroiditis, type I diabetes mellitus, uveitis (immune-mediated), vasculitis (immune-mediated)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Nursing Guidelines

1. Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
2. Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
3. Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.
4. Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
5. Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

6. Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
7. Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.
8. Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.
9. Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.
10. Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab.
11. Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.
12. Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.
13. Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias or numbness, tingling to the study team immediately.

10.2 Pemetrexed (Alimta)

Background: Pemetrexed is a multitargeted antifolate (MTA). Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase, the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis.

Formulation

Commercially available as a sterile lyophilized powder for intravenous infusion available in single-dose 100 and 500 mg vials.

Preparation, storage and administration

Follow your institutional standards.

Pharmacokinetic information

Distribution: V_{dss}: 16.1 L

Protein Binding: ~73% to 81%

Metabolism: Pemetrexed undergoes limited hepatic metabolism. Unchange pemetrexed accounts for the majority of the drug-related material in urine.

Half-life elimination: Normal renal function: 3.5 hours; Cl_{cr} 40-59 mL/minute: 5.3-5.8 hours

Excretion: Urine (70% to 90% as unchanged drug)

Potential Drug Interactions

Increased Effect/Toxicity: The administration of ibuprofen 400 mg every 6 hours to patients resulted in a 22% increase in AUC and a 16% increase in C_{MAX}. These alterations are no greater than those observed in patients with moderate renal impairment (CrCl 45 mL/min) and do not fall outside of what is considered an acceptable increase in exposure. Therefore, ibuprofen (400 mg every 6 hours) can be given concurrently with pemetrexed in patients with normal renal function (CrCl greater than or equal to 80 mL/min).

Ethanol/Nutrition/Herb Interactions: Lower ANC nadirs occur in patients with elevated baseline cystathionine or homocysteine concentrations. Levels of these substances can be reduced by folic acid and vitamin B_{12} supplementation.

Known potential adverse events

Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy (in patients who received folate and B_{12} supplementation); dose limiting toxicities include myelosuppression (neutropenia, thrombocytopenia); fatigue and dermatitis.

Common known potential toxicities, > 10%:

Cardiovascular: Chest pain, edema, hypertension

Central nervous system: Fatigue, fever, depression

Dermatologic: Rash/desquamation, alopecia

Gastrointestinal: Anorexia, nausea, constipation, vomiting, diarrhea, stomatitis

Hematologic: Anemia, leukopenia, neutropenia

Neuromuscular & skeletal: Neuropathy

Respiratory: Dyspnea, pharyngitis

Miscellaneous: Infection

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Thrombosis/embolism, cardiac ischemia

Endocrine & metabolic: Dehydration

Gastrointestinal: Dysphagia/esophagitis/odynophagia

Hematologic: Thrombocytopenia, febrile neutropenia

Hepatic: ALT increased, AST increased

Neuromuscular & skeletal: Arthralgia

Renal: Creatinine clearance decreased, serum creatinine increased

Miscellaneous: Allergic reaction/hypersensitivity

Rare known potential toxicities, <1% (Limited to important or life-threatening)

Colitis, renal failure

Drug procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Nursing Guidelines

1. Monitor blood counts. Instruct patient to report fevers >101°, excessive fatigue, bruising, or unusual bleeding.
2. Advise patient about possible rash, pruritus and the need to report these problems, which can be treated by steroids.
3. Supply warm packs to injection site if arm becomes inflamed.
4. Administer antiemetics and antidiarrheals as ordered.
5. Instruct patient that adequate hydration is important. Patient should report inability to maintain hydration.
6. Instruct patient in energy-conserving techniques.
7. Advise patient about possible hair loss.
8. Monitor liver and renal function tests.
9. Advise patient that urinary tract infections (UTIs) are possible, instruct in the signs and symptoms of a UTI and tell patients to report any of these to the health care team immediately.
10. Advise patient about possibility of mouth sores. Emphasize good oral care.
11. Advise patient that he/she should contact his/her physician in the event of trouble swallowing folic acid pills.

10.3 Carboplatin (Paraplatin®, CBDCA)

Background: Carboplatin is an alkylating agent which covalently binds to DNA; interferes with the function of DNA by producing intrerstrand DNA cross-links.

Formulation

Commercially available for injection as:

Solution Reconstituted: 150 mg.

Solution: 10 mg/mL (5 mL, 15 mL, 45 mL, 60 mL)

Preparation, storage and administration

Follow institutional standards.

Pharmacokinetic information

Distribution: $V_{d:}$ 16 L/kg; into liver, kidney, skin, and tumor tissue.

Protein binding: 0%; however the platinum from carboplatin becomes irreversibly bound to plasma proteins.

Metabolism: Minimally hepatic to aquated and hydroxylated compounds.

Half-life elimination: CrCl > 60 mL/min: Carboplatin: 2.6-5.9 hours (based on dose of 300-500 mg/m^2); Platinum (from carboplatin): ≥ 5 days.

Excretion: Urine (~70% as carboplatin within 24 hours; 3% to 5% as platinum within 1-4 days).

Potential Drug Interactions

Increased Effect/Toxicity: Aminoglycosides increase risk of ototoxicity and/or nephrotoxicity.

Known potential adverse events

Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy. **Note**: Myelosuppression is dose related, schedule related, and infusion-rate dependent (increased incidences with higher doses, more frequent doses, and longer infusion times) and, in general, rapidly reversible upon discontinuation.

Common known potential toxicities, > 10%:

Central nervous system: Pain

Endocrine & metabolic: Hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia

Gastrointestinal: Vomiting, abdominal pain, nausea

Hematologic: Myelosuppression (dose related and dose limiting; nadir at ~21 days; recovery by ~28 days), leukopenia, anemia, neutropenia, thrombocytopenia

Hepatic: Alkaline phosphatase increased, AST increased

Hypersensitivity: Hypersensitivity

Neuromuscular & skeletal: Weakness

Renal: Creatinine clearance decreased, BUN increased

Less common known potential toxicities, 1% - 10%:

Central nervous system: Peripheral neuropathy, neurotoxicity

Dermatologic: Alopecia

Gastrointestinal: Constipation, diarrhea, stomatitis/mucositis, taste dysgeusia

Hematologic: Hemorrhagic/bleeding complications

Hepatic: Bilirubin increased

Infection: Infection

Local: Pain at the injection site

Neuromuscular & skeletal: Peripheral neuropathy

Ocular: Visual disturbance

Otic: Ototoxicity

Renal: Creatinine increased

Rare known potential toxicities, <1% (Limited to important or life-threatening)

Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, dehydration, embolism, erythema, febrile neutropenia, hemolytic anemia (acute), hemolytic uremic syndrome, hyper-/hypotension, injection site reaction (pain, redness, swelling), limb ischemia (acute), malaise, metastases, pruritus, skin rash, tissue necrosis (associated with extravasation), urticaria, vision loss

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Nursing Guidelines

1. Monitor CBC and PLTs. Watch for profound neutropenia and give low count precautions and instructions as necessary. Nadir occurs at approximately day 21 with recovery at day 28-30. Thrombo-neutro-leukopenia may be cumulative. Thrombocytopenia can be dose-limiting and is more pronounced than with cisplatin. It can be more severe in patients with previous chemotherapy, concurrent radiation therapy, or patients with impaired renal function. Instruct patient to immediately report any unusual bruising or bleeding. Anemia (70-90% of patients) may be symptomatic with asthenia being the most common complaint. Instruct patient in energy saving lifestyle.
2. Assess baseline renal function (creatinine clearance). Reduced renal function can contribute to an increased risk of thrombocytopenia.
3. Monitor fluid status - encourage hydration.
4. Advise patient of probable taste alterations. Frequent oral hygiene is helpful. Instruct patient in appropriate interventions to achieve and maintain optimal nutritional status.
5. Older patients (>65) may experience some peripheral neuropathy with paresthesias. Instruct patients to report any tingling, burning, loss of sensation.
6. Mild nausea and vomiting occur in up to 94% of patients, 6-12 hours after treatment and may persist for 24 hours or longer. Diarrhea/cramping/constipation has been experienced by approximately 17%. Premedicate with antiemetics/antidiarrheals—evaluate effectiveness.
7. Administer following Taxol (in regimens that contain both drugs) to maximize cell kill.
8. Patients have experienced allergic reactions while receiving carboplatin. Watch for signs and symptoms of hypersensitivity reactions. If these occur, stop drug immediately, notify MD, and treat appropriately.

11.0 MEASUREMENT OF EFFECT

11.1 Patient reported outcome measures

11.1.1 Comprehensive Geriatric Assessment (CGA-Appendix I)

For the secondary clinical study observation with the Comprehensive Geriatric Assessment (CGA), patients will complete the CGA prior to treatment at baseline (Day1 of Cycle 1). Using previously described methodology from Hurria and others and following patients prospectively over time, we will determine whether the baseline CGA assessment is able to predict grade 3 or worse adverse events in a similar manner as it does in older, chemotherapy-treated patients [21]. It will take approximately twenty five minutes to complete this questionnaire.

11.1.2 Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF-Appendix II)

For the secondary translational study observation that focuses on fatigue, patients will complete the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF; Appendix II) prior to treatment on Day 1 of the first three cycles (every 3 weeks for the first 9 weeks only) and end of treatment. This 30-item instrument asks questions directly relevant to fatigue, has been psychometrically validated, and serves as a well-accepted instrument for clinical trials that focus on fatigue. This instrument has been reviewed and compared to other instruments by Stein and Jacobson [37]. Incorporating a questionnaire that is specific to fatigue seems appropriate and necessary for the translational work that also focuses on fatigue. As pointed out in a recent concept review from the NCI, we recognize that a "unique feature of the MFSI-SF is that it captures the full spectrum of the fatigue symptom profile using 5 empirically derived subscales: 1) general fatigue, 2) emotional fatigue, 3) physical fatigue, 4) mental fatigue and 5) vigor." As per NCI guidance, we intend to report total score as well as scores from 5 subscales based on study arm and patient demographics. Moreover, precedent exists within the Alliance for Clinical Trials for using this questionnaire [38]. It will take about 5 minutes to complete this measure.

11.1.3 Godin Leisure Time Exercise Questionnaire (GLTE-Appendix III)

Similarly, we will ask patients to complete the Godin Leisure-Time Exercise Questionnaire (GLTE), a previously validated and frequently used questionnaire that has demonstrated strong correlation between patient responses and activity, as assessed by means of an accelerometer among ill patients [39]. The brevity of this questionnaire also makes it a good choice because of minimization of patient burden. The GLTE will be graded based on prior instructions on the Oncology Nursing Society website, which divides patients into 3 groups where score of 24 or more is considered "active", 14-23 is considered "moderately active", and less than 14 is "insufficiently active/sedentary". This questionnaire will be completed prior to treatment on Day 1 of the first three cycles (every 3 weeks for the first 9 weeks only) and end of treatment. It will take about 5 minutes to complete this measure.

11.1.4 Linear Analogue Self-Assessment (LASA-Appendix IV)

In addition, cognizant of patient-burden from questionnaire completion, we will have patients complete a Linear Analogue Self-Assessment (LASA), a short series of 13 items that has been previously validated [40,41,42,43]. The LASA is used to assess patient quality of life, sleep disturbance and other patient-reported symptoms and concerns that may arise during cancer therapy. The LASA is particularly appealing because of its brevity and diminishment of patient burden. This questionnaire will be completed prior to treatment on Day 1 of the first three cycles (every 3 weeks for the first 9 weeks only) and end of treatment. It will take about 5 minutes to complete this measure.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue until disease progression or unacceptable toxicity. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and following up time periods.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression in the judgement of the treating oncologist.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients will undergo scheduled follow up assessments on Day 1 of every cycle, (every 3 weeks for all patients) until end of treatment. See study calendar (Section 5.0). All patients will be followed annually for survival until 5 years following registration or death whichever occurs first.

12.3.2 Follow-up for Patients who Stop Study Treatment Early

Follow up for patients who stop due to toxicity, or receive non protocol therapy:

Patients who discontinue study treatment due to toxicity or receive non-protocol therapy will be followed annually for survival only until 5 years following registration. They should be encouraged to complete end of treatment patient-reported questionnaire. The reason for discontinuation will be recorded on an Off-treatment form.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason for discontinuation of therapy on data forms.
- Follow the patient for protocol study observations as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., survival only) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study design

This is a phase II, open-label, multicenter clinical trial of non-small cell lung cancer patients of 70 years of age or older receiving MK-3475 (pembrolizumab) with or without chemotherapy as their first line of treatment.

13.2 Sample Size, Accrual Time and Study Duration

A minimum sample size of 90 evaluable patients will be enrolled to address the primary study observation. We anticipate accruing an additional 10 patients to account for cancellations, major trial violations, or other reasons; and therefore the maximum projected accrual for this trial is 100 patients.

Accrual rate estimate is 6 patients per month, including a 6 month ramp up period, the whole accrual period is estimated to be 23 months. Based on clinical experience in this older age group, we expect most patients to complete treatment within 2 years from starting therapy. Including an accrual period of 23 months, we anticipate that the primary study observation will be achieved approximately 47 months after trial activation.

13.3 Primary Study Observation

The primary objective of this study is to estimate the adverse event profile of MK-3475 (pembrolizumab) in non-small cell lung cancer patients who are 70 years of age or older and who are treated with MK-3475 (pembrolizumab) +/- chemotherapy in a first-line setting. The primary outcome of interest is grade 3 or worse solicited adverse events listed in Section 9.1 as defined per NCI CTCAE v 5.0. Any eligible patient to have received at least one cycle of treatment will be considered evaluable.

13.4 Power Justification and Primary Analysis

The sample size for this trial was determined considering both accrual feasibility for this patient population as well as a reasonable precision in estimating the proportion of patients who experience grade 3 or worse adverse events while receiving MK-3475 (pembrolizumab).

The proportion of patients who experience grade 3 or worse adverse events in the first six months of treatment will be summarized by frequency and percentage along with a 95% CI separately by type of therapy (monotherapy or combination therapy) as well as combining the two cohorts.

We assume that at least 50% of patients will receive monotherapy with pembrolizumab. If the adverse event rates for the monotherapy and the combination therapy groups appear to be similar, we will consider combining the two cohorts when estimating the adverse event rates. Otherwise, they will be estimated separately. Table 1 shows the precision in terms of the width of the 95% confidence interval for rates of adverse events (proportion of patients experiencing AEs) ranging from 10% to 90%, using the Clopper-Pearson exact confidence interval method. The widths of the 95% CI range from 19% to 31% when the therapy cohorts are analyzed separately and they range from 13% to 22% when the cohorts are analyzed together.

Below is the estimation precision for various scenarios of observed proportions of patients receiving monotherapy or combination of chemotherapy and immunotherapy (n = 45) or the combined cohort (n = 90) with AEs.

Confidence interval estimates for adverse event rates:

Observed proportion of patients with AEs	Separate cohorts (N = 45)		Combined cohort (N = 90)	
	95% CI limits	95% CI width	95% CI limits	95% CI width
.1	(0.031, 0.227)	0.196	(0.047, 0.181)	0.135
.3	(0.173, 0.455)	0.282	(0.208, 0.406)	0.198
.5	(0.347, 0.653)	0.305	(0.393, 0.607)	0.215
.7	(0.545, 0.827)	0.282	(0.594, 0.792)	0.198
.9	(0.773, 0.969)	0.196	(0.819, 0.953)	0.135

13.5 Analysis Plans for Secondary, Exploratory Objectives

13.5.1 Overall Survival

Overall survival will be summarized using the Kaplan-Meier estimator, separately by monotherapy or combination therapy as well as by the combined cohort. The event is death from any cause. Patients who are alive at the last follow-up will be censored at the last follow-up time. The time to event is the time interval from study registration to death or the last follow-up whichever occurs first.

13.5.2 Quality of Life

The overall quality of life score (the first question of the LASA questionnaire) at each time point as well as change from baseline will be summarized by mean (standard deviation), median (range) along with a longitudinal plot. The median QOL change from baseline to week 9 along with a 95% CI will be estimated using the Hodges-Lehmann method.

13.5.3 Comprehensive Geriatric Assessment

Items of the geriatric assessment questionnaire will be summarized by mean (standard deviation) and median (range) for continuous variables and frequency (percentage) for categorical data. The CGA-based risk score will be computed for each patient. [21] The CGA-based risk scores range between 0 and 19. The risk score is a summation of the following clinical and CGA factors (number in parentheses is the score for the factor): age ≥72 (2), GI or GU cancer (2), standard chemotherapy dose (2), polychemotherapy (2), hemoglobin <11g/dL for male or <10 g/dL for female (3), creatinine clearance <34 ml/min (3), fair or worse hearing (2), 1 or more falls in last 6 months (3), taking medications with some help or unable to (1), ability to walk 1 block is somewhat limited or limited a lot (2), decreased social activity because of physical/emotional health limited at least sometimes. Patients will be classified into one of the 3 risk groups (low: 0 – 5, medium: 6 – 9, and high: 10 – 19). The rate of grade 3 and worse AEs will be summarized for each risk group. The ability of the CGA-based risk score to predict toxicity will be evaluated by comparing the rates of grade 3 or worse AEs among the three risk groups using a chi-square test. For reporting purposes, we will provide the frequency of grade 3 or worse AEs by CGA-based risk group.

If the CGA-based risk score developed by Hurria et al,[21] does not predict grade 3 or worse AEs, we will use the data from this trial to explore development of a new CGA-based risk score for this patient population following the methods of Hurria et al. We will first consider evaluate the association between grade 3 or worse AEs with each of the demographics, clinical factors, and items of the geriatric assessment using the chi-square test. All variables that reached a p-value of less than .1 will be considered in the model building procedure using multivariate logistic regression with best subset selection method[44]. The risk score for each risk factor will be calculated by dividing the coefficient of the variable by the smallest coefficient in the final model. The risk score will be

computed for each patient by summing over the scores for individual factors in the final model. The sample will be divided into 3 risk categories approximately by low (first quartile of scores), medium (2nd and 3rd quartiles), and high (last quartile). The risk score will be internally validated using 10-fold cross-validation.

13.5.4. To disaggregate the solicited adverse events and identify potential causes of individual adverse events.

Individual solicited adverse events listed in Section 9.1 will be tabulated and potential association between baseline demographics and clinical factors and individual adverse events will be evaluated in an exploratory and hypothesis generating manner; including but not limited to multi-variate logistic regression models considering the baseline demographics and the presence/absence of the AE.

13.5.5 Fatigue, Exercise and other Symptoms and Concerns Questionnaires (exploratory objectives)

Response from the MFSI-SF and the GLTE questionnaires will be scored using established algorithm as described in Sections 11.1.2 and 11.1.3. The subscores and the total scores will be summarized by mean (standard deviation), median (range) along with a longitudinal plot. The mean score change from baseline along with a 95% CI will be estimated.

Other LASA symptoms and concerns will be analyzed in the same manner as described in Section 13.5.2. The subscale will be summarized.

13.5.6 Time to treatment failure (exploratory objective)

Treatment failure is defined as premature discontinuation (discontinuation of treatment before 34 cycles for patients on 3-week cycle and before 17 cycles for patients on 6-week cycle) of treatment due to disease progression, adverse events, death, or patient's choice. Time to treatment failure is defined as the time interval from study registration to premature discontinuation or the last follow-up whichever occurs first. Patients who are lost follow-up without the defined event prior to 35 cycles will be censored at the time of their last follow-up. Time to treatment failure will be estimated using the Kaplan-Meier estimator.

13.6 Study Monitoring (reports, summaries)

This study will be monitored by the study team, including the study chair, the study statisticians, and other appropriate members of the study team on an anticipated quarterly basis upon enrollment of the first patient, although the team reserves the possibility of modifying this frequency as appropriate. Reports containing a summary of adverse events by treatment cohort will be reviewed. We will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related," to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event. The study team will also monitor the accrual rate.

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.7 Adverse Event Stopping Rule

The study team will be monitoring if:

- 4 out of the first 10 patients to become evaluable for adverse events experience a grade 4 or grade 5 adverse event deemed to be at least possibly related to study treatment.
- At any time after the first 10 patients become evaluable for adverse events, 40% or more patients experience a grade 4 or grade 5 adverse event deemed to be at least possibly related to study treatment.

If the previous boundaries are crossed, the study will be assessed for suspension (but not suspended until the team has been able to discuss). In addition, each grade 5 event will be reviewed on a case by case basis in a real time fashion to determine whether study accrual should be suspended.

13.8 Feasibility

An interest and feasibility survey was sent to Alliance Community Oncology Committee members and demonstrated that 86% (28 respondents) stated that they see patients eligible for this study; 96% of 25 respondents indicated an interest in enrolling patients to such a trial. From the survey responses alone, interested sites would readily enroll to this trial. Conservatively, we estimate that we would enroll 6 patients per month with a 6 month ramp up with completion of accrual in 23 months.

13.9 Descriptive Factors

a) concomitant chemotherapy (yes versus no)

b) gender (male versus female)

c) baseline performance score

d) patient age at enrollment (>/= 80 years of age versus younger)

e) whether cancer treatment was started prior to trial enrollment (yes versus no)

f) Smoking history (defined as a patient who self-reports having smoked 100 or more cigarettes in his/her lifetime): yes versus no

g) PD-L1 expression (tumor proportion score (TPS))

13.10 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses. The geographical region served by the Alliance, has a population which includes approximately 13.5% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 12% of patients will be classified as minorities by race and about 56% of patients will be women. Expected sizes of race by gender subsets for patients registered to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	1	1	2
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	2	2	0	0	4
White	40	40	4	4	88
More Than One Race	0	0	0	0	0
Total	45	45	5	5	100

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 2 required sub-studies within A171901. All patients who consent to participate in the main study (A171901) are required to provide blood samples for the biomarker analyses (A171901-ST1) and pharmacokinetic analyses (A171901-PP1).

14.1 Correlative Science: Using Immune Markers to Track Fatigue in Older Patients who Receive Pembrolizumab on Alliance A171901 (Alliance A171901-ST1)

14.1.1 Background

It is becoming increasingly recognized that cancers can thrive upon evading the immune system. Malignancies such as melanoma and renal cell carcinoma are known to exploit the programmed death 1 (PD-1) pathway in order to evade the immune system through adaptive immune resistance. [45, 46] Monoclonal antibodies targeting PD-1 have recently been introduced, and have been shown to improve survival when used in patients with advanced clear cell renal cell carcinoma (ccRCC) who have previously failed 1-2 prior anti-angiogenic therapies.[47]

The success of PD-1 blockade therapy in treatment of solid cancers is dependent on the presence of pre-existing tumor-reactive CD8+ T lymphocytes[46]. We and others have established that PD-1 and CD11a can be used to identify tumor-reactive CD8+ cytotoxic T lymphocytes in the peripheral blood or in tumor tissues [48-50].We observed that patients with advanced cancers have high levels of $CD11a^{high}PD\text{-}1^{+}$ $CD8^{+}$ T cells in peripheral blood [48].

On the other hand, we recently identified that CX3CR1 defined a PD-1 therapy-responsive CD8+ T cells with effector memory phenotype and function[25]. In responders to PD-1 therapy or combined (chemotherapy), CX3CR1 identified an increased CD8 T cell population with effector function and endure cytotoxic chemotherapy drugs[25]. Thus, measurement of CX3CR1+ among CD11a high CD8 T cells will give us a full coverage of therapy-responsive T cell population for understanding the potential cellular mechanism underlying clinical outcomes in patients following immunotherapy or combined therapy.

14.1.2 Objectives

To evaluate whether older patients who experience fatigue or other adverse effects would be correlated with a change of PD-1 therapy-responsive T cell subset (i.e. $CX3CR1^{+}$ $CD11a^{high}CD8^{+}$ T-cells) in their peripheral blood from baseline (prior to therapy) to post therapy.

14.1.3 Methods

Our study will aim to collect 30 mL of whole blood at four time-points in the patient's care: prior to treatment on Day 1 of the first 3 cycles, and at end of treatment. (Please see Section 6.2 and CSM for more details). Patients are always assessed at these time points as per routine clinical care pathways relating to their treatment, therefore, the research blood draws should be coordinated with the blood they would have drawn as part of standard clinical care, to minimize the number of venipunctures.

Specimen processing:

Overview: After receipt by the Alliance biobank at Mayo Clinic, specimens will be processed by the lab of [redacted] at Mayo Clinic. From whole blood, peripheral blood mononuclear cells (PBMCs) will be isolated. Flow cytometry will be used to identify the phenotype and frequency of T-cells. Output data will be stored in confidential

electronic data files and appropriate measured will be used to protect patient confidentiality.

Flow cytometry analysis: PBMC samples will be thawed on the day of analysis, and be incubated with appropriate antibodies to identify cell surface markers (CD3, CD8, CD11a, and CX3CR1) and functional markers (Ki67 for proliferation, Bim for pro-apoptosis and Granzyme B for effector function). All these markers will be presented as percentage of change from baseline to post -treatment for the same patient.

The data collected from the samples, as described above, will be sent using encrypted secure spreadsheets to the Alliance SDC A171901 Statistician to prepare analysis datasets in conjunction with the clinical/outcome data. The A171901 Statistician will then coordinate the analyses with the A171901-ST1 Correlative Science Co-Chair, [redacted] Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

Statistical Analysis: The levels of CX3CR1+ CD8+ T-cells will be summarized at Day 1 at each cycle. The level of CX3CR1+ CD8+ T-cells at each time point will be plotted against MSFI-SF scores and the GLTE scores to explore the correlation between CX3CR1+ CD8+ T-cells and fatigue and activity levels.

14.2 Pharmacokinetics and Population Pharmacokinetics of Pembrolizumab (Alliance A171901-PP1)

14.2.1 Background

MK-3475 (Pembrolizumab) is an anti-PD-1 targeted monoclonal (IGg4 kappa) antibody with a molecular weight of 149 Kda. It is FDA approved for the treatment of a number of solid tumors including melanoma, non-small cell lung cancer, head and neck cancer, renal cell cancer (refer FDA approved product label[51]).

14.2.2 Objectives

1. To determine the extent to which pembrolizumab demonstrates time dependent decrease in clearance in older adult patients (aged ≥70 years) with non-small cell lung cancer being treated with pembrolizumab monotherapy or in combination with cytotoxic chemotherapy.
2. To determine the intrapatient and interpatient variability in clearance in older adult (≥70 years) patients with non-small cell lung cancer receiving pembrolizumab monotherapy and when combined with cytotoxic chemotherapy.
3. To preliminarily explore the correlation between pembrolizumab exposure (AUC) with observed immune related toxicities in this older adult (aged ≥70 years) patient population receiving pembrolizumab monotherapy and when combined with cytotoxic chemotherapy.

14.2.3 Pharmacodynamics

Based on dose/exposure efficacy and safety relationships, there were no clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with melanoma or NSCLC.

14.2.4 Pharmacokinetics and Population Pharmacokinetics

Pembrolizumab when administered is usually dosed at 200 mg intravenously every 3 weeks for most of its indications. It has a geometric mean (CV) elimination half-life of 22 days (CV 35%) and its geometric mean volume of distribution is 6.0 L (CV =20%), being primarily distributed in the vascular compartment. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increases dose proportionally in the dose range of 2 to 10 mg/kg. Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] at steady state than that after the first dose [252 mL/day (37%)]. The elimination of IgG based monoclonal antibodies such as pembrolizumab in humans is complex including target mediated drug disposition with non-linear and linear components and protease mediated degradation processes.[1]

Population pharmacology analyses for pembrolizumab suggested that the following factors had no clinically important effect on the its clearance (CL): age (range: 15 to 94 years), sex, race (89% White), renal impairment (eGFR $\geq$ 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin $\leq$ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden.[51,1]

This pharmacokinetic substudy is predicated on the primary hypotheses that:

a) In the older adult population of non-small cell cancer patients the time varying clearance of pembrolizumab is > 40% decrease from initial clearance when pembrolizumab is administered as monotherapy or in combination with cytotoxic chemotherapy.

b) The profile of decreasing pembrolizumab clearance over time extends beyond the defined pembrolizumab time to steady state (16 weeks).

14.2.5 Methods

Venous blood samples will be obtained in 5ml in red top tubes and allowed to clot for at least 30 minutes at room temperature, centrifuged and serum aliquots stored at -80°C until shipped. Serum pembrolizumab trough concentrations (C_0) will be obtained at baseline (pre-treatment i.e. pre infusion cycle 1, and then pre infusion on cycles 2, 3 and 6 and on one later cycle if the patient is still being treated with pembrolizumab (e.g pre-infusion on cycle 9 or cycle 12). See Section 6.2 and the CSM for additional instructions. These samples will have the time of day they were obtained documented in the case report forms in Medidata Rave. At clinic follow up visits where PK samples for pembrolizumab are being obtained drug pre-infusion details of the time and day of last dose of study drug will be documented in Medidata Rave as well.

Serum pembrolizumab concentrations will be measured using an ELISA assay based on that developed by researchers at NCI. This assay has a limit of detection of ~ 1 -2 ng/mL and is similar to the assay described by Pluim et al[52].

The trough concentrations (C_{min}) of pembrolizumab will be analyzed using the C_{min} model in NONMEM to derive the relevant PK parameters of AUC, Clearance (CL) and apparent volume of distribution (Vd_{ss}).

14.2.6 Analyses

The Alliance Statistics and Data Center (SDC) A171901 Statistician to prepare analysis datasets in conjunction with clinical/outcome data. Analyses will be conducted using the

analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

Objective 1: To determine the intrapatient (pembrolizumab time dependent clearance) and interpatient variability in clearance in older adult (≥70 years) patients with non-small cell lung cancer receiving pembrolizumab monotherapy or combined with cytotoxic chemotherapy

Objective 2: To explore the relationship between Pembrolizumab exposure (AUC) and immune related toxicities when pembrolizumab is administered as monotherapy or when combined with cytotoxic chemotherapy in non-small cell lung cancer patients ≥70 years of age.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

15.1 Geriatric Assessment Training

At each participating site, a research nurse or clinical research professional (CRP) (person who intends to administer the geriatric assessment) will receive training on administration of the geriatric assessment using the online video training module through the Compliance, Learning, and SOP Solutions (CLASS) website, hyperlink below. Per Section 4.2.2, **at least one staff member must complete this training for the site to receive site registration approval.**

Note: Site staff should only attempt to access the training if a) their site has commenced the site registration process for the study and there is an IRB/CIRB approval on file with the CTSU, *and* b) they are on a participating organization roster at the site. If these conditions are not met, users will be unable to access the training module.

[redacted]

By going to the web address above, staff will be brought to the CTEP-IAM Single Sign On page, where they must enter their CTEP-IAM account username and password. After logging in to CLASS, staff will be brought to the CLASS Dashboard. By clicking the Catalog tile, a list of available courses will be displayed. The Alliance Geriatric Assessment training is provided in the list of available courses. To gain access to the course and begin training, click the Enroll button associated with the course.

Once the first site member has completed their training, CLASS will automatically communicate with the Regulatory Support System (RSS) and the protocol-specific training requirement will be complied. Assuming all other regulatory requirements have been satisfied, the site will receive site registration approval.

Alliance Geriatric Assessment training completed in CLASS will be valid for five years. Site staff whose training has expired will receive an email to retake the training. Site staff who have taken the same Alliance Geriatric Assessment training in CLASS for a different study within five years will not need to take it again for A171901.

Any questions or concerns regarding accessing the training module in CLASS may be directed to the CLASS Help Desk at [redacted]

Any further questions or concerns regarding administering the geriatric assessment may be directed to the study chair.

16.0 REFERENCES

1. Leven C, Padelli M, Carré J-L, Bellissant É, Misery L. Immune checkpoint inhibitors in melanoma: a review of pharmacokinetics and exposure–response relationships. *Clinical pharmacokinetics*. 2019:1-13.
2. Marrone KA, Forde PM. Cancer Immunotherapy in Older Patients. *Cancer journal (Sudbury, Mass)*. Jul/Aug 2017;23(4):219-222. doi:10.1097/ppo.0000000000000268
3. Elias R, Giobbie-Hurder A, McCleary NJ, Ott P, Hodi FS, Rahma O. Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. *Journal for immunotherapy of cancer*. 2018;6(1):26.
4. Jatoi A, Hillman S, Stella P, et al. Should elderly non–small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. *Journal of clinical oncology*. 2005;23(36):9113-9119.
5. Dao D, Zemla T, Jatoi A, et al. Older-Patient-Specific Cancer Trials: A Pooled Analysis of 2,277 Patients (A151715). *The oncologist*. 2019;24(6):e284-e291.
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *New England Journal of Medicine*. 2016;375(19):1823-1833.
7. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *The lancet oncology*. 2016;17(11):1497-1508.
8. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *New England journal of medicine*. 2018;378(22):2078-2092.
9. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975:103-115.
10. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *The oncologist*. 2017;22(8):963-971.
11. Grossi F, Crinò L, Misino A, et al. Efficacy and safety of nivolumab in elderly patients (pts) with advanced squamous non small cell lung cancer (Sq-NSCLC) participating in the expanded access programme (EAP) in Italy. *Annals of Oncology*. 2016;27(suppl_6)
12. Freeman M, Weber J. Subset analysis of the safety and efficacy of nivolumab in elderly patients with metastatic melanoma. *Journal for immunotherapy of cancer*. 2015;3(S2):P133.
13. Moerbeek M, Teerenstra S. *Power analysis of trials with multilevel data*. Chapman and Hall/CRC; 2015.
14. Lachin JM. Statistical considerations in the intent-to-treat principle. *Controlled clinical trials*. 2000;21(3):167-189.
15. Tallarico M, Foster J, Seisler D, et al. Toxicities and related outcomes of elderly patients (pts)(≥ 65 years) with hematologic malignancies in the contemporary era (Alliance A151611). Am Soc Hematology; 2016.
16. Jatoi A, Foster NR, Egner JR, et al. Older versus younger patients with metastatic adenocarcinoma of the esophagus, gastroesophageal junction, and stomach: a pooled analysis of eight consecutive North Central Cancer Treatment Group (NCCTG) trials. *International journal of oncology*. 2010;36(3):601-606.
17. Schild SE, Stella PJ, Brooks BJ, et al. Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2005;103(11):2349-2354.
18. Hurria A, Lichtman SM, Gardes J, et al. Identifying vulnerable older adults with cancer: integrating geriatric assessment into oncology practice. *Journal of the American Geriatrics Society*. 2007;55(10):1604-1608.
19. Hurria A. Geriatric assessment in oncology practice. *Journal of the American Geriatrics Society*. Nov 2009;57 Suppl 2:S246-9. doi:10.1111/j.1532-5415.2009.02503.x

20. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *Journal of clinical oncology*. 2011;29(10):1290.
21. Hurria A, Mohile S, Gajra A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *Journal of Clinical Oncology*. 2016;34(20):2366.
22. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue, version 2.2015. *Journal of the National Comprehensive Cancer Network*. 2015;13(8):1012-1039.
23. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nature medicine*. 2002;8(8):793.
24. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nature medicine*. 1999;5(12):1365.
25. Yan Y, Cao S, Liu X, et al. CX3CR1 identifies PD-1 therapy-responsive CD8+ T cells that withstand chemotherapy during cancer chemoimmunotherapy. *JCI Insight*. Apr 19 2018;3(8)doi:10.1172/jci.insight.97828
26. Pereira G, Prestes J, Tibana R, Shiguemoto G, Navalta J, Perez S. Acute resistance training affects cell surface markers for apoptosis and migration in CD4+ and CD8+ lymphocytes. *Cellular immunology*. 2012;279(2):134-139.
27. Bellmunt J, De Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *New England Journal of Medicine*. 2017;376(11):1015-1026.
28. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *New England Journal of Medicine*. 2016;374(26):2542-2552.
29. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *New England Journal of Medicine*. 2015;372(26):2509-2520.
30. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *The Lancet Oncology*. 2017;18(11):1493-1501.
31. Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *The Lancet*. 2017;390(10105):1853-1862.
32. Lemery S, Keegan P, Pazdur R. First FDA approval agnostic of cancer site—when a biomarker defines the indication. *The New England journal of medicine*. 2017;377(15):1409-1412.
33. Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *The Lancet*. 2011;377(9779):1749-1759.
34. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *New England Journal of Medicine*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005
35. Shumway D, Griffith KA, Jagsi R, Gabram SG, Williams GC, Resnicow K. Psychometric properties of a brief measure of autonomy support in breast cancer patients. *BMC medical informatics and decision making*. 2015;15(1):51.
36. Immune-mediated adverse reactions have been reported in patients receiving MK-3475. Adverse events potentially related to MK-3475 may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475, administration of corticosteroids and supportive care.
37. Accessed July 27, 2019. http://www.cas.usf.edu/~jacobsen/HANDOUT.FSI&MFSI.pdf;
38. Barton DL, Liu H, Dakhil SR, et al. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *Journal of the National Cancer Institute*. 2013;105(16):1230-1238.
39. Motl RW, Bollaert RE, Sandroff BM. Validation of the Godin Leisure-Time Exercise Questionnaire classification coding system using accelerometry in multiple sclerosis. *Rehabilitation psychology*. 2018;63(1):77.

40. Jean-Pierre P, Figueroa-Moseley CD, Kohli S, Fiscella K, Palesh OG, Morrow GR. Assessment of cancer-related fatigue: implications for clinical diagnosis and treatment. *The Oncologist*. 2007;12(Supplement 1):11-21.
41. Hyland ME, Sodergren SC. Development of a new type of global quality of life scale, and comparison of performance and preference for 12 global scales. *Quality of Life Research*. 1996;5(5):469-480.
42. Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. *Clinical Pharmacology & Therapeutics*. 1983;34(2):234-239.
43. Locke DE, Decker PA, Sloan JA, et al. Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *Journal of pain and symptom management*. 2007;34(6):628-638.
44. Hocking R, Leslie R. Selection of the best subset in regression analysis. *Technometrics*. 1967;9(4):531-540.
45. Dronca RS, Liu X, Harrington SM, et al. T cell Bim levels reflect responses to anti-PD-1 cancer therapy. *JCI Insight*. May 5 2016;1(6)doi:10.1172/jci.insight.86014
46. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. Nov 27 2014;515(7528):568-71. doi:10.1038/nature13954
47. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *The New England journal of medicine*. Sep 25 2015;doi:10.1056/NEJMoa1510665
48. Liu X, Gibbons RM, Harrington SM, et al. Endogenous tumor-reactive CD8 T cells are differentiated effector cells expressing high levels of CD11a and PD-1 but are unable to control tumor growth. *Oncoimmunology*. Jun 1 2013;2(6):e23972. doi:10.4161/onci.23972
49. Gros A, Robbins PF, Yao X, et al. PD-1 identifies the patient-specific CD8+ tumor-reactive repertoire infiltrating human tumors. *The Journal of clinical investigation*. May 1 2014;124(5):2246-59. doi:10.1172/JCI73639
50. Gros A, Parkhurst MR, Tran E, et al. Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. *Nat Med*. Apr 2016;22(4):433-8. doi:10.1038/nm.4051
51. Product label for Pembrolizumab (KEYTRUDA®). Accessed November 11, 2019. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287
52. Pluim D, Ros W, van Bussel MT, Brandsma D, Beijnen JH, Schellens JH. Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid. *Journal of pharmaceutical and biomedical analysis*. 2019;164:128-134.
53. Fillenbaum GG, Smyer MA. The development, validity, and reliability of the OARS multidimensional functional assessment questionnaire. *J Gerontol*. Jul 1981;36(4):428-34.
54. Stewart AL, & Ware, J.E. Jr. *Measuring functioning and well-being: The Medical Outcomes Study approach.* . Duke University Press; 1992.
55. Loprinzi CL, Laurie JA, Wieand HS, et al. Prospective evaluation of prognostic variables from patient-completed questionnaires. North Central Cancer Treatment Group. *J Clin Oncol*. Mar 1994;12(3):601-7.
56. Therneau TM. How many stratification factors are “too many” to use in a randomization plan? *Controlled Clinical Trials*. 1993;14(2):98-108. doi:10.1016/0197-2456(93)90013-4
57. Koenig H, Parkerson GR, Jr., Meador KG. Religion index for psychiatric research. Letter. *The American journal of psychiatry*. Jun 1997;154(6):885-6.
58. Mahoney J, Drinka TJ, Abler R, et al. Screening for depression: single question versus GDS. Research Support, Non-U.S. Gov't. *Journal of the American Geriatrics Society*. Sep 1994;42(9):1006-8.
59. Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. *Evaluation of chemotherapeutic agents*. Columbia University Press; 1948:191-205.
60. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society*. Feb 1991;39(2):142-8.

APPENDIX I: COMPREHENSIVE GERIATRIC ASSESSMENT

GERIATRIC ASSESSMENT SURVEY

To be completed by Physician, Nurse, or CRA:
Responsible person name (*Physician, Nurse, or CRA*)

Assessment Period (as applicable to this study) ☐ Pre-treatment ☐☐ Cycle # ☐ End of Treatment

---

PATIENT QUESTIONNAIRE

Patient Instructions: If you are unable to complete the questionnaire, a member of your health care team will assist you. Please do not have a family member complete the questionnaire for you.

☐ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) ☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

A. BACKGROUND INFORMATION

1. What is the highest grade you finished in school? *(Mark one with an X.)*

□ 8th grade or less
□ 9-11th grade
□ High school graduate/GED
□ Associate degree/some college
□ Vocational/ technical school
□ Bachelor's degree
□ Advanced degree
□ I prefer not to answer

2. What is your marital status? *(Mark one with an X.)*

☐ Married
☐ Domestic partnership
☐ Widowed
☐ Divorced
☐ Separated
☐ Never married
☐ I prefer not to answer

3. With whom do you live? *(Mark all that apply with an X.)*

☐ Spouse / partner
☐ Girlfriend / boyfriend
☐ Children aged 18 years or younger
☐ Children aged 19 years or older
☐ Parent(s)/parent(s)-in-law
☐ Live alone
☐ Others, specify: _____
☐ Other relative, specify: _____

4. What is your current employment status? *(Mark one with an X.)*

☐ Employed 32 hours or more per week ☐ Unemployed

☐ Employed less than 32 hours per week ☐ Retired

☐ Homemaker ☐ Full-time student

☐ Disabled ☐ Part-time student

☐ On medical leave ☐ Other, specify: _____

B. DAILY ACTIVITIES*

PATIENT INSTRUCTIONS: Indicate your response by marking an X in one box per question.

1. Can you use the telephone…

   ☐ without help, including looking up and dialing;

   ☐ with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the phone number or dialing); or

   ☐ are you completely unable to use the telephone?

2. Can you get to places out of walking distance…

   ☐ without help (can travel alone on buses, taxis, or drive your own car);

   ☐ with some help (need someone to help you or go with you when traveling); or

   ☐ are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes (assuming you have transportation) …

   ☐ without help (taking care of all shopping needs yourself, assuming you have transportation);

   ☐ with some help (need someone to go with you on all shopping trips); or

   ☐ are you completely unable to do any shopping?

4. Can you prepare your own meals…

   ☐ without help (plan and cook full meals yourself);

   ☐ with some help (can prepare some things but unable to cook full meals yourself); or

   ☐ are you completely unable to prepare any meals?

5. Can you do your housework…

   ☐ without help (can clean floors, etc);

   ☐ with some help (can do light housework but need help with heavy work); or

   ☐ are you completely unable to do any housework?

6. Can you take your own medicines…

   ☐ without help (in the right doses at the right time);

   ☐ with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or

   ☐ are you completely unable to take your medicines?

7. Can you handle your own money…

   ☐ without help (write checks, pay bills, etc.);

   ☐ with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or

   ☐ are you completely unable to handle money?

* OARS IADL[53]

C. PHYSICAL ACTIVITIES*

1. The following items are activities you might do during a typical day. Does your health limit you in these activities? **(*Mark an X in the box on each line that best reflects your situation.*)**

Activities	Limited a lot	Limited a little	Not limited at all
a. Vigorous activities such as: running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities such as: moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several blocks	☐	☐	☐
i. Walking one block	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

* MOS, Physical Functioning Scale[54]

D. CURRENT HEALTH RATING*

Which one of the following phrases best describes you at this time? *(Mark one with an X.)*

☐ Normal, no complaints, no symptoms of disease

☐ Able to carry on normal activity, minor symptoms of disease

☐ Normal activity with effort, some symptoms of disease

☐ Care for self, unable to carry on normal activity or do active work

☐ Require occasional assistance but able to care for most of personal needs

☐ Require considerable assistance for personal care

☐ Disabled, require special care and assistance

☐ Severely disabled, require continuous nursing care

* Patient KPS[55]

E. FALLS

How many times have you fallen in the last 6 months? ☐☐☐

F. YOUR HEALTH

1. Your General Health*

Patient Instructions: Do you have any of the following illnesses at the present time, and if so, how much does it interfere with your activities: **Not at all, Somewhat or A Great Deal?** *(Mark an X in the box that best reflects your answer.)*

		If you have this illness:				
		How much does it interfere with your activities?				
Illness	**No**	**Yes**		**Not at all**	**A little**	**A great deal**
a. Other cancers or leukemia	☐	☐	→	☐	☐	☐
b. Arthritis or rheumatism	☐	☐	→	☐	☐	☐

Illness	No	Yes		If you have this illness: How much does it interfere with your activities? Not at all	A little	A great deal
c. Glaucoma	☐	☐	→	☐	☐	☐
d. Emphysema or chronic bronchitis	☐	☐	→	☐	☐	☐
e. High blood pressure	☐	☐	→	☐	☐	☐
f. Heart disease	☐	☐	→	☐	☐	☐
g. Circulation trouble in arms or legs	☐	☐	→	☐	☐	☐
h. Diabetes	☐	☐	→	☐	☐	☐
i. Stomach or intestinal disorders	☐	☐	→	☐	☐	☐
j. Osteoporosis	☐	☐	→	☐	☐	☐
k. Liver disease	☐	☐	→	☐	☐	☐
l. Kidney disease	☐	☐	→	☐	☐	☐
m. Stroke	☐	☐	→	☐	☐	☐
n. Depression	☐	☐	→	☐	☐	☐

* OARS IADL[53]

2. How is your eyesight (with glasses or contacts)? *(Mark one with an X.)*

☐ Excellent

☐ Good

☐ Fair

☐ Poor

☐ Totally blind

3. How is your hearing (with a hearing aid, if needed)? *(Mark one with an X.)*

☐ Excellent

☐ Good

☐ Fair

☐ Poor

☐ Totally deaf

4. Do you have any other physical problems or illnesses (other than listed in questions 1-4) at the present time that seriously affect your health?

☐ No

☐ Yes, specify: ☐

If yes, how much does this interfere with your activities? *(Mark one with an X.)*

☐ Not at all ☐ Somewhat ☐ A great deal

* OARS IADL[53]

G. NUTRITIONAL STATUS

1. Have you lost weight involuntarily over the past 6 months?

☐ No

☐ Yes

If yes, how much?

☐☐☐ pounds

2. What is your weight now?

☐☐☐ pounds

3. What was your weight 6 months ago?

☐☐☐ pounds

H. HEALTH QUESTIONNAIRE*

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please mark an "X" in the box on each line that best reflects your situation.

How much of the time during the past month:	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
1. has your daily life been full of things that were interesting to you?	☐	☐	☐	☐	☐	☐
2. did you feel depressed?	☐	☐	☐	☐	☐	☐
3. have you felt loved and wanted?	☐	☐	☐	☐	☐	☐
4. have you been a very nervous person?	☐	☐	☐	☐	☐	☐
5. have you been in firm control of your behavior, thoughts, emotions, feelings?	☐	☐	☐	☐	☐	☐
6. have you felt tense or high-strung?	☐	☐	☐	☐	☐	☐
7. have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
8. have you felt emotionally stable?	☐	☐	☐	☐	☐	☐
9. have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
10. have you felt restless, fidgety, or impatient?	☐	☐	☐	☐	☐	☐
11. have you been moody, or brooded about things?	☐	☐	☐	☐	☐	☐

12. have you felt cheerful, light-hearted?	☐	☐	☐	☐	☐	☐
13. have you been in low or very low spirits?	☐	☐	☐	☐	☐	☐
14. were you a happy person?	☐	☐	☐	☐	☐	☐
15. did you feel you had nothing to look forward to?	☐	☐	☐	☐	☐	☐
16. have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
17. have you been anxious or worried?	☐	☐	☐	☐	☐	☐

* MHI-17[54] - Stewart, A.L. and Ware, J.E., 1992

I. SOCIAL ACTIVITIES*

1. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? *(Mark one with an X.)*

   ☐ All of the time
   ☐ Most of the time
   ☐ Some of the time
   ☐ A little of the time
   ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition? *(Mark one with an X.)*

   ☐ Much less socially active than before
   ☐ Somewhat less socially active than before
   ☐ About as socially active as before
   ☐ Somewhat more socially active as before
   ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems? *(Mark one with an X.)*

   ☐ Much more limited than others
   ☐ Somewhat more limited than others
   ☐ About the same as others
   ☐ Somewhat less limited than others
   ☐ Much less limited than others

* MOS, Social Activities[54]

J. SOCIAL SUPPORT*

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (*Mark an X in the box on each line that best reflects your situation.*)

	None of the Time	A Little of the Time	Some of the Time	Most of the Time	All of the Time
1. Someone to help you if you were confined to bed.	☐	☐	☐	☐	☐
2. Someone you can count on to listen to you when you need to talk.	☐	☐	☐	☐	☐
3. Someone to give you good advice about a crisis.	☐	☐	☐	☐	☐
4. Someone to take you to the doctor if needed.	☐	☐	☐	☐	☐
5. Someone to give you information to help you understand a situation.	☐	☐	☐	☐	☐
6. Someone to confide in or talk to about yourself or your problem.	☐	☐	☐	☐	☐
7. Someone to prepare your meals if you were unable to do it yourself.	☐	☐	☐	☐	☐
8. Someone whose advice you really want.	☐	☐	☐	☐	☐
9. Someone to help you with daily chores if you were sick.	☐	☐	☐	☐	☐
10. Someone to share your most private worries and fears with.	☐	☐	☐	☐	☐
11. Someone to turn to for suggestions about how to deal with a personal problem.	☐	☐	☐	☐	☐
12. Someone who understands your problems.	☐	☐	☐	☐	☐

* MOS Social Support Survey [56]

K. SPIRITUALITY/RELIGION*

Directions: Please answer the following questions about your religious beliefs and/or involvement. (Please mark an "X" in the box on each line that best reflects your situation.)

1. How often do you attend church, synagogue, or other religious meetings? *(Mark one with an X.)*

☐ More than once per week
☐ Once a week
☐ A few times a month
☐ A few times a year
☐ Once a year or less
☐ Never

2. How often do you spend time in private religious activities, such as prayer, meditation, or Bible study? *(Mark one with an X.)*

☐ More than once a day
☐ Daily
☐ Two or more times per week
☐ Once a week
☐ A few times a month
☐ Rarely or never

The following section contains 3 statements about religious belief or experience. Please mark the extent to which each statement is true or not true for you.

3. In my life, I experience the presence of the Divine (i.e., God). *(Mark one with an X.)*

☐ Definitely true of me
☐ Tends to be true
☐ Unsure
☐ Tends *not* to be true
☐ Definitely *not* true

4. My religious beliefs are what really lie behind my whole approach to life. *(Mark one with an X.)*

☐ Definitely true of me
☐ Tends to be true
☐ Unsure
☐ Tends *not* to be true
☐ Definitely *not* true

5. I tried hard to carry my religion over into all other dealings in my life. *(Mark one with an X.)*

☐ Definitely true of me

☐ Tends to be true

☐ Unsure

☐ Tends *not* to be true

☐ Definitely *not* true

*DUREL: Duke University ReligionIndex[57]– Koenig et al., 1997

L. YOUR FEELINGS*

1. Do you often feel sad or depressed? *(Mark one with an X.)*

☐ No ☐ Yes

2. How would you describe your level of anxiety, on average? Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

0	1	2	3	4	5	6	7	8	9	10
No anxiety										Anxiety as bad as It can be

*Mahoney et al., 1994; LASA[58]

M. QUESTIONS CONCERNING THE QUESTIONNAIRE

1. Were there any questions difficult to understand? ☐ No ☐ Yes

If Yes, which questions were they?

2. Was the time it took to answer all the questions too long, just right or too short?

☐ Too short → How long would you have liked the questionnaire to be? ☐☐ minutes

☐ Just right

☐ Too long → How long would you have liked the questionnaire to be? ☐☐ minutes

Which items would you remove?

3. Did you find any of the questions upsetting? ☐ No ☐ Yes

If Yes, which questions were they?

Could you tell me why they were upsetting?

4. Do you think the questionnaire left out any questions that were important to ask?

Thank you for your participation.

Geriatric Assessment: Healthcare Professional Questionnaire

To be completed by Physician, Nurse, or CRA

I. This form completed by: ***(Mark all that apply with an X.)*** Assessment Period (as applicable to this study)

☐ Physician ☐ Nurse ☐ CRA ☐ Pre-treatment ☐☐ Cycle # ☐ End of Treatment

☐ **Mark box with an "X", if form was not completed at specified timepoint and specify reason:**

(Mark one with an X.) ☐ Patient refused ☐ Patient withdrew consent ☐ Not done

☐ Other, specify _____

(For assessment date, record approximate date form was to be completed.)

II. FUNCTIONAL STATUS

A. KPS (Healthcare professional rated*)
Please rate your assessment of patient's Karnofsky Performance Status as of date this form is completed. *(Scale is listed below.)*

☐☐☐ %

%	CRITERIA
100	Normal: no complaints; no evidence of disease.
90	Able to carry on normal activity; only minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very sick; hospitalization necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

* Physician KPS[59]

B. Timed "Up and Go"*

INSTRUCTIONS: The timed "Up and Go" measures, in seconds, the time it takes for an individual to stand up from a standard arm chair (approximate seat height of 46 cm [approximately 1.5 ft]), walk a distance of 3 meters (approximately 10 feet), turn, walk back to the chair, and sit down again. The subject wears his/her regular footwear and uses their customary walking aid (none, cane, walker, etc.) No physical assistance is given. The subject starts with his back against the chair, his arm resting on the chair's arm, and his walking aid in hand. He is instructed that on the word "go", he is to get up and walk at a comfortable and safe pace to a line on the floor 3 meters (approximately 10 feet) away, turn, and return to the chair and sit down again. The subject walks through the test once before being timed in order to become familiar with the test. Either a wrist watch with a second hand or a stop-watch can be used to time the performance.

Time to perform "Up and Go" ☐☐.☐ seconds

* Timed "Up and Go"[60]

III. COGNITION ***This section is only completed Pretreatment and at the end of treatment***

6-ITEM ORIENTATION-MEMORY-CONCENTRATION TEST**					
	Patient's Response	**Maximum errors**	**Score**	**Weight**	**Final score**
1. What <u>year</u> is it now? [without looking at a calendar]	☐☐☐☐	1	☐☐ x	4 =	☐☐
2. What <u>month</u> is it now? [without looking at a calendar]	☐☐	1	☐☐ x	3 =	☐☐
Memory Phrase: Repeat this phrase after me: 'John Brown, 42 Market Street, Chicago'					
3. About what <u>time</u> is it? [within 1 hour – without looking at your watch]	☐☐:☐☐	1	☐☐ x	3 =	☐☐
4. <u>Count</u> backwards 20 to 1.		2	☐☐ x	2 =	☐☐
5. Say the months in reverse order.		2	☐☐ x	2 =	☐☐
6. Repeat the Memory Phrase.		5	☐☐ x	2 =	☐☐
				TOTAL SCORE:	☐☐

Scoring: For items 1 to 3, the response is either correct (score 0) or incorrect (score 1). For items 4 to 6, add one point for each error (item 4 and 5 maximum error is 2; for item 6, maximum error is 5); total all scores in "Final Score" column. Data from participants found to have gross cognitive impairment as determined by the Orientation-Memory-Concentration Score ≥11 will be excluded from the analysis. Maximum score = 28.

** OMC – Katzman, R., et al., 1983; Kawas, C., et al., 1995

IV. SCORING ***This section is only applicable if OMC-Test is completed Pretreatment and Post treatment***

Did the patient score ≥11 on the 6-Item Orientation-Memory-Concentration Test?

☐ No

☐ Yes (**If yes, notify the patient's treating physician.)**

This question is only applicable to question #1 in "Section K. Your Feelings" from the Patient Questionnaire.

1. How did the patient answer the question "Do you often feel sad or depressed?" in the Patient Questionnaire *(Section K)*?

☐ No

☐ Yes **(If yes, notify the patient's treating physician.)**

V. NUTRITION

What is the patient's height? (*from patient's chart*) ☐☐☐ cm

What is the patient's current weight? (*from patient's chart*) ☐☐☐ kg

What was the patient's weight approximately 6 months ago? *(from patient's chart or patients self report)* ☐☐☐ kg

Calculated Body Mass Index: ☐☐.☐

Percent Unintentional Weight Loss: ☐☐.☐%

VI. QUESTIONS REGARDING THE QUESTIONNAIRES

A. Were any of the questionnaires in the "Geriatric Assessment – Healthcare Professional Questionnaire" difficult for you to administer?

☐Yes ☐No

If no, please proceed to the next question.

If yes, please indicate which questionnaire was difficult to administer? *(Mark all that apply with an X.)*

- ☐ KPS Healthcare Professional Rated (page 1)
- ☐ Timed Up and Go (page 2)
- ☐ 6-Item Orientation-Memory-Concentration Test (page 2)
- ☐ Other: Please specify _____

B. Were any of the questionnaires in the "Geriatric Assessment – Patient Questionnaire" difficult for the patient to complete?

☐Yes ☐No

B. If no, please proceed to the next question. If yes, please indicate which questionnaire(s) was difficult for the patient to complete? *(Mark all that apply with an X.)*

- ☐ Background Information (page 1)
- ☐ Daily Activities (page 2-3)
- ☐ Physical Activities (page 3)
- ☐ Current Health Rating (page 4)
- ☐ Falls (page 4)
- ☐ Your Health (page 4-5)
- ☐ Nutritional Status (page 7-8)
- ☐ Health Questionnaire (page 9)
- ☐ Social Activities (page 10)
- ☐ Social Support (page 11)
- ☐ Spirituality or religion (page 12)
- ☐ Your Feelings (page 13)

C. Was the patient able to complete "Geriatric Assessment – Patient Questionnaire" on his/her own?

☐Yes ☐No

If no, why? *(Mark all that apply with an X.)*

- ☐ Not literate (does not read or write)
- ☐ Visual problem
- ☐ Fatigue
- ☐ Questions too difficult (above the patient's reading ability)

☐ Other: specify_____

D. Length of time to complete both the Patient and Healthcare Professional Questionnaires

Length of time to complete healthcare professional questionnaire ☐☐☐ minutes

Length of time to complete patient questionnaire ☐☐☐ minutes

Total length of time to complete both questionnaires ☐☐☐ minutes

Completed by: _____ Date form completed: ☐☐ / ☐☐ / ☐☐☐☐

(Last name, First name) *M M D D Y Y Y Y*

APPENDIX II: MFSI-SF

MFSI-SF

Below is a list of statements that describe how people sometimes feel. Please read each item carefully, then circle the one number next to each item which best describes **how true each statement has been for you in the past 7 days.**

		Not at all	A little	Moderately	Quite a bit	Extremely
1.	I have trouble remembering things	0	1	2	3	4
2.	My muscles ache	0	1	2	3	4
3.	I feel upset	0	1	2	3	4
4.	My legs feel weak	0	1	2	3	4
5.	I feel cheerful	0	1	2	3	4
6.	My head feels heavy	0	1	2	3	4
7.	I feel lively	0	1	2	3	4
8.	I feel nervous	0	1	2	3	4
9.	I feel relaxed	0	1	2	3	4
10.	I feel pooped	0	1	2	3	4
11.	I am confused	0	1	2	3	4
12.	I am worn out	0	1	2	3	4
13.	I feel sad	0	1	2	3	4
14.	I feel fatigued	0	1	2	3	4
15.	I have trouble paying attention	0	1	2	3	4
16.	My arms feel weak	0	1	2	3	4
17.	I feel sluggish	0	1	2	3	4
18.	I feel run down	0	1	2	3	4
19.	I ache all over	0	1	2	3	4
20.	I am unable to concentrate	0	1	2	3	4
21.	I feel depressed	0	1	2	3	4
22.	I feel refreshed	0	1	2	3	4
23.	I feel tense	0	1	2	3	4
24.	I feel energetic	0	1	2	3	4
25.	I make more mistakes than usual	0	1	2	3	4
26.	My body feels heavy all over	0	1	2	3	4
27.	I am forgetful	0	1	2	3	4
28.	I feel tired	0	1	2	3	4
29.	I feel calm	0	1	2	3	4
30.	I am distressed	0	1	2	3	4

APPENDIX III: GODIN LEISURE-TIME EXERCISE QUESTIONNAIRE

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. |_|	2. |_|	3. |_|

APPENDIX IV: LINEAR ANALOGUE SELF-ASSESSMENT (LASA)

LINEAR ANALOGUE SELF ASSESSMENT

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

7. the frequency of your pain?

0	1	2	3	4	5	6	7	8	9	10
No pain										Constant pain

8. the severity of your pain, on the average?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

9. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Constant tiredness

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10
No support										Highest level of support

11. your financial concerns?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

12. your legal concerns (will, advanced directives, etc.)?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

13. Did you experience trouble sleeping?

0	1	2	3	4	5	6	7	8	9	10
Not at all									as bad as it can be	

APPENDIX V ELECTRONIC PATIENT-REPORTED OUTCOMES (EPRO) INSTRUCTIONS

1.0 Introduction

Electronic collection of patient-reported outcomes is preferred but not mandatory. Patients will need to use their own device (IOS or Android phone or tablet), **or** a device provided by their institution. Short term data will only appear on the patient's/site device until responses are completed. The patient data will import directly into the database once the patient clicks the submit button and will no longer be on the device.

Sites can use a site-specific tablet for different study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users.

Site staff access

Site users of ePRO and the Patient Cloud require the same access as those using Rave. Access to the trial in the Patient Cloud is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access the Patient Cloud via iMedidata, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in the Patient Cloud until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance).

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or by contacting the [redacted]

2.0 Security

All data are encrypted on the device (128 bit on file +https transfer) and the app requires a user to have a username and password. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "submit," the data is securely transferred over https between the device and internal relay. No identifying information is stored in iMedidata (only email address is stored).

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and sponsors in the Patient Cloud Relay.

The ePRO application is Part 11 compliant and acts as a gateway between device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

3.0 CRP Training for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud for CRAs.

4.0 Checklist for activities prior to consenting a patient

- Site staff must have already completed required eLearning for the Patient Cloud application. See last bullet with hyperlink to training video library. See Section 1.0 of this Appendix for instructions on site staff access.
- Accept study invitation at [redacted]

Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

- Verify the IOS or Android operating system is using the most current version
- Verify Patient Cloud app is using the most current version
- Refer to [redacted] to review Quick reference guides

5.0 Instructions for ePRO patient registration

Please visit the Medidata Learning Tool for additional screen shots and video tutorials on how to register participants to the study.

i. The patient registration process starts in iMedidata. Begin by clicking on the Patient Cloud Registration link for this study.

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now the first patient can be registered. (Please note that the patient must have already been registered in OPEN to generate a patient ID). Select subject ID (patient ID) and select a Country / Language from the drop down, (these are the only required data fields). The patient initials are optional, but may help in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The patient added will appear at the top of the table and will include the date the patient was added, the subject ID, initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which determines if the patient has registered. When the patient has registered the status will change from invited to registered.

6.0 Patient Users

To use the Patient Cloud app, patients will need to use their own device (IOS, Android phone or tablet) (for those who choose to use their own device). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Patient compliance: The patient data imports directly from her/his device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

Patient Instructions for Accessing the Patient Cloud App using their personal device

Downloading the Patient Cloud App:

Please ensure that the patient downloads the following app from the app store, and not Patient cloud ePRO (which is the legacy app).

If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. **If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section**.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e- mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the App Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app.
2. Tap the Play Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Registering on the App:

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud app.

Note: You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL [redacted] on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App after registration:

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap Forgot Password, and follow the instructions provided.

Setting a PIN Code:

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap Forgot PIN and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password:

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms:

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

APPENDIX VI EPRO INSTRUCTION FLOW CHART FOR PATIENTS

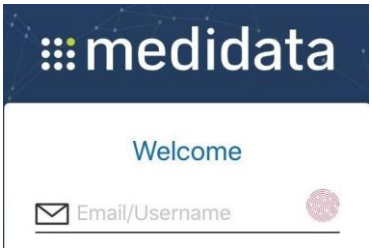
Download the Patient Cloud app

Create a username and password for the Patient Cloud app by selecting the 'Have an Activation Code?' option on the login screen. Use the activation code from your clinic.

Log in to the Patient Cloud app

See your forms on the main screen

Complete, review, and submit your forms



Tip: Your username must be in email format (for example, jodiesmith20@email.com).

Tip: When a form is due, you will see the alarm clock with the date and time the form will close.

For help with the Patient Cloud app, please ask your study team!

APPENDIX VII PATIENT INFORMATION SHEETS

PATIENT INFORMATION SHEET
BASELINE

Patient Completed Quality of Life Booklet (Baseline/Week 1)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed before you start study treatment.

2. The booklet contains 4 set of questions:
   a. **Comprehensive Geriatric Assessment questionnaire**
   b. **Multidimensional Fatigue Symptom Inventory Short form (MFSI-SF)**
   c. **Godin Leisure Time Exercise Questionnaire**
   d. **Linear Analogue Self-Assessment**

3. Directions on how to complete this set of questions are written on the top of the page.

4. Please return your booklet, in the envelope provided or in person when you are finished.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (Weeks 2-9) and End of treatment

---

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed once every 3 weeks for the first 9 weeks after the study begins, and at the end of study treatment. If you have a clinic visit at this time, please complete it on that day, before you receive any treatment.

2. The booklet contains 3 set of questions:
   a. **Multidimensional Fatigue Symptom Inventory Short form (MFSI-SF)**
   b. **Godin Leisure Time Exercise Questionnaire**
   c. **Linear Analogue Self-Assessment**

3. Directions on how to complete this set of questions are written on the top of the page.

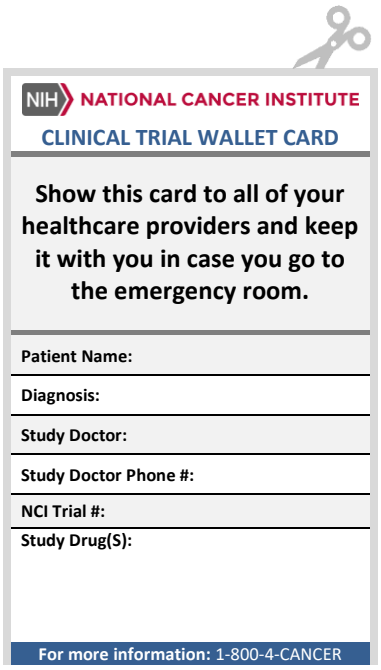
4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions. A nurse/research coordinator will also call you at the end of every week and they can answer questions you might have.

5. It is very important that you return the booklet to us, whether you finish the study or not.

6. When the booklet is complete, return it in the provided envelope.

Thank you for taking the time to help us.

APPENDIX VIII PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER

APPENDIX IX PATIENT THANK YOU LETTERS

Guidance for Disseminating
Thank You Letters to Trial Participants

Trial Participant Thank You Letter

We ask that the physician use the template to prepare a letter thanking the participant for enrolling in this Alliance trial. The template is intended as a guide and can be downloaded from the study page on the Alliance website at [redacted] As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by Alliance and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through.

We appreciate your help in this effort.

Sample Template

[PARTICIPANT NAME] [DATE] [PARTICIPANT ADDRESS]

Dear [PARTICIPANT SALUTATION],

Thank you for agreeing to take part in this important research study. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

There are many reasons why individuals choose to participate in a clinical trial. Sometimes it is because they want access to a specific medication or because they want to do whatever they can to help someone else with cancer. Whatever your reason for participating, you are making a contribution towards finding better treatments and ultimately eliminating this disease for future patients.

You will receive high quality care while participating in this clinical trial. My research staff and I will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other participants.

On behalf of [INSTITUTION] and the Alliance for Clinical Trials in Oncology, we thank you again for your participation in this clinical trial and look forward to partnering with you.

Sincerely, [PHYSICIAN NAME]