Title: A Phase 1b Study to Evaluate TAK-659 in Combination With Nivolumab in Patients With Advanced Solid Tumors

NCT Number: NCT02834247

Protocol Approve Date: 27 April 2017

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL AMENDMENT

A Phase 1b Study to Evaluate TAK-659 in Combination With Nivolumab in Patients With Advanced Solid Tumors

TAK-659 in Combination With Nivolumab in Advanced Solid Tumors

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
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Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "sponsor", or "Takeda"

Study Number: C34003

IND Number: 130,508 **EudraCT Number:** 2016-000853-10

Compound: TAK-659

Date: 27 April 2017 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Amendment Type	Region
01 April 2016	Initial Protocol	Not applicable	Global
03 May 2016	01	Not applicable	Global
27 April 2017	02	Not applicable	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 11.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	Europe
Serious adverse event and pregnancy reporting	See Section 11.2	See Section 11.2
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the IB, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 11.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02. The primary purposes of this amendment are to add the option of a new cohort to evaluate a fixed dose of nivolumab, to remove time-bound references to the nivolumab United States Prescribing Information (USPI), to clarify how a study cycle is defined in the event of study drug interruption due to an adverse event (AE), to update the disease assessment criteria, to provide information on treatment after disease progression, and to update the guidelines for TAK-659 and nivolumab dose modifications.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only. For specific descriptions of text changes and where those changes are located, see Appendix J.

Changes in Amendment 02

1. Update approved indications for nivolumab.
2. Update information regarding nonclinical studies of TAK-659 in combination with anti-programmed cell death protein 1 therapy.
3. Update summaries of TAK-659 clinical experience and risks and benefits.
4. Add an option to conduct a nivolumab fixed-dose evaluation cohort.
5. Identify how a study cycle is defined and the requirement for the start of a new cycle in the event of a study drug interruption, and provide a source of further guidance on calculating cycle length.
6. Clarify that the maximum tolerated dose/maximally administered dose/recommended phase 2 dose will be determined using weight-based nivolumab dosing.
7. Clarify the use of blood samples for biomarker analysis.
8. Update the estimated number of patients in the study.
9. Update the inclusion criterion regarding minimum creatinine clearance laboratory value for entry into the study.
10. Update the inclusion criterion regarding minimum hemoglobin laboratory value for entry into the study.
11. Update the inclusion criteria regarding permitted lipase and amylase concentrations values for entry into the study.
12. Update the inclusion criterion regarding permissible blood pressure in hypertensives patients for entry into the study.
13. Clarify that patients in the non-small cell lung cancer cohort with epidermal growth factor receptor or anaplastic lymphoma kinase genomic alternation should have had progressive disease (PD) on United States Food and Drug Administration–approved therapy.

14. Update exclusion criteria regarding patients with history of autoimmune disease, type I diabetes mellitus, childhood asthma, and thyroid disorders.
15. Update the restrictions on corticosteroid-based medication.
16. Clarify exclusion criterion regarding previous anticancer treatments.
17. Update exclusion criterion regarding patients with another malignancy.
18. Update the restrictions on the use of non-oncology vaccine therapies.
19. Update language regarding use of P-glycoprotein and/or strong cytochrome P450 3A inhibitors or inducers and clarify exceptions to their use for treatment of an AE requiring a TAK-659 hold.
20. Update the language for dose-expansion patients regarding activated partial thromboplastin time or plasma thromboplastin.
21. Provide additional instruction on how to address missed doses of study drug.
22. Update dose-limiting toxicity evaluation period.
23. Update the guidelines for TAK-659 and nivolumab dose modifications for hematologic and nonhematologic toxicity.
24. Clarify use of concomitant medications and procedures.
25. Add information on the management of diarrhea, edema, rash, hypophosphatemia, and enzyme elevations.
26. Clarify that smoking history should be collected with medical history.
27. Include pulse oximetry in the collection of vital signs.
28. Update list of laboratory tests to include creatine phosphokinase and cardiac troponin I and troponin T.
29. Update pregnancy testing to include both urine and serum pregnancy testing.
30. Update the disease assessment criteria regarding verification of response and verification of progression.
31. Update how pseudo disease progression is defined.
32. Clarify that tumor assessments should be collected for patients who have interruption(s) in study drug administration.
33. Indicate that additional exploratory independent review of study imaging data may occur if deemed necessary.
34. Add section about treatment beyond disease progression.
35. Clarify timing of tumor biopsy sampling.
36. Specify that cytokine/chemokine measurements will be taken from serum.

37. Clarify study drug dosing instructions on days when predose pharmacokinetic (PK) samples are scheduled.
38. Add to the PK measurements section a rationale for conducting PK sampling at any time during the clinic visit on Cycle 1 Day 8 during dose expansion.
39. Update reasons for completion of treatment.
40. Indicate that the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, not modified RECIST version 1.1, will be used to measure PD.
41. Update procedures for monitoring AEs and the period of observation.
42. Clarify that PK parameters will be summarized using descriptive statistics.
43. Indicate that the relationship between PK and pharmacodynamics changes may be evaluated.
44. Update language regarding informed consent forms.
45. Clarify language regarding study-site monitoring visits.
46. Remove time-bound references to the nivolumab USPI.
47. Update the Schedule of Events to include additional tests when nivolumab is dosed.
48. Update timing of vital sign measurements for Cycle 1 Day 1.
49. Clarify language regarding disease response assessments to include all relevant sites of disease.
50. Clarify language regarding purpose of pharmacodynamic assessments.
51. Update responsibilities of investigator.
52. Add RECIST version 1.1 as appendix.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** TAK-659	
Title of Protocol: A Phase 1b Study to Evaluate TAK-659 in Combination With Nivolumab in Patients With Advanced Solid Tumors	**IND No.:** 130,508	**EudraCT No.:** Not applicable
Study Number: C34003	**Phase:** 1b	

Study Design:

This is an open-label, multicenter, phase 1b, dose escalation study of TAK-659 in combination with nivolumab in patients with advanced solid tumors. The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2). In the dose escalation phase, the patient population will consist of all-comer patients with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: 1) patients with metastatic triple-negative breast cancer (TNBC) who have had ≥1 prior line of chemotherapy; 2) patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has progressed on or after a prior platinum-based chemotherapy; and 3) patients with locally advanced or metastatic head and neck squamous cell carcinoma (HNSCC) that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

It is estimated that 126 patients will be enrolled in the study: approximately 9 to 12 patients among the dose escalation cohorts evaluating weight-based dosing of nivolumab, 3 to 6 patients in a possible nivolumab fixed-dose evaluation cohort (if it is opened), and approximately 36 patients (30 evaluable patients+15% drop off) in each of the 3 dose expansion cohorts.

Once enrolled in the study, patients will be administered TAK-659 orally once daily (QD) during each 28-day treatment cycle. Patients receiving the combination therapy will also receive nivolumab once every 2 weeks intravenously (IV) over 60 minutes on Day 1 and Day 15 of each 28-day treatment cycle (for patients who receive 2 weeks of TAK-659 monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15). On days when both TAK-659 and nivolumab will be administered, the TAK-659 dose will be administered first followed by the nivolumab infusion (infusion to begin within 30 minutes after the TAK-659 dose). Patients, including those who achieve a complete response, may receive study treatment until they experience disease progression (PD) or unacceptable toxicities.

While the maximum tolerated dose (MTD)/maximally administered dose (MAD)/recommendation phase 2 dose (RP2D) of TAK-659 are being determined, the starting dose of nivolumab will be 3 mg/kg IV. The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may also be evaluated, if appropriate. Dose escalation will continue until the MTD is reached, or until 100 mg QD of TAK-659 (the MAD) is determined to be safe and tolerable, or until a RP2D, if different from the MTD or MAD, has been identified on the basis of the safety, tolerability, and preliminary pharmacokinetic (PK) and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 patients will be evaluated at the RP2D (the MTD, MAD, or a lower dose as determined) before making a decision to advance to further dose expansion.

After the RP2D of TAK-659 has been identified, on the basis of evaluation of the combination with a weight-based dose of nivolumab (3 mg/kg), this RP2D of TAK-659 may be evaluated in combination with a fixed dose of 240 mg IV nivolumab following discussion between the investigator and sponsor. For single-agent nivolumab, the fixed dose is expected to have equivalent exposure, safety, and efficacy as the weight-based (3 mg/kg) dose. If the nivolumab fixed dose is evaluated, 3 patients will be initially enrolled into the cohort. Following evaluation of the safety, efficacy, and any available PK data, along with discussions between the investigator and sponsor, 3 additional patients may be enrolled into the cohort for a total of 3 to 6 patients. Following evaluation of this fixed-dose cohort (if it is run), the dose of nivolumab may be switched from the 3 mg/kg weight-based dose to a fixed dose of 240 mg for all patients ongoing in the study at the time of the switch and those to be enrolled after the switch. This decision will be made on

the basis of an assessment of the change in clinical practice in different regions and upon discussion and agreement between the investigators and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all patients in the dose expansion phase will be 3 mg/kg, unless the direct conversion to a fixed dose of nivolumab is justified by other available data.

After the combination TAK-659 RP2D (the MTD, MAD, or a lower dose) is determined, expansion cohorts are planned in patients with TNBC, NSCLC, and HNSCC. Thirty response-evaluable patients will be enrolled in each expansion cohort, including approximately 10 patients in each cohort who are able to provide evaluable serial tumor biopsies. Additionally, each expansion cohort will include 24 response-evaluable patients who are naïve to anti-programmed cell death protein 1 (PD-1)/anti-programmed cell death 1 ligand 1 (PD-L1) therapy and 6 response-evaluable patients who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable patients in each expansion cohort will first receive single-agent treatment with TAK-659 for 2 weeks at the RP2D previously determined in combination with nivolumab. Following the 2-week, single-agent treatment, TAK-659 treatment will continue (at the same dose) in combination with nivolumab during Week 3 and beyond.

The subset of expansion patients who will be treated with single-agent TAK-659 at its combination RP2D during Weeks 1 and 2 should have accessible tumors for core or excisional biopsy and provide permission for the biopsies to be taken. These patients will undergo mandatory biopsies before single-agent TAK-659 treatment begins, at the end of the 2-week treatment window, and after 6 weeks of treatment with TAK-659 in combination with nivolumab; an optional biopsy will also be taken at the time of PD. The biopsies will be used for biomarker analysis evaluating the effect of TAK-659 on tumor cells and on immune/stromal cells supporting tumor tissue.

The remaining 20 response-evaluable patients in each expansion cohort will receive TAK-659 at its RP2D in combination with nivolumab, starting from Week 1, Day 1.

During dose escalation, serial blood samples for assessment of TAK-659 plasma PK will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15, the days on which both TAK-659 and nivolumab are administered. Although the risk of drug-drug interaction between TAK-659 and nivolumab is predicted to be low, TAK-659 plasma PK following combination administration in the dose escalation will be compared with historical plasma PK following single-agent administration to confirm no clinically meaningful differences in TAK-659 PK between the single-agent and combination settings. For purposes of population PK analysis, sparse collection of PK samples will occur in the expansion cohorts during both the single-agent and combination administration periods.

All patients in the expansion cohorts will be treated until PD, occurrence of unacceptable toxicities, withdrawal due to other reasons, or the study is terminated by the sponsor. The objectives of these expansion cohorts are to evaluate efficacy of TAK-659 in combination with nivolumab as measured by overall response rate (ORR) and to determine the safety and tolerability of TAK-659 in combination with nivolumab.

Primary Objectives:

- To determine the MTD/RP2D of TAK-659 when administered in combination with nivolumab (dose escalation).
- To determine the efficacy of TAK-659 plus nivolumab as measured by ORR (dose expansion).

Secondary Objectives:

- To determine the safety and tolerability of TAK-659 when administered in combination with nivolumab.
- To evaluate other efficacy measures such as disease control rate (response plus stable disease), duration of response (DOR), rate of PD at 6 months, progression-free survival (PFS), and overall survival (OS).
- To characterize the plasma PK of TAK-659 when administered in combination with nivolumab.

Patient Population:

Dose escalation: Patients aged 18 years or older with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment.

Dose expansion: Patients aged 18 years or older with:

- Metastatic TNBC with ≥1 prior line of chemotherapy.

- Locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy.
- Locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

Number of Patients: It is estimated that 126 patients will be enrolled in the study: approximately 9 to 12 patients among the dose escalation cohorts evaluating weight-based dosing of nivolumab, 3 to 6 patients in the possible nivolumab fixed dose evaluation cohort, and approximately 36 patients in each of the 3 dose expansion cohorts.	**Number of Sites:** Estimated total: Approximately 25 sites in North America and Europe
Dose Level(s): **TAK-659**: oral daily dosing with 3+3 dose escalation planned at 60 and 100 mg. The RP2D determined in combination with nivolumab during dose escalation will be used for the possible fixed-dose evaluation cohort and dose expansion cohorts. **Nivolumab**: 3 mg/kg IV dosing over 60 minutes every 2 weeks (Day 1 and Day 15 of each 28-day cycle). If the 240 mg fixed-dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg, on the basis of change in clinical practice and discussion between the investigator and sponsor. For patients participating in the 2-week monotherapy run-in with TAK-659, the first dose will be on Cycle 1 Day 15.	**Route of Administration:** TAK-659: Oral Nivolumab: IV
Duration of Treatment: Treatment will continue until disease progression (PD), unacceptable toxicities, completion of the study, or withdrawal due to other reasons. The estimated treatment duration is 12 months.	**Period of Evaluation:** PFS follow-up of 6 months (for patients who discontinue due to reasons other than PD) and OS follow-up of 12 months from the last dose of study drug are planned.

Main Criteria for Inclusion:

For indication-specific expansion cohorts:

TNBC

- Patients with histologically confirmed, metastatic TNBC with measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [1].
- Triple-negative disease (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 negativity) confirmed on a histological biopsy of a metastatic tumor lesion (receptor conversion not allowed).
- Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment followed by TAK-659 plus nivolumab combination treatment (approximately 10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the patient.
- One, 2, or 3 line(s) of chemotherapy for metastatic disease and with progression of disease on last treatment regimen.
  - For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior

line of therapy.

  - Prior treatment must include an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting with the exception for patients who are clinically contraindicated for these chemotherapies.

NSCLC

- Locally advanced or metastatic (stage IIIB, stage IV, or recurrent) NSCLC with measurable lesions per RECIST version 1.1.
- PD during or following at least 1 prior treatment. Patients should have received a prior platinum-containing, 2-drug regimen for locally advanced, unresectable/inoperable or metastatic NSCLC had or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (eg, chemoradiation) regimen with curative intent.
- Patients with epidermal growth factor receptor or anaplastic lymphoma kinase genomic alternations should have PD on prior United States Food and Drug Administration-approved therapy for these aberrations.
- Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment followed by TAK-659 plus nivolumab combination treatment (approximately 10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the patient.

HNSCC

- Histologically confirmed recurrent or metastatic HNSCC (oral cavity, pharynx, larynx), stage III/IV, and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
  - Histologically confirmed recurrent or metastatic squamous cell carcinoma of unknown primary or nonsquamous histologies (eg, mucosal melanoma) are not allowed.
  - Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx is allowed, but these patients will not be included as response-evaluable patients for efficacy analysis of HNSCC.
- Measurable disease per RECIST 1.1.
- Tumor progression or recurrence within 6 months of the last dose of platinum-based therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.
- Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment followed by TAK-659 plus nivolumab combination treatment (approximately 10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the patient.

Main Criteria for Exclusion:

- Active brain metastases or leptomeningeal metastases.
- Active or a history of known autoimmune disease.
- Diagnosis of immunodeficiency or any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment.
- History of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on screening chest computed tomography scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- History of interstitial lung disease.
- Prior therapy with experimental antitumor vaccines; any T cell co-stimulation agents or inhibitors of checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody; or other agents specifically targeting T cells are also prohibited. However, in each of the expansion cohorts, 6 response-evaluable patients with prior exposure to anti-PD-1 or anti-PD-L1 agents will be allowed for enrollment.

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

- MTD or RP2D (dose escalation).
- ORR as assessed by the investigator per RECIST version 1.1 (dose expansion).

Secondary Endpoints:

- Percentage of patients with adverse events (AEs), Grade 3 and Grade 4 AEs, serious AEs, and discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range that are of clinical significance.
- Disease control rate.
- DOR.
- Rate of PD at 6 months.
- PFS.
- OS.
- Summary statistics of TAK-659 maximum (peak) plasma concentration, first time to reach maximum (peak) plasma concentration, and area under the plasma concentration versus time curve over the dosing interval on Cycle 1, Days 1 and 15, by dose escalation cohort.

Statistical Considerations:

The MTD/MAD (in combination with 3 mg/kg IV nivolumab) will be estimated by a standard 3+3 method using data collected in the dose escalation phase.

AEs will be summarized by treatment group and overall. Categorical variables such as ORR, disease control rate, and rate of PD at 6 months will be tabulated by treatment group and overall. Time to event variables such as DOR, PFS, and OS will be analyzed using Kaplan-Meier survival curves, and Kaplan-Meier medians (if estimable) will be provided. PK parameters will be summarized using descriptive statistics.

Sample Size Justification: During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 12 to 18 dose-limiting toxicity-evaluable patients will be enrolled (including 3 to 6 patients in the possible nivolumab fixed-dose evaluation cohort). The MTD/RP2D cohort will have at least 6 patients.

The sample sizes for each expansion cohort are estimated using a 1-sided exact binomial test at a significance level of α=0.1 with a power of 80%. Each cohort uses a null hypothesis of response rate ≤20%, versus an alternative hypothesis of response rate ≥40% for patients who are naïve to anti-PD/PD-L1 and any other immune-directed antitumor therapies. Therefore, approximately 24 response-evaluable patients for each cohort will be needed. In addition, 6 response-evaluable patients with prior exposure to a PD-1 or PD-L1 inhibitor will be enrolled in each expansion cohort. In total, 30 response-evaluable patients for each cohort and 90 response-evaluable patients in total (~108 patients based on a 15% drop-out rate) will be needed for all expansion cohorts.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve over the dosing interval
BUN	blood urea nitrogen
CL/F	apparent oral clearance
C_{max}	maximum (peak) plasma concentration
CO_2	carbon dioxide
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor deoxyribonucleic acid
C_{trough}	trough concentration
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
EC_{50}	concentration producing half-maximal response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOT	end of treatment
EU	European Union

Abbreviation	Term
FDA	Food and Drug Administration
FIH	first-in-human
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemical
IRB	institutional review board
ITAM	immunoreceptor tyrosine-based activating motif
IV	intravenous(ly)
LDH	lactate dehydrogenase
LMP2A	latent membrane protein 2A
MAD	maximally administered dose
MDSC	myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease (disease progression)
PD-1	programmed cell death protein 1
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PE	physical examination
PFS	progression-free survival
P-gp	P-glycoprotein

Abbreviation	Term
PK	pharmacokinetic(s)
PO	per os; by mouth (orally)
PR	partial response
PT	plasma thromboplastin
PTE	pretreatment event
PTR	peak–trough ratio
Q2W	once every 2 weeks
QD	quaque die; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QTcB	Bazett corrected QT interval
QTcF	Friderichia corrected QT interval
Rac	accumulation ratio
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reactions
SYK	spleen tyrosine kinase
$t_{1/2}$	terminal disposition half-life
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
T_{max}	time to reach maximum (peak) plasma concentration
TNBC	triple-negative breast cancer
ULN	upper limit of the normal range
US	United States
USPI	United States Prescribing Information
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Diseases Under Study

4.1.1.1 Triple-Negative Breast Cancer

Worldwide, breast cancer is the leading type of cancer in women, accounting for 25% of all cases [2]. Triple-negative breast cancer (TNBC) represents 10% to 20 % of invasive breast cancers; it is an aggressive, heterogeneous subset of breast cancer that demonstrates an absence of estrogen and progesterone receptors and no overexpression of human epidermal growth factor receptor 2 (HER2). TNBC tends to be more prevalent in African-American women, is associated with deprivation status, and includes patients with a family history of breast cancer and *BRCA1* mutations. At diagnosis, patients with TNBC tend to be younger, and their cancer is generally more advanced, at a higher grade, and with higher mitotic indices than patients with hormone- and *HER2*-derived breast cancers [3]. Currently, there is no targeted therapy for TNBC. Patients may be offered a lumpectomy with radiation therapy with or without neoadjuvant therapy [4-7]. Chemotherapy is also a therapeutic option and would typically either be an anthracycline-based regimen combining docetaxel, doxorubicin, and cyclophosphamide, or a non-anthracycline-based regimen combining docetaxel and cyclophosphamide [5,8]. Following progression after standard chemotherapeutic regimens, patients have a very poor prognosis. Resistance to current standard anthracyclines and taxane therapies limits the available options for previously treated patients with metastatic TNBC to a small number of non-cross-resistant regimens, and there is currently no preferred standard chemotherapy. Duration of response is usually short, rapid relapse is very common, and median survival is just 13 months [9].

4.1.1.2 Non-Small Cell Lung Cancer

Lung cancer, classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), remains the leading cause of cancer-related mortality worldwide. NSCLC, including squamous cell carcinoma and nonsquamous cell carcinoma (adenocarcinoma, large cell carcinoma, and others), accounts for more than 80% of all lung cancer cases. Treatment of patients with NSCLC depends upon the cell type (squamous and nonsquamous), tumor stage, molecular characteristics, and an assessment of the patient's overall medical condition. Patients with stage I, II, or III NSCLC are generally treated with curative intent using surgery, chemotherapy, radiation therapy, or a combined modality approach. Systemic therapy is generally indicated for patients who present with advanced disease, including those who present with inoperable, locally advanced or metastatic disease (stage IV), or recurring disease following initial definitive treatment. The majority of patients with NSCLC are diagnosed at an advanced stage; therefore, the standard treatment, which commonly includes a combination of chemotherapy and radiation therapy, focuses mainly on disease control and maintenance of quality of life. The platinum-based doublet is a standard frontline chemotherapy in this advanced setting for squamous NSCLC and nonsquamous NSCLC with no presence of driver mutations such as activating mutations of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Following the

platinum-based doublet therapy, the standard second-line therapy for NSCLC has been docetaxel. Recent approval of immune checkpoint inhibitors, including nivolumab and pembrolizumab, as preferred subsequent therapy options for patients with either metastatic nonsquamous or squamous cell lung cancer who have progressed on or after platinum-based therapy, was based on improved overall survival (OS) when evaluated against docetaxel (median OS of 12.2 vs 9.4 months). However, the OS for patients with NSCLC in the advanced setting is still dismal, making it an area of highly unmet medical need that attracts extensive research and development efforts [10].

4.1.1.3 Head and Neck Squamous Cell Carcinoma

Head and neck cancers are a heterogeneous group of neoplasms that typically originate from the mucosal lining of the lip, oral cavity, nasopharynx, larynx, and hypolarynx. Biologically, they are generally similar, with 85% of head and neck cancers being squamous cell carcinomas; they are, therefore, called head and neck squamous cell carcinoma (HNSCC) [11,12]. HNSCC is the fifth most common cancer diagnosed worldwide and the eighth most common cause of cancer death [13]. There are 500,000 new cases each year worldwide [14]. These cancers tend to occur in men in their 60s and 70s and are associated with environmental and lifestyle risk factors, including smoking, alcohol consumption, exposure to ultraviolet light and certain workplace chemicals, and infection with the human papillomavirus [14]. If detected early, HNSCC is highly curable; however, these cancers are frequently aggressive and often are first noticed only when they have spread to the lymph nodes. Radiation therapy is the most common form of treatment for HNSCC. Surgery and carbon dioxide (CO_2) laser surgery are also used, often including the removal of cervical lymph nodes to reduce the possibility of the disease spreading. Radiotherapy and surgery may be used in combination, and the intention of these treatment modalities is curative. Chemotherapy is generally used to create a hostile environment for metastasis either as an additional or adjuvant treatment. Typically, the chemotherapy will combine a platinum-based therapy (carboplatin or cisplatin) with a taxane (taxotere, paclitaxel, or docetaxel), sometimes including fluorouracil cetuximab to treat throat cancer. The 5-year survival rate for patients with HNSCC is 40% to 50% [14].

4.1.2 Study Drug

4.1.2.1 TAK-659

TAK-659 is a selective, reversible, and potent inhibitor of spleen tyrosine kinase (SYK) and FLT3 being developed for oncology indications, the pathogenesis of which are either driven by or significantly contributed to by SYK- and/or FLT3-mediated signaling. TAK-659 inhibits SYK purified enzyme with a concentration producing 50% inhibition (IC_{50}) of 2.0 and 3.2 nM using 2 methods. In cultured human tumor cells, TAK-659 potently inhibited SYK activity in hematopoietic-derived cell lines (Section 4.1.3). In a broad kinase panel, TAK-659 demonstrated a more than 50-fold selectivity for SYK over 290 other protein kinases screened. Subsequent dose response analysis independently confirmed the potency of TAK-659 on 4 of these enzymes (FLT3, ZAP-70, JAK3, and vascular endothelial growth factor receptor 2) with potency ranging from 4.6 to 135 nM.

4.1.2.2 Nivolumab

Nivolumab (Opdivo; Bristo-Myers Squibb) is a human immunoglobulin G4 monoclonal antibody that blocks the interaction between the programmed cell death protein 1 (PD-1) and its ligands, programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2). Binding of PD-L1 or PD-L2 to the PD-1 receptor, found on the surface of T cells, inhibits T-cell proliferation and cytokine production. Up-regulation of PD-L1 and PD-L2 occurs in tumors. The cross-talk between tumor and T cells through the PD-1/ligand interaction in the tumor microenvironment leads to inhibition of active T-cell immune surveillance of tumors. Inhibition of PD-1, therefore, can block this negative regulatory pathway and allow T cells to regain the ability to attack tumors [15,16]. Nivolumab, an anti-PD-1 checkpoint inhibitor, is currently approved in the United States (US) either as a monotherapy or in combination with ipilimumab in advanced melanoma. Nivolumab is approved in the European Union (EU) for advanced melanoma. Following initial approval in melanoma, nivolumab was approved in the US for the treatment of metastatic NSCLC after prior chemotherapy and in the European Union for the treatment of squamous cell NSCLC after prior chemotherapy. It is also approved in the United States for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy and for the treatment of patients with metastatic or recurrent HNSCC following progression on platinum-based therapy. More recently, the US Food and Drug Administration (FDA) granted accelerated approval for nivolumab for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy. See the current versions of the Opdivo United States Prescribing Information [USPI] [17] and Summary of Product Characteristics [SmPC] [18] for further details on indications approved in the United States and European Union, respectively.

While the maximum tolerated dose (MTD)/maximally administered dose (MAD)/recommended phase 2 dose (RP2D) of TAK-659 are being determined, nivolumab will be administered at a starting dose of 3 mg/kg intravenous (IV) infusion over 60 minutes once every 2 weeks (Q2W). As a result of the nivolumab label change to a fixed dose for most indications approved in the United States, TAK-659 may be evaluated in combination with fixed-dose nivolumab (240 mg) per USPI in this study. If the fixed dose of nivolumab is evaluated, the dose of nivolumab may be switched from the 3 mg/kg weight-based dose to a fixed dose of 240 mg for all patients ongoing in the study at the time of the switch and those to be enrolled after the switch. This decision will be made on the basis of an assessment of the change in clinical practice in different regions and upon discussion and agreement between the investigators and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all patients in the dose expansion phase will be 3 mg/kg, unless the direct conversion to a fixed dose of nivolumab is justified by other available data.

The most common side effects of nivolumab are fatigue, shortness of breath, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. A variety of serious immune-mediated adverse reactions have also been observed in patients receiving nivolumab, including pneumonitis,

colitis, hepatitis, nephritis, hypothyroidism and hyperthyroidism, and other immune-mediated adverse reactions [17].

Further details regarding the clinical experience with nivolumab may be found in the current versions of the approved Opdivo USPI [17] or SmPC [18].

4.1.3 Nonclinical Experience

TAK-659 potently inhibited SYK activity in hematopoietic malignancy-derived, cultured human cell lines, including T-cell lymphoblastoma, megakaryoblastoma, and acute myelogenous leukemia (AML), with a concentration producing half-maximal response (EC_{50}) ranging from 11 to 775 nM in sensitive cell systems. In an additional study in cultured human tumor cells treated with TAK-659, the EC_{50} ranged from 134 to >25,000 nM, with the greatest inhibitory effects observed in 2 diffuse large B-cell lymphoma (DLBCL) cell lines (OCI-Ly10 and HBL-1).

TAK-659 demonstrated significant antitumor activity after oral (PO) administration in HBL-1 (DLBCL cell line model; 120 mg/kg; $p<0.005$); PHTX-95L (primary DLBCL tumor; 30, 60, and 120 mg/kg; $p<0.001$); OCI-Ly10 (activated B-cell–like DLBCL cell line model; 30, 60, and 90 mg/kg; $p<0.001$); TMD8 (DLBCL cell line model; 60 and 90 mg/kg; $p<0.001$ and 0.01, respectively); MV-4-11 (AML cell line model; 30 and 60 mg/kg; $p<0.001$); KG-1 (AML cell line model; 60 mg/kg; $p<0.001$); and PHTXM-Ga-32 (gastric cancer model; 60 mg/kg; $p<0.001$) mouse xenograft models. Tumor growth inhibition correlated with markers of SYK pathway modulation in the models in which it was analyzed (eg, HBL-1, PHTX-95L, and OCI-Ly10) and showed antitumor activity after TAK-659 treatment. Additionally, pharmacodynamic analysis of MV-4-11 tumors from mice treated with TAK-659 demonstrated an apparent reduction of SYK phosphorylation at tyrosine residues Y525/526 (phosphorylated SYK Y525/526) and an increase in terminal biomarker cleaved caspase-3, a critical marker of apoptosis.

Nonclinical studies show that SYK inhibition results in loss of myeloid-derived suppressor cells (MDSCs) and activation of T-cell response both in vitro and in vivo. TAK-659 in combination with anti-PD-1 therapy has shown regulation of B cells, NK cells, and macrophages in syngeneic nonclinical mouse models. The combination effects in immune cells are model and context dependent, and combination activity would be greatest in tumors where SYK-mediated MDSC or B-cell immunosuppression is active. The nonclinical combination treatment of TAK-659 and anti-PD-1 therapy provides therapeutic advantage over single-agent treatment with durable tumor growth inhibition, maintained complete responses (CRs), and a vaccinal memory effect. This effect could be indirectly attributed to the decrease in CD11b+ MDSC or B220+ B cells in the tumor-infiltrating lymphocytes (TILs) of TAK-659-treated tumors.

TAK-659 is a small molecule that inhibits SYK and FLT3 and is currently under development for the treatment of patients with advanced malignancies. The compound that will be administered in human clinical trials is the citrate salt, and all references to it in this document are expressed as TAK-659.

4.1.4 Clinical Experience

Three different data cutoff dates were used to provide the most current clinical information given that the ongoing studies are in various stages of execution. The most current disposition data for Studies C34001, C34002, and C34003 are provided from the 22 October 2016 data cutoff date. The most current safety and efficacy data for Study C34001 are provided from the 07 October 2016 data cutoff date. The most current safety and efficacy data for Study C34002 are provided from the 18 September 2016 data cutoff date.

As of 22 October 2016, 111 patients have been dosed with TAK 659 in 3 ongoing studies, including 82 patients in the first-in-human (FIH) Study C34001, 26 patients in Study C34002, and 3 patients in Study C34003.

In Study C34001, the TAK-659 dose was escalated from 60 mg to 120 mg (60 mg [10 patients], 80 mg [4 patients], 100 mg [15 patients], and 120 mg [7 patients]). The MTD for patients with lymphoma and solid tumors has been determined to be 100 mg once daily (QD). Expansion cohorts for patients with lymphoma were opened in December 2015, and patients in the expansion phase of the study are treated at the MTD/RP2D of 100 mg. Of the 82 patients treated in this study (60 lymphoma, 19 solid tumors, and 3 chronic lymphocytic leukemia [CLL]), 63 patients had discontinued from study by the data cutoff date. The reasons for discontinuation included progressive disease (PD) (37 patients), adverse events (AEs) (13 patients), protocol violation (1 patient), symptomatic deterioration (4 patients), and other (8 patients).

In Study C34002, the TAK-659 dose has been escalated from 60 mg to 160 mg across a total of 26 patients, and the MTD/RP2D has not yet been determined. Of the 26 patients treated in this study, 16 patients had discontinued from the study as of the data cutoff date. The reasons for discontinuation included PD (3 patients), AEs (10 patients), withdrawal by patient (1 patient), and other (2 patients).

In Study C34003, the TAK-659 dose has been evaluated in 3 patients at 60 mg with plans to escalate to 100 mg. At the time of the data cutoff, all 3 patients were still on study.

The reported AEs were generally as expected on the basis of nonclinical toxicology findings of TAK-659 and the patient populations being studied. As of 07 October 2016, the most common treatment-related AEs reported in Study C34001 (≥20% of patients) have been aspartate aminotransferase (AST) increased (35 patients [44%]), amylase increased (27 patients [34%]), lipase increased (22 patients [28%]), alanine aminotransferase (ALT) increased (19 patients [24%]), fatigue (18 patients [23%]), and diarrhea (17 patients [21%]). The most common Grade 3 or greater treatment-related AEs (≥5% of patients) have been amylase increased (15 patients [19%]), neutropenia (12 patients [15%]), hypophosphatemia (9 patients [11%]), lipase increased (8 patients [10%]), anemia (7 patients [9%]), blood creatine phosphokinase (CPK) increased (6 patients [8%]), and pyrexia (4 patients [5%]). Further investigations are required to determine the clinical significance of the laboratory abnormalities, many of which have been asymptomatic, such as amylase and lipase increased, AST and ALT increased, and blood CPK increased.

As of 07 October 2016, there were 20 on-study deaths in Study C34001. Three of the AEs that led to death were considered treatment related (multi-organ failure following sepsis, disseminated

varicella, and respiratory failure in the presence of *Pneumocystis jiroveci* pneumonia; cytomegalovirus and aspergillus infection; and right pneumothorax and renal failure). The other causes of the deaths included PD (8 patients), pneumonia and sepsis (2 patients each), and hypoxia, pulmonary embolism, hepatic encephalopathy, ascites, and septic shock (1 patient each).

In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 mantle cell lymphoma), 17 patients had responded to treatment per investigator report as of 07 October 2016. Eight patients with DLBCL achieved a complete response (CR), and 4 achieved a partial response (PR). Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with follicular lymphoma (FL) achieved PRs. One patient with CLL achieved a PR, and a second achieved a PR after the data cutoff date.

As of 18 September 2016, there were 7 on-study deaths in Study C34002, none of which was deemed treatment related. To date, the safety profile in Study C34002 appears to be similar to that of Study C34001. Early signs of antileukemic activity have been observed in a number of patients who have demonstrated significant reductions in both peripheral blast and bone marrow blast counts; however, no formal responses per IWG 2003 criteria [2] have been reported as of the cutoff date.

Additional details on clinical experience with TAK-659 are provided in the TAK-659 Investigator's Brochure (IB).

4.1.4.1 Clinical Pharmacokinetics of TAK-659

Preliminary pharmacokinetic (PK) results are available from the dose-escalation portion of Study C34001 following single-agent QD administration of 60 to 120 mg TAK-659 to patients with advanced solid tumors or lymphomas and from the dose-escalation portion of Study C34002 following single-agent QD administration of 60 to 160 mg TAK-659 to patients with relapsed/refractory AML. For Study C34001, preliminary plasma PK results are available in 34 patients (17 lymphoma, 17 solid tumor) after single dosing and in 25 patients (14 lymphoma, 11 solid tumor) after repeated QD dosing for 15 days; preliminary urine PK results are available from 19 patients (12 lymphoma, 7 solid tumor). For Study C34002, preliminary plasma PK results are available in 21 patients after single dosing and in 13 patients after repeated QD dosing for 15 days.

Among patients with advanced solid tumors, TAK-659 exhibited fast absorption after oral administration of an immediate–release tablet formulation (median T_{max} [time of first occurrence of C_{max} (maximum observed concentration)] of 2-3 hours on Days 1 and 15 of Cycle 1). Approximate steady-state PK conditions appeared to be achieved by Cycle 1 Day 8 upon comparison of predose (trough) concentrations available during Cycle 1. Moderate variability was observed in steady-state dose-normalized area under the plasma concentration versus time curve over the dosing interval (AUC_{τ}) when pooled across the 60 to 120 mg dose range (coefficient of variation of approximately 40% on Day 15). Following repeated QD dosing, TAK-659 was characterized by mean accumulation of 2.6-fold. The mean peak-to-trough fluctuation over the steady-state dosing interval was 3.2. The mean terminal disposition half-life is predicted to be

between 24 and 48 hours and will be confirmed in the expansion phase of Study C34001. Because of limited sample size at some dose levels, dose proportionality was not evaluated in patients with solid tumors. However, among the AML patient population, there was no obvious deviation from dose proportionality across the 60 to 160 mg range.

The mean ratio of TAK-659 renal clearance to apparent oral clearance was 0.30 in patients with solid tumors. Although the exact contribution of renal clearance to systemic clearance is unknown because absolute bioavailability is unknown, the contribution is expected to be at least 30% of systemic clearance. On average, unbound renal clearance (based on creatinine clearance calculated by the Cockcroft-Gault equation) was 2.7-fold higher than estimated glomerular filtration rate, suggesting that active tubular secretion is the major component of renal clearance. Preliminary analyses including patients with solid tumors, lymphoma, or AML demonstrated a relationship between creatinine clearance and TAK-659 apparent oral clearance, suggesting that renal function can affect TAK-659 systemic exposure.

In vitro studies indicated that TAK-659 undergoes metabolism in human liver microsomes and hepatocytes. Cytochrome P450 (CYP) 3A4/5 contributed to the majority (69.1%-73.0%) of TAK-659 metabolism in human liver microsomes, with relatively minor contributions by CYP2D6 (16.6%-30.9%) and CYP1A2 (0%-8.4%). The relative contribution of hepatic metabolism to systemic clearance is currently unknown. Current in vitro and clinical PK data suggest that hepatic metabolism and renal excretion are pathways of TAK-659 elimination in humans.

Additional details on TAK-659 PK are provided in the TAK-659 IB.

4.1.5 Risks and Benefits

TAK-659 has been administered to a total of 111 patients as of 22 October 2016; thus, it is not currently possible to describe with certainty the potential adverse effects of the compound.

4.1.5.1 Potential Risks from Nonclinical Studies

Potential risks identified from nonclinical studies in dogs and rats include the following:

- Lymphoid and hematopoietic effects (including lymphoid depletion and myelosuppression) that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased susceptibility to infection, bleeding, and/or anemia.
- Epithelial effects on the intestinal tract, urinary tract, and lens. Intestinal effects included minimal-to-slight mucosal hemorrhaging. Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis that led to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.
- Reproductive system effects, including decreased spermatozoa and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries.
- Possible mutation of deoxyribonucleic acid.

- Growth plate thickening and disorganization (not relevant to adults).

Lymphoid and hematopoietic effects and reproductive system effects are considered important potential risks.

4.1.5.2 Potential Risks from Clinical Studies

Potential risks based on clinical observations are summarized below.

On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, asymptomatic lipase or amylase elevations are reported commonly (≥10% of patients). Patients in Study C34003 will have frequent monitoring of lipase and amylase as outlined in the Schedule of Events (Appendix A). Cases of pneumonitis have been reported in clinical studies with BCR pathway kinase inhibitors, including TAK-659, and pneumonitis is considered an important potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

The benefits of TAK-659 have not been established; however, early signs of clinical antitumor activity were seen. In Study C34001, of the 48 response-evaluable patients with lymphoma (40 DLBCL, 5 indolent NHL, 2 CLL, and 1 mantle cell lymphoma), 17 patients had responded to treatment per investigator report as of 07 October 2016. Eight patients with DLBCL achieved a CR, and 4 patients achieved a PR. Four patients with indolent lymphomas responded. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR, and 3 patients with FL achieved PRs. One patient with CLL achieved a PR, and a second achieved a PR after the data cutoff date.

Further details regarding the benefits and risks associated with TAK-659 may be found in the current version of the TAK-659 Investigator's Brochure.

Nivolumab is an approved agent for the treatment of HNSCC, melanoma, NSCLC, renal cell carcinoma, and urothelial carcinoma (accelerated approval). The risks associated with the nivolumab administration should be referenced in accordance with the current USPI [17] or SmPC [18].

4.1.5.3 Potential Overlapping Toxicities for the Combination of TAK-659 and Nivolumab

The combination of TAK-659 with nivolumab has been administered to a limited number of patients, and at present, there are no identified risks for the combination; hence, all reported AEs are considered unexpected for the purpose of regulatory reporting. All the TAK-659 data in this section on the occurrence of AEs are from Studies C34001 and C34002 as of the 22 October 2016 data cutoff from a total 108 patients across these 2 studies.

The potential risks, AEs with occurrence rates equal to or greater than 10%, and the warnings and precautions of each drug, including data from nonclinical and clinical studies, have been reviewed. Potential overlapping toxicities of the combination include pneumonitis, rash, elevation of AST and ALT, diarrhea, and embryofetal toxicity.

Severe pneumonitis or interstitial lung disease (2.2%), including fatal cases (0.9%), have occurred with nivolumab treatment. Three events of Grade 3 or higher pneumonitis have been reported in patients treated with TAK-659. Rash is reported as the most common adverse drug reaction (21%) in patients with melanoma treated with nivolumab, with an incidence of Grade 3 or 4 events of only 0.4%. Rash has been reported in 18% of patients receiving TAK-659, and 4% of rash events were Grade 3 or 4. Per the nivolumab label, the rates of elevated AST and ALT in a melanoma clinical trial were 28% and 26%, respectively. The corresponding rates for TAK-659 were 52% and 31%, respectively. Immune-mediated colitis occurred in 2.2% of patients receiving nivolumab treatment. Diarrhea (32%) has been reported in patients receiving TAK-659 with 3% identified as Grade 3 or higher. There is no clinical evidence of embryofetal toxicity for nivolumab or TAK-659, which is a potential risk of both drugs when administered to pregnant women based on the reproductive effects observed in animal studies. These toxicities are expected to be manageable with adequate monitoring and standard of care.

For more detailed information on the adverse reactions associated with nivolumab, please refer to the most recent USPI or SmPC for nivolumab.

4.1.5.4 Drug-Drug Interaction Risk Assessment for the Combination of TAK-659 and Nivolumab

No formal PK drug-drug interaction (DDI) studies have been conducted with TAK-659 in humans. In vitro studies indicate that TAK-659 is a substrate of P-glycoprotein (P-gp) and is metabolized by cytochrome P450 (CYP)3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.40% for these respective CYP enzymes. Consequently, there is a potential risk for TAK-659 PK to be altered by drugs that are strong CYP3A inhibitors or inducers or P-gp inhibitors or inducers.

Therapeutic proteins like nivolumab are not expected to directly inhibit or induce drug-metabolizing enzymes or transporters. In addition, nivolumab is not thought to indirectly affect activities of drug-metabolizing enzymes or transporters via modulation of proinflammatory cytokines. Therefore, the risk of nivolumab affecting TAK-659 PK is low.

As a therapeutic protein, nivolumab is expected to be catabolized into amino acids by protein degradation processes and not expected to be a substrate of drug-metabolizing enzymes and transporters. Therefore, there is low risk of TAK-659 affecting nivolumab PK via inhibition or induction of drug-metabolizing enzymes or transporters.

4.2 Rationale for the Proposed Study

Although the role of SYK in hematological cancers is well known, the data on the relevance of SYK in solid tumors are emerging. Limited data suggest that SYK may play alternate roles in carcinogenesis under different circumstances. For example, 6 of 10 HNSCC cell lines found to express SYK, and the SYK expression in head and neck tumor cells seems to induce chemomigration. Inhibition of SYK in HNSCC cell lines resulted in inhibition of migration, haptotaxis, and engagement with matrix proteins [19]. Nasopharyngeal carcinoma, an unusually highly metastatic tumor, expresses Epstein-Barr virus (EBV) latent membrane protein 2A (LMP2A) in most clinical specimens. LMP2A contains an immunoreceptor tyrosine-based

activating motif (ITAM) domain, which is important for SYK activation. This suggests that SYK may have a contributing role in the transformation process in this tumor type [20]; as such, an inhibitor of SYK may also demonstrate antitumor activity in some solid tumor settings. Such EBV-driven subsets of tumors were reported in gastric cancer also [21], and SYK was found to be overexpressed in retinoblastoma where SYK inhibition led to myeloid cell leukemia 1 degradation and resulted in caspase mediated apoptosis [22]. In H16N-2 breast cancer cells that overexpress C35 protein, SYK inhibition either by pharmacological agent or by small interfering ribonucleic acid (RNA) knock-down resulted in reduced colony size and numbers upon 3D culture [23]. In addition, a subset of breast cancer cell lines (including 28 patient-derived cell lines) enriched for basal-like subtype showed viability effects with SYK inhibition, suggesting potential therapeutic opportunities for SYK inhibitors in a molecularly defined subset of cancers [24].

Recent studies have shown that MDSCs use CD79A-ITAM signaling that uses SYK as a signaling mediator. FLT3 and its ligand have been shown to induce MDSCs in vitro [25]. MDSC-mediated immune suppression has been reported in many solid tumors [26]. In addition, a role of B cells in tumor immunity has been studied, and the requirement of B cells for tumor growth and metastasis has been documented [27]. SYK is known to be essential for development, growth, and maintenance of B cells.

Nonclinical studies show that SYK inhibition results in loss of MDSCs and activation of T-cell response both in vitro and in vivo. TAK-659 in combination with anti-PD-1 therapy has shown regulation of B cells, NK cells, and macrophages in syngeneic nonclinical mouse models. The combination effects in immune cells are model and context dependent, and combination activity would be greatest in tumors where SYK-mediated MDSC or B-cell immunosuppression is active. The nonclinical combination treatment of TAK-659 and anti-PD-1 therapy provides therapeutic advantage over single agent treatment with durable tumor growth inhibition, maintained complete responses, and a vaccinal memory effect. This effect could be indirectly attributed to the decrease in CD11b+ MDSC or B220+ B cells in the TILs of TAK-659-treated tumors.

Therefore, the addition of TAK-659 to an anti-PD-1 agent could improve tumor regression via modulation of the tumor-infiltrating immune cells and other immune cells in the tumor microenvironment. The make-up of the tumor microenvironment, which differs among different tumor types, will drive the choice of diseases to be evaluated in this study. Tumors in which there is MDSC or B-cell suppression are of particular interest: nonclinical assessment suggests that tumors such as TNBC, NSCLC, and HNSCC show MDSC-mediated tumor immunosuppression.

This study intends to clinically evaluate the combination effect of TAK-659 and nivolumab in 3 advanced solid tumor types (TNBC, NSCLC, and HNSCC). With the reference response rate of ~20% observed with nivolumab monotherapy in each of these indications, added benefit of this combination regimen will be assessed by whether a significantly improved overall response rate (ORR; target ORR of 40%) is observed, along with assessment of other efficacy measures such as duration of response (DOR) and survival benefit. While the majority of the patients in each of the cohorts (24/30 response-evaluable patients) should be naïve to anti-PD-1, anti-PD-L1, and any other immune-directed antitumor therapies, a small subset of 6/30 response-evaluable patients with prior exposure to an anti-PD-1 or anti-PD-L1 agent will be enrolled to observe any

combination effect of TAK-659 plus nivolumab in this relapsed/refractory setting with regard to the PD-1/PD-L1 blockade. In addition, after determining a safe and tolerable combination dose for TAK-659 when co-administered with nivolumab during the initial dose escalation stage of the study, a 2-week, single-agent TAK-659 treatment period before combination therapy is planned in 10 response-evaluable patients in each of the expansion cohorts. Correlative science studies are planned in pretreatment and posttreatment tumor biopsies and peripheral blood samples taken from these patients with the intent of having more mechanistic understanding of the role of SYK in the tumor immunity and direct tumor effect, if any.

4.2.1 Rationale for Dose and Schedule Selection

TAK-659 has been evaluated as a single-agent given orally on a continuous daily dosing schedule in its FIH dose escalation study (C34001) in patients with advanced solid tumors or lymphoma. Four dose levels (60, 80, 100, and 120 mg QD) have been evaluated in Study C34001, and the MTD has been determined to be 100 mg QD. Following the safety expansion of the 100 mg cohort, Study C34001 is currently in the dose expansion phase, evaluating the efficacy, safety, and tolerability of TAK-659 administered at the 100 mg dose level in 5 different cohorts of B-lymphocyte malignancies. Early signs of clinical activity in lymphoma were demonstrated across all doses evaluated in the escalation phase of the study, including 3 PRs and 1 CR among patients with relapsed/refractory DLBCL and 3 PRs among patients with relapsed/refractory FL. These responses were observed at doses of 60 (1 PR), 80 (1 PR), 100 (3 PR and 1 CR), and 120 mg QD (1 PR). These data suggest that doses in the tolerable dose range of 60 to 100 mg are pharmacologically active. Preliminary data show that TAK-659 exhibits an acceptable PK profile across the 60 to 100 mg dose levels that supports continuous QD dosing.

In addition, TAK-659 is being evaluated as a single agent in relapsed/refractory AML in Study C34002, which includes phase 1b dose escalation and phase 2 dose expansion phases. The TAK-659 dose has been escalated from 60 mg to 160 mg with the MTD/RP2D remaining to be determined.

In the dose escalation phase of Study C34003, the starting dose of TAK-659 will be 60 mg QD in combination with nivolumab (3 mg/kg IV Q2W). Dose escalation of TAK-659 will follow a standard 3+3 escalation scheme. Considering the low risk of DDI between TAK-659 and nivolumab, no significant changes in TAK-659 exposure are expected when TAK-659 is given in combination with nivolumab versus as a single agent. On the basis of the dose escalation experience with TAK-659 in Studies C34001 and C34002, dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg QD dose is demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may be evaluated on the basis of safety, tolerability, and preliminary PK and efficacy data if available, following agreement between investigators and the sponsor. However, the dose of TAK-659 cannot be escalated beyond 100 mg, which is the MTD for single-agent TAK-659 in solid tumors and lymphoma.

After the RP2D of TAK-659 has been identified, on the basis of evaluation of the combination with a weight-based dose of nivolumab (3 mg/kg), this RP2D of TAK-659 may be evaluated in

combination with a fixed dose of 240 mg IV nivolumab following discussion between the investigator and sponsor. For single-agent nivolumab, the fixed dose is expected to have equivalent exposure, safety, and efficacy as the weight-based (3 mg/kg) dose. If the nivolumab fixed dose is evaluated in combination with the TAK-659 RP2D, 3 patients will be initially enrolled into the cohort. Following evaluation of the safety, efficacy, and any available PK data, along with discussions between the investigator and sponsor, 3 additional patients may be enrolled into the cohort for a total of 3 to 6 patients. Following evaluation of this fixed-dose cohort (if it is run), the dose of nivolumab may be switched from the 3 mg/kg weight-based dose to a fixed dose of 240 mg for all patients ongoing in the study at the time of the switch and those to be enrolled after the switch. This decision will be made on the basis of an assessment of the change in clinical practice in different regions and upon discussion and agreement between the investigators and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all patients in the dose expansion phase will be 3 mg/kg, unless the direct conversion to a fixed dose of nivolumab is justified by other available data.

4.2.2 Rationale for PK Assessments

During dose escalation, serial blood samples will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15 to characterize the plasma PK of TAK-659 when administered in combination with nivolumab. Specifically, serial plasma PK assessments will be used to describe single- and repeat-dose concentration-time profiles of TAK-659, calculate PK parameters, and contribute to population PK model development. Although the risk of DDI between TAK-659 and nivolumab is predicted to be low, TAK-659 plasma PK following combination administration with nivolumab will be compared with historical plasma PK from single-agent studies to confirm that there are no clinically meaningful differences in TAK-659 PK between the single-agent and combination settings.

In dose expansion cohorts, blood samples for plasma PK will be collected during Cycles 1 through 4 using a limited sampling strategy to contribute to population PK analyses of TAK-659.

Plasma PK data collected in the dose escalation and expansion cohorts may be used individually or in combination with data from other studies to explore the relationship between TAK-659 PK and pharmacodynamic effects, pharmacogenomics in drug-metabolizing enzymes and/or transporters, safety parameters, and clinical response.

4.2.3 Rationale for Biomarker Analysis (Correlative Science Studies)

4.2.3.1 Tumor Tissue Measurement

Although nonclinical data suggest a role for SYK and/or FLT3 in the induction and maintenance of immunosuppressive cells contributing to tumor growth, combination of a SYK or FLT3 inhibitor with an immune checkpoint inhibitor has not been tested to date. Therefore, it is important to understand the effect of TAK-659 on infiltrating immune cells, tumor microenvironment, and differentiation/maintenance of immune cells, and to identify possible patient selection markers for the combination of TAK-659 with nivolumab by conducting correlative science studies.

Immunohistochemical (IHC) studies on tumor samples have been conducted to identify immune cell components responsible for antitumor effects and those associated with tumor growth. For example, an analysis of TILs in a large cohort of NSCLC patients revealed that an elevated CD3 or CD8 signal was statistically significantly associated with longer survival [28]. In addition, levels of proteins expressed on tumor cells that can modulate immune cells responsible for antitumor activity have been investigated, and IHC measurement of the expression of PD-L1 was developed as a companion diagnostic for the immune checkpoint inhibitor pembrolizumab [29]. An alternative approach is to deconvolute data of messenger RNA expression based on specific signatures identified for subsets of immune cells of interest [30]. This strategy may allow analysis of a larger number of immune cell subsets than is possible with the IHC assay. It also may potentially improve our understanding of the pharmacological effects of TAK-659, alone or in combination with nivolumab, and possibly identify candidate biomarkers of clinical response to the combination.

It is known that somatic mutations found in tumors can be recognized by the patient's own immune system [31], and it has been demonstrated recently that efficacy of another PD-1 inhibitor, pembrolizumab, was mostly seen in patients with colorectal cancer with high mutation burden [32]. Therefore, analysis of somatic mutations in tumors may also help identify biomarkers predictive of clinical response to the combination.

These analyses will be performed using serial biopsies taken from a subset of patients who have accessible tumors and who consent to sequential tumor biopsies as described above. In addition, archival tumor tissue will be collected from the rest of the patients and may be subjected to the same analyses.

4.2.3.2 Analysis of Biomarkers Using Peripheral Blood

TILs and other hematopoietic cells that make up the tumor microenvironment may be detected in peripheral blood, as those cells are generated and/or mature in host organs such as the bone marrow, lymph nodes, and spleen. Peripheral blood mononuclear cells (PBMCs) have been profiled to delineate changes in such circulating immune regulatory and effector cells as developing prognostic biomarkers, being used as response markers, and supporting proposed mechanisms of action from nonclinical studies [33]. As these immune cells produce and/or act on cytokines and chemokines in the tumor microenvironment and supporting organs, peripheral blood may contain detectable amounts of cytokines and chemokines that could potentially be used as a biomarker of response. Circulating tumor DNA (ctDNA) has been used to estimate tumor burden and profile mutations in lieu of tumor tissue samples that require obtaining a biopsy [34]. Therefore, blood samples will be collected for all patients in the dose expansion cohorts and analyzed for biomarkers as described. CCI [redacted]

4.2.4 Rationale for Pharmacogenomic Assessments

CCI [redacted]

CCI

[redacted]

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objectives are:

- To determine the MTD/RP2D of TAK-659 when administered in combination with nivolumab (dose escalation).
- To determine the efficacy of TAK-659 plus nivolumab as measured by ORR (dose expansion).

5.2 Secondary Objectives

The secondary objectives are:

- To determine the safety and tolerability of TAK-659 when administered in combination with nivolumab.
- To evaluate other efficacy measures such as disease control rate (response plus stable disease [SD]), DOR, rate of PD at 6 months, progression-free survival (PFS), and OS.
- To characterize the plasma PK of TAK-659 when administered in combination with nivolumab.

5.3 Tertiary/Exploratory Objectives

The exploratory objectives are:

CCI

[redacted]

5.4 Additional Objectives

The additional objective is to collect TAK-659 plasma concentration data to contribute to population PK analyses.

6.0 STUDY ENDPOINTS

6.1 Primary Endpoints

The primary endpoints are:

- MTD (dose escalation).
- RP2D (dose escalation).
- ORR as assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [1] (dose expansion).

6.2 Secondary Endpoints

The secondary endpoints are:

- Percentage of patients with AEs.
- Percentage of patients with Grade 3 and Grade 4 AEs.
- Percentage of patients with serious adverse events (SAEs).
- Percentage of patients who discontinued due to AEs.
- Clinically significant laboratory values.
- Clinically significant vital sign measurements.
- Disease control rate.
- DOR.
- Rate of PD at 6 months.
- PFS.
- OS.
- Summary statistics of TAK-659 maximum (peak) plasma concentration (C_{max}) on Cycle 1 Days 1 and 15, by dose escalation cohort.
- Summary statistics of TAK-659 T_{max} on Cycle 1 Days 1 and 15, by dose escalation cohort.
- Summary statistics of TAK-659 AUC_{τ} on Cycle 1 Days 1 and 15, by dose escalation cohort.

6.3 Exploratory Endpoints

The exploratory endpoints are:

CCI

[redacted]

CCI

[redacted]

6.4 Additional Endpoints

The additional endpoints are:

- Summary statistics of TAK-659 apparent oral clearance (CL/F), peak-trough ratio (PTR), accumulation ratio (Rac), and trough concentration (C_{trough}) on Cycle 1 Day 15 by dose escalation cohort.
- Summary statistics of TAK-659 plasma concentrations on Cycle 1 Days 1 and 15 by dose escalation cohort.
- TAK-659 plasma concentration-time data contributing to population PK analyses.

7.0 STUDY DESIGN

7.1 Overview of Study Design

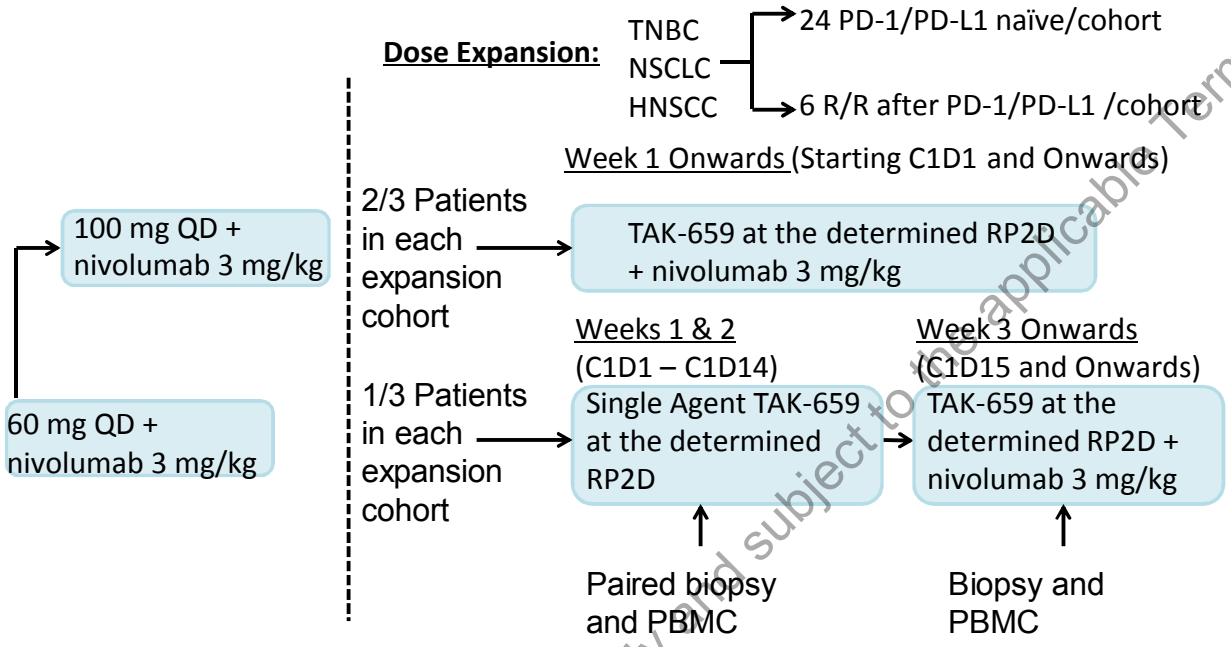
This is an open-label, multicenter, phase 1b, dose escalation study of TAK-659 in combination with nivolumab in patients with advanced solid tumors. The study will include a dose escalation phase (Part 1) and a dose expansion phase (Part 2). In the dose escalation phase, the patient population will consist of all-comer patients with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: 1) patients with metastatic TNBC who have had ≥1 prior line of chemotherapy; 2) patients with locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy; and 3) patients with locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

It is estimated that 126 patients will be enrolled in the study: approximately 9 to 12 patients among the dose escalation cohorts evaluating weight-based dosing of nivolumab, 3 to 6 patients in the nivolumab fixed-dose evaluation cohort (if it is opened), and approximately 36 patients (30 evaluable patients+15% drop off) in each of the 3 dose expansion cohorts.

Once enrolled in the study, patients will be administered TAK-659 PO QD during each 28-day treatment cycle. Patients receiving the combination therapy will also receive nivolumab Q2W IV over 60 minutes on Day 1 and Day 15 of each 28-day treatment cycle (for patients who receive 2 weeks of TAK-659 monotherapy before starting combination treatment, the first nivolumab infusion will be administered on Cycle 1 Day 15). On days when both TAK-659 and nivolumab are administered, the TAK-659 dose will be administered first followed by the nivolumab infusion (infusion to begin within 30 minutes after the TAK-659 dose). Patients, including those who achieve a CR, may receive study treatment until they experience PD or unacceptable toxicities.

The Study Schema is presented in Figure 7.a.

Figure 7.a Study Schema



CXDX=Cycle X Day X, R/R=relapsed/refractory.

While the MTD/MAD/RP2D of TAK-659 are being determined, the starting dose of nivolumab will be 3 mg/kg IV. The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg dose has been demonstrated (Section 9.4). Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) may be also evaluated if appropriate. Dose escalation will continue until the MTD is reached, until 100 mg QD of TAK-659 (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, has been identified on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 patients will be evaluated at the RP2D (the MTD, MAD, or a lower dose) before making a decision to advance to further dose expansion.

After the RP2D of TAK-659 has been identified, on the basis of evaluation of the combination with a weight-based dose of nivolumab (3 mg/kg), this RP2D of TAK-659 may be evaluated in combination with a fixed dose of 240 mg IV nivolumab following discussion between the investigator and sponsor. For single-agent nivolumab, the fixed dose is expected to have equivalent exposure, safety, and efficacy as the weight-based (3 mg/kg) dose. If the nivolumab fixed dose is evaluated in combination with the TAK-659 RP2D, 3 patients will be initially enrolled into the cohort. Following evaluation of the safety, efficacy, and any available PK data, along with discussions between the investigator and sponsor, 3 additional patients may be enrolled into the cohort for a total of 3 to 6 patients. If ≥1 out of 6 patients experiences dose-limiting toxicity (DLT) during Cycle 1, or significant safety issues are seen in Cycle 2 and beyond,

re-evaluation of the TAK-659 RP2D when administered with a fixed dose of nivolumab is permitted

The dose of nivolumab in the expansion cohorts will be either 3 mg/kg or 240 mg IV, dependent on whether the 240 mg fixed-dose cohort is evaluated. If the 240 mg fixed-dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg, on the basis of change in clinical practice and discussion between the investigator and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all patients in the dose expansion phase will be 3 mg/kg.

After the combination TAK-659 RP2D (the MTD, MAD, or a lower dose) is determined, expansion cohorts are planned in patients with TNBC, NSCLC, and HNSCC. Thirty response-evaluable patients will be enrolled in each expansion cohort. Each expansion cohort will include 24 patients who are naïve to anti-PD-1/anti-PD-L1 therapy and 6 patients who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable patients in each expansion cohort will first receive 2 weeks of single-agent TAK-659 at its RP2D previously determined in combination with nivolumab before starting combination therapy and will provide paired tumor biopsies during this period; these patients can be either naïve to or relapsed/refractory to anti-PD1/anti-PDL1 therapy. Following the 2-week single-agent treatment, TAK-659 treatment will continue (at the same dose) in combination with nivolumab during Week 3 and beyond.

During dose escalation, the Cycle 1 DLT-evaluation period typically will be 28 days. However, in the event of a nivolumab dosing interruption, a cycle length may be extended. If the second dose of nivolumab planned for Cycle 1 Day 15 is held and then dosed within the original 28-day cycle, the dose will be considered the second dose of Cycle 1, leading to a cycle with a maximum total of 42 days. The actual doses of TAK-659 received during this 28- to 42-day DLT-evaluation period will be assessed against the planned doses of TAK-659 (daily dose × cycle days) to determine whether the patient has received at least 75% of planned doses of TAK-659 to be DLT evaluable. When the second dose is administered, procedures at the original scheduled visit (ie, Cycle 1 Day 15) should be performed. If the second dose of nivolumab is interrupted for a period of time that extends beyond the original 28-day cycle, this dose will be considered missed. In this case, independent of whether the patient has received 75% of the planned doses of TAK-659, the patient will receive only one of the 2 nivolumab doses planned for Cycle 1 and, therefore, is not evaluable for DLT.

In Cycle 2 and beyond, during escalation and during the expansion phase of the study, if a nivolumab dose is delayed because of AEs, when the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if nivolumab is delayed past the next scheduled time point per protocol and TAK-659 dosing is also interrupted, the next scheduled time point will be delayed until dosing with either drug resumes.

The subset of expansion patients who will be treated with single-agent TAK-659 at its combination RP2D during Weeks 1 and 2 should have accessible tumors for core or excisional biopsy and provide permission for the biopsies to be taken. These patients will undergo mandatory biopsies before single-agent TAK-659 treatment begins, at the end of the 2-week treatment window, and after 6 weeks of treatment with TAK-659 in combination with nivolumab; an

optional biopsy will also be taken at the time of PD. The biopsies will be used for biomarker analysis evaluating the effect of TAK-659 on tumor cells and on immune/stromal cells supporting tumor tissue.

In addition to analysis of tumor biopsy samples as described above for a subset of patients in each expansion cohort, blood samples will be collected from all patients enrolled in the expansion phase of the study and analyzed for posttreatment changes in immune cell populations in the course of treatment, levels of cytokines and chemokines known for or deemed relevant to tumor growth or antitumor activity of TAK-659 or the combination, and ctDNA quantity and characteristics. The result will be compared with that obtained from the analysis of paired tumor biopsy samples and used to identify a biomarker(s) that would enable monitoring the activity of TAK-659 and the combination in future studies using peripheral blood samples. In addition, postdose change of a biomarker(s) may be evaluated for its (their) association with clinical responses from treatment with TAK-659 in combination with nivolumab.

A part of the biopsied and archived tumor samples may be used to identify a biomarker(s) correlating with the clinical activity of the combination of TAK-659 and nivolumab. Archived tumor samples will be collected from patients enrolled both in the dose escalation and in the expansion phase, except for those who consent to serial tumor biopsies for pharmacodynamic assessment.

The remaining 20 response-evaluable patients in each expansion cohort will receive TAK-659 at its RP2D in combination with nivolumab, starting at Week 1 Day1.

During dose escalation, serial blood samples will be collected for 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15 to characterize the plasma PK of TAK-659 when administered in combination with nivolumab. Although the risk of DDI between TAK-659 and nivolumab is predicted to be low, TAK-659 plasma PK following combination administration with nivolumab will be compared with historical plasma PK from single-agent studies to confirm no clinically meaningful differences in TAK-659 PK between the single-agent and combination settings. In the dose expansion cohorts, blood samples for plasma PK will be collected during Cycles 1 through 4 using a limited sampling strategy to contribute to population PK analyses of TAK-659.

All patients in the expansion cohorts will be treated until PD or occurrence of unacceptable toxicities. The objectives of these expansion cohorts are to evaluate efficacy of TAK-659 in combination with nivolumab as measured by ORR and to determine the safety and tolerability of TAK-659 in combination with nivolumab.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, effective 14 June 2010 [35]. DLTs are defined in Section 9.3.

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-659 when administered in combination with nivolumab.

Radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) will be employed to assess the status of the patient's underlying disease. An

evaluation of disease response using RECIST version 1.1 [1] will be performed at Screening/Baseline (within 28 days before the first study drug administration), predose at the end of Cycles 2, 4, and 6 (between Days 22 and 29), and then predose at the end of every 3 cycles thereafter (ie, between Days 22 and 29 of Cycles 9, 12, etc).

7.2 Number of Patients

It is estimated that 126 patients will be enrolled in the study from approximately 25 study centers in North America and Europe: approximately 9 to 12 patients among the dose escalation cohorts evaluating weight-based dosing of nivolumab, 3 to 6 patients in the possible nivolumab fixed-dose evaluation cohort (if it is opened), and approximately 36 patients (30 evaluable patients+15% dropout) in each of the 3 dose expansion cohorts. Enrollment is defined as the time of the initiation of the first dose of study drug.

Patients in the escalation cohorts who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced. Patients in the expansion cohorts who are not evaluable for response will be replaced.

7.3 Duration of Study

Patients, including those who achieve a clinical response, may receive TAK-659+nivolumab until they experience PD or until completion of the study. Patients will discontinue treatment if they have an unacceptable TAK-659+nivolumab-related or possibly related toxicity. For information on treatment beyond PD, see Section 10.4.16.

Patients will be followed for 28 days after the last dose of TAK-659+nivolumab to permit the detection of any delayed treatment-related AEs. However, immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis as described in nivolumab USPI) will be followed to resolution or stabilization, or the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first.

Patients who stop treatment for any reason other than PD will continue to have follow-up visits for PFS. The PFS follow-up visit should be conducted at the site every 2 months (up to 6 months after the first dose of study drug) or 3 months from the last dose of study drug until PD for a maximum of 6 months from the date of the last dose of study drug. After the occurrence of PD, patients will continue to have follow-up visits for OS every 2 months until 12 months from the date of the last dose of study drug. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every 2 months until death, loss to follow-up, or withdrawal of consent to further follow-up for up to 12 months after discontinuation of the study drug. The final analyses for the clinical study report will be conducted after all patients enrolled in the study have had the opportunity to complete 6 cycles of treatment with TAK-659+nivolumab.

It is anticipated that this study will last for approximately 30 months (6 months escalation, 18 months expansion, and 6 months treatment after last patient in).

8.0 STUDY POPULATION

Dose escalation: patients with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment.

Dose expansion:

- Metastatic TNBC with ≥1 prior line of chemotherapy.
- Locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy.
- Locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy.

8.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male or female patients aged 18 years or older.
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (refer to Appendix D for a description of the scale).
3. Female patients who:
   - Are postmenopausal for at least 1 year before the Screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method, at the same time (see Appendix H), from the time of signing the informed consent through 180 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

4. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
5. Suitable venous access for the study-required blood sampling, including PK and pharmacodynamic sampling.
6. Clinical laboratory values and other measures as specified below within 28 days before the first dose of study drug:
   - Total bilirubin must be ≤1.5×the upper limit of normal (ULN).
   - ALT and AST must be ≤2.5×ULN.
   - Creatinine clearance must be ≥60 mL/minute as estimated by the Cockcroft Gault equation (see Appendix E) or based on urine collection (12 or 24 hours).
   - Hemoglobin must be ≥9 g/dL, absolute neutrophil count (ANC) must be ≥1500/µL, and platelet count must be ≥75,000/µL.
   - Lipase must be ≤1.5×ULN and amylase ≤1.5×ULN with no clinical symptoms suggestive of pancreatitis and cholecystitis.
   - Blood pressure ≤Grade 1 (hypertensive patients are permitted if their blood pressure is controlled to ≤Grade 1 by hypotensive medications and glycosylated HbA1C ≤6.5%).
7. Recovered (ie, ≤Grade 1 toxicity) from the reversible effects of prior anticancer therapy.
8. To be enrolled in the dose escalation phase of the study, patients must have:
   - Histologically confirmed diagnosis of advanced solid tumor with a radiographically or clinically evaluable disease. Measurable disease as defined by RECIST version 1.1 [1] is not required for participation in the dose escalation of the study.
   - One or more prior lines of therapy and no effective therapeutic options available based on investigator assessment. Prior exposure to marketed immune checkpoint inhibitors, such as nivolumab and pembrolizumab, is permitted during dose escalation.
9. To be enrolled in the TNBC expansion cohort, patients must have:
   - Histologically confirmed, metastatic TNBC with measurable disease per RECIST version 1.1.
   - Triple-negative disease (estrogen receptor, progesterone receptor, and HER2 negativity) confirmed on a histological biopsy of a metastatic tumor lesion (receptor conversion not allowed).
   - Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment for 2 weeks followed by TAK-659 plus nivolumab combination treatment (~10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy

of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at PD with additional consent from the patient.

- One, 2, or 3 prior lines of chemotherapy for metastatic disease and with progression of disease on last treatment regimen.
  - For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior line of therapy.
  - Prior treatment must include an anthracycline and/or a taxane in the neoadjuvant, adjuvant, or metastatic setting with the exception for patients who are clinically contraindicated for these chemotherapies.

10. To be enrolled in the NSCLC expansion cohort, patients must have:
    - Locally advanced or metastatic (stage IIIB, stage IV, or recurrent) NSCLC with measurable lesions per RECIST version 1.1.
    - PD during or following at least 1 prior treatment. Patients should have received a prior platinum-based 2-drug regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (eg, chemoradiation) regimen with curative intent.
    - Patients with EGFR or ALK genomic alternations should have PD on prior US FDA-approved therapy for these aberrations.
    - Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment for 2 weeks followed by TAK-659 plus nivolumab combination treatment (~10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at progression with additional consent from the patient.
11. To be enrolled in the HNSCC expansion cohort, patients must have:
    - Histologically confirmed recurrent or metastatic HNSCC (oral cavity, pharynx, or larynx) that is stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
      - Histologically confirmed recurrent or metastatic squamous cell carcinoma of unknown primary or nonsquamous histologies (eg, mucosal melanoma) are not allowed.

  - Histologically confirmed recurrent or metastatic carcinoma of the nasopharynx is allowed, but these patients will not be included as response-evaluable patients for efficacy analysis of HNSCC.

- Measurable disease per RECIST version 1.1.
- Tumor progression or recurrence within 6 months of the last dose of platinum-based therapy in the adjuvant (ie, with radiation after surgery), primary (ie, with radiation), recurrent, or metastatic setting.
- Safely accessible tumor lesions (based on investigator's assessment) for serial pretreatment and posttreatment biopsies are required for patients receiving TAK-659 monotherapy run-in treatment for 2 weeks followed by TAK-659 plus nivolumab combination treatment (~10/30 response-evaluable patients); adequate, newly obtained, core or excisional biopsy of a metastatic tumor lesion not previously irradiated is required. Mandatory biopsies will be taken before TAK-659 monotherapy, after the 2 weeks of TAK-659 monotherapy, and after 6 weeks of TAK-659 plus nivolumab combination therapy. An optional biopsy may be taken at progression with additional consent from the patient.

8.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Active brain metastases or leptomeningeal metastases.
2. Active or suspected autoimmune disease or a history of known autoimmune disease, with the exception of:
   - Patients with vitiligo, type I diabetes mellitus, resolved childhood asthma/atopy, residual hypothyroidism due to autoimmune condition requiring only hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.
3. Any condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days before first dose of study drug.
   - Corticosteroids for topical use or in nasal spray are allowed, as are inhaled steroids and adrenal replacement steroid doses >10 mg daily in the absence of active autoimmune disease.
4. History of pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia, or evidence of active pneumonitis on the Screening chest CT scan; history of radiation pneumonitis in the radiation field (fibrosis) is permitted.
5. History of interstitial lung disease.
6. Prior therapy with experimental antitumor vaccines; any T-cell co-stimulation agents or inhibitors of checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or

anti-CTLA-4 antibody; or other agents specifically targeting T cells are prohibited. However, for dose escalation, prior treatment with the marketed inhibitors of the immune checkpoint pathway, such as nivolumab and pembrolizumab, is allowed. In addition, in each of the expansion cohorts, 6 response-evaluable patients with prior exposure to anti-PD-1 or anti-PD-L1 agents (including both marketed and investigational) will be allowed to enroll.

7. Any serious medical or psychiatric illness, including drug or alcohol abuse, that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
8. Life-threatening illness unrelated to cancer.
9. Female patients who are lactating and breast-feeding or a positive serum pregnancy test during the Screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
10. Systemic anticancer treatment (including investigational agents) or radiotherapy <2 weeks before the first dose of study treatment (≤4 weeks for antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine) or have not recovered from acute toxic effects from prior chemotherapy and radiotherapy.
11. Prior treatment with investigational agents ≤21 days (≤4 weeks for monoclonal antibodies with evidence of PD) or ≤5×their half-lives (whichever is shorter) before the first dose of study treatment. A minimum of 10 days should elapse from prior therapy to initiating protocol therapy.
12. Major surgery within 14 days before the first dose of study drug and not recovered fully from any complications from surgery.
13. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug.
14. Known human immunodeficiency virus (HIV) positive (testing not required).
15. Known hepatitis B surface antigen-positive or known or suspected active hepatitis C infection (testing not required).
16. Patients with another malignancy within 2 years of study start. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.
17. Any clinically significant comorbidities, such as uncontrolled pulmonary disease, known impaired cardiac function or clinically significant cardiac disease (specified below), active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.

    Patients with any of the following cardiovascular conditions are excluded:

    - Acute myocardial infarction within 6 months before starting study drug.

- Current or history of New York Heart Association Class III or IV heart failure (see Appendix F).
- Evidence of current uncontrolled cardiovascular conditions including cardiac arrhythmias, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Fridericia corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the Screening period.
- Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that in the opinion of the investigator are considered to be clinically significant.

18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-659 including difficulty swallowing tablets; diarrhea >Grade 1 despite supportive therapy.
19. Use or consumption of any of the following substances:
    - Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, the use of these agents is not permitted during the study (see Section 9.6 for details). See Appendix G for a nonexhaustive list of strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the US FDA draft DDI guidance.
    - Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. In general, the use of these agents is not permitted during the study (see Section 9.6 for details). See Appendix G for a nonexhaustive list of strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the US FDA draft DDI guidance.
    - Non-oncology vaccine therapies for prevention of infectious diseases (eg, human papillomavirus [HPV] vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted but must be discussed with the sponsor's medical monitor and may require a washout period before and after administration of vaccine.
    - Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are prohibited during the study.
20. For dose expansion patients who will have tumor biopsies collected:
    - ECOG performance status >1.

- Activated partial thromboplastin time (aPTT) or plasma thromboplastin (PT) outside the institution's standard of care.
- Platelet count <75,000/μL.
- Known bleeding diathesis or history of abnormal bleeding, or any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure.
- Ongoing therapy with any anticoagulant or antiplatelet agents (eg, aspirin, clopidogrel, coumadin, heparin, or warfarin) that cannot be held to permit tumor biopsy.

9.0 STUDY DRUG

9.1 Study Drug Administration

All protocol-specific criteria for administration of study drugs must be met and documented before study drug administration. Study drugs will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

9.1.1 TAK-659

TAK-659 will be dosed PO QD in 28-day cycles. TAK-659 should be taken on an empty stomach at least 1 hour before and no sooner than 2 hours after ingestion of food and/or beverages other than water. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed dose. Patients should swallow the tablets whole; the tablets should not be chewed, crushed, or manipulated in any way before swallowing. Administration of the tablets will be guided by the dosing tables included in the Pharmacy Manual.

Patients should be instructed to take TAK-659 at approximately the same time each day and to not take more than the prescribed dose at any time. On clinic visit days, patients should be instructed to hold their dose until predose assessments are performed in the clinic, except for the Cycle 1 Day 8 visit for patients enrolled in expansion cohorts: for this visit, patients should be instructed to take their TAK-659 dose at home before their clinic visit. The intent of this exception is to ensure that blood PK samples are collected among different patients at random times after TAK-659 dosing for purposes of population PK analyses.

9.1.2 Nivolumab

The previously approved fixed-dose regimen of nivolumab in the United States is 3 mg/kg IV Q2W. Recently, the US FDA modified the dosage regimen for nivolumab for the currently approved indications for renal cell carcinoma, metastatic melanoma, and NSCLC. The approval modifies the Dosage and Administration section of the label by replacing the single-dose regimen of nivolumab (3 mg/kg IV Q2W) with the new recommended regimen of 240 mg IV Q2W until disease progression or intolerable toxicity for renal cell carcinoma, metastatic melanoma, and NSCLC [17].

The approval was based on population PK analyses and dose/exposure-response analyses demonstrating the comparability of the PK exposure, safety, and efficacy of the proposed new dosing regimen with the previously approved regimen. On the basis of simulations by the population PK model, the US FDA determined that the overall exposure with the 240 mg Q2W fixed dose is similar (<6% difference) to the 3 mg/kg Q2W dose. The difference in exposure is not likely to have a clinically meaningful effect on safety and efficacy because dose/exposure response relationships appear to be relatively consistent in these 2 indications. (US Food and Drug Administration. Modification of the Dosage Regimen for Nivolumab. fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm520871.htm Accessed 23 March 2017.)

In this study, patients receiving the combination therapy will receive 3 mg/kg IV dosing over 60 minutes every 2 weeks (Day 1 and Day 15 of each 28-day cycle). If the 240 mg fixed-dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg based on change in clinical practice and discussion between the investigator and sponsor. On days on which both TAK-659 and nivolumab are administered, the TAK-659 dose will be administered first followed by the nivolumab infusion (infusion to begin within 30◦minutes after the TAK-659 dose). For patients participating in the 2-week monotherapy run-in with TAK-659, the first dose will be on Cycle 1 Day 15.

9.2 Missed Doses and Infusion Delays

If a patient does not take the TAK-659 dose at his/her scheduled dosing time (±6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments on that day or subsequent days to account for the missed dose, for example, by taking a double dose of TAK-659 on the following day. Patients should record any skipped doses in their dosing diaries (see the Study Manual) and resume dosing at the next scheduled time with the prescribed dosage.

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after TAK-659 ingestion, patients should not re-dose following emesis and should record the time of the emesis in his/her dosing diary (see the Study Manual). Patients should resume dosing at the next scheduled time with the prescribed dosage.

Patients with nivolumab infusion delays of greater than 6 weeks should normally discontinue treatment and enter the Follow-up period, with the exception of cases where benefit-risk may justify continued study therapy (eg, patient deriving clinical benefit who requires prolonged steroid taper for management of non-DLT AEs). These situations require consultation and agreement between the investigator and medical monitor.

9.3 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE version 4.03, effective 14 June 2010 [35]. These criteria are provided in the Study Manual. DLT is defined as any of the following events that are considered by the investigator to be at least possibly related to therapy with study drug (either TAK-659 or nivolumab or both). AEs in which the relationship to study drug cannot be ruled out should be considered possibly related to study drug.

- Grade 4 neutropenia (ANC <500 cells/mm^3) unresolved to ≤Grade 1 (ANC >1500 cells/mm^3) or baseline for more than 7 consecutive days in the absence of growth factor support.
- ≥Grade 3 neutropenia (ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as an oral temperature ≥38.5°C.
- Grade 4 thrombocytopenia (<25,000/mm^3) unresolved to ≤Grade 1 (>75,000/mm^3) or baseline for more than 7 consecutive days or a platelet count <10,000/mm^3 at any time.
- ≥Grade 3 thrombocytopenia (<50,000/mm^3) with clinically significant bleeding.

- Grade 4 anemia.
- Any Grade 3 or greater nonhematological toxicity with the following exceptions:
  - ≥Grade 3 nausea and/or vomiting that has not resolved to <Grade 3 within 72 hours upon optimal antiemetic and/or antidiarrheal treatment. (All patients should receive optimal antiemetic and/or antidiarrheal treatment according to standard of care. An optimal antiemetic regimen is defined as one that employs both a 5-hydroxytryptamine 3 serotonin receptor [5-HT_3] antagonist and a corticosteroid given in standard doses and according to standard schedules.)
  - Transient Grade 3 fatigue (≤1 week).
  - Grade 3 arthralgia/myalgia.
  - Asymptomatic lipase elevation (<Grade 4) in the absence of significant amylase elevation (<Grade 3) considered not dose limiting following agreement between the sponsor and investigators.
  - Asymptomatic amylase elevation (<Grade 4) in the absence of significant lipase elevation (<Grade 3) considered not dose limiting following agreement between the sponsor and investigators.
  - Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3) considered not dose limiting following agreement between the sponsor and investigators.
  - Isolated ≥Grade 3 abnormalities of other laboratory parameters that resolve to ≤Grade 1 in ≤7 days without clinical sequelae or need for therapeutic intervention considered not dose-limiting following agreement between the sponsor and investigators.
  - Grade 3 rash lasting ≤7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.

The DLT evaluation period is 28 to 42 days during the first cycle of TAK-659 plus nivolumab treatment. Although DLT-like events may occur at any point during treatment, only DLTs observed during Cycle 1 of treatment will influence dose escalation decisions and MTD determination per the 3+3 escalation schema. While the primary escalation schema is designed to determine MTD based on Cycle 1 DLTs, cumulative toxicity beyond Cycle 1 will be considered in assessing the overall tolerability of a given dose and consequently influence the dose escalation decision and selection of the RP2D.

9.4 Dose Escalation Rules

The dose escalation phase of the study is designed to determine the DLTs and MTD and/or RP2D of TAK-659 when given in combination with nivolumab. Approximately 9 to 12 patients are expected to be enrolled into the TAK-659 escalation cohorts based on the planned 2 dose-level escalation for TAK-659 (Table 9.a) when administered with a weight-based dose regimen of nivolumab (3 mg/kg IV); the exact number of patients to be enrolled will depend on the actual

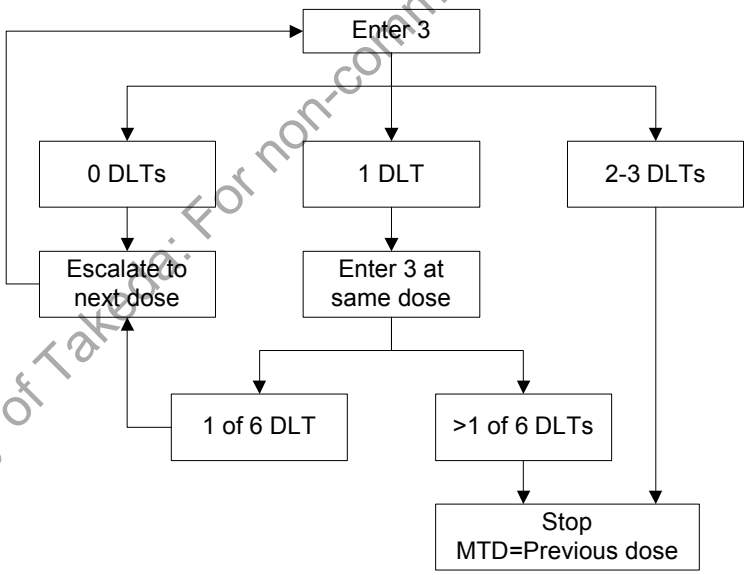
number of dose-level cohorts required, which may deviate from the dose escalation plan based on toxicities and the PK/pharmacodynamic results observed during the initial dose levels. Following the determination of the TAK-659 RP2D in combination with 3 mg/kg nivolumab, nivolumab may be evaluated at a fixed dose of 240 mg following discussion between the investigator and sponsor and administered in combination with TAK-659 at the determined RP2D to approximately 3 to 6 patients.

The starting dose of nivolumab will be 3 mg/kg IV Q2W on Day 1 and Day 15 of 28-day cycles. The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme (see Figure 9.a), and dosing of TAK-659 will increase to 100 mg QD (Table 9.a) provided that the safety and tolerability of the 60 mg dose has been demonstrated.

1. If 0 of 3 patients experiences DLT, dose escalation will proceed to the next higher dose level, at which 3 patients will be enrolled.
2. If 1 of 3 patients experiences DLT, 3 more patients will be enrolled at that same dose level.
3. Escalation will continue if 1 of 6 patients experiences DLT.
4. If 2 or more patients at any dose level experience DLT, dosing will stop, and the previous dose level will be considered the MTD. Following consultation between the sponsor and investigators, either the previous dose level will be considered the MTD (if 6 or more patients have been studied at that dose level), the previous dose level will be expanded (if fewer than 6 patients have been studied at that dose level), or a dose level intermediate between the current and the previous dose level will be evaluated.

Figure 9.a is a diagrammatical representation of these rules.

Figure 9.a Dose Escalation Algorithm



Dose escalation of TAK-659 will not exceed 100 mg QD, the single-agent MTD for TAK-659 as established in the FIH dose escalation study of TAK-659 (C34001). More conservative dose escalation—including evaluation of the intermediate dose (eg, 80 mg QD) or de-escalation at a 20 mg increment from the starting dose of 60 mg QD of TAK-659 (eg, 40 mg) if determined to be not tolerable, expansion of an existing dose level, or an alternative regimen/schedule—is permissible following written confirmation of discussions between the sponsor and the investigators if such measures are needed for patient safety, for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659, or for adjustment based on the initial characterization of PK of TAK-659 in combination with nivolumab.

Dose escalation continues until the MTD is reached, or until 100 mg QD of TAK-659 (the MAD) is determined to be safe and tolerable, or until an RP2D, if different from the MTD/MAD, has been identified on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. At least 6 patients will be evaluated at the RP2D (the MTD, MAD, or at a lower dose as determined) before making a decision to advance further dose expansion.

Escalation will be based on safety as determined in Cycle 1. While the primary escalation schema is designed to determine a classical Cycle 1-based MTD, dose escalation may be halted at any time after consultation between the sponsor and investigators if cumulative toxicity beyond Cycle 1 indicates that a given dose exceeds a tolerable RP2D. In case of immune-related AEs, which often occur during nivolumab treatment with a typical onset beyond the first 28 days of treatment, evaluation of the incidence, severity, onset, and frequency of associated dose modification/discontinuation of nivolumab in Cycle 1 and beyond will contribute to the general tolerability assessment for a given dose cohort of TAK-659 plus nivolumab, which consequently may influence the dose escalation decision and RP2D determination following discussions between investigators and the sponsor.

Table 9.a Planned Dose Levels of TAK-659

Dose Level	Dose (Unit)
-1	40 mg
1	60 mg
2	100 mg (a)

More conservative dose escalation, including evaluation of intermediate doses, dose de-escalation at a 20 mg increment from the starting dose of 60 mg QD, if determined to be not tolerable, expansion of an existing dose level, and an alternative dose schedule/regimen are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity and preliminary PK and efficacy of TAK-659.
(a) The maximal dose to be assessed is 100 mg QD of TAK-659.

DLT-evaluable patients in each dose cohort will consist of patients who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if in Cycle 1, the patient has been treated with 75% of planned doses of TAK-659 in Cycle 1 (depending on cycle length) plus 2 doses of nivolumab, and observed for ≥28 to 42 days (unless DLT occurs before the

end of the 28- to 42-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur. Patients who do not meet these minimum requirements will be regarded as ineligible for DLT evaluation for the given dose cohort and may be replaced within the same cohort.

The dose escalation is planned for TAK-659 only. While the MTD/MAD/RP2D of TAK-659 are being determined, the starting dose of nivolumab will be 3 mg/kg IV. The fixed dose of nivolumab (240 mg) might be used as an equivalent weight-based dose of nivolumab (3 mg/kg) for further evaluation and determination of the TAK-659 MTD/RP2D following discussions between the investigators and the sponsor.

9.5 Dose Modification Guidelines

Patients on study drug(s) in both Part 1 (dose escalation) and Part 2 (dose expansion) of the study will be evaluated weekly during Cycle 1 (Days 1, 8, 15, and 22); on Day 1 and Day 15 of Cycles 2, 3, and 4; and on Day 1 of Cycle 5 and beyond. In cases in which either TAK-659 or nivolumab monotherapy continues following discontinuation of the other drug due to toxicities, patients will be evaluated at monthly visits on Day 1 of each cycle (with the exception of Cycle 1, in which weekly visits are required) until PD or discontinuation due to other reasons.

Toxicities are to be assessed according to the NCI CTCAE version 4.03, effective 14 June 2010 [35]. The causal relationship of each AE should be assessed in relation to TAK-659, nivolumab, or both so that dose modifications can be made accordingly. Administration and dose modification of nivolumab will follow prescribing information for nivolumab and also the guidance described in this section (see Section 9.8). Dose modification guidelines for hematologic and nonhematologic toxicities are described separately below for both study drugs based on the type and severity of AEs, causality determination by investigators, and safety and tolerability profiles of each of the study drugs. Of note, only dose interruption and discontinuation, not dose reductions, are allowed for nivolumab. Further clarification can be obtained in consultation with the sponsor project clinician (or designee).

Per the dose modification guidelines, patients who have the study drug held because of treatment-related or possibly related AEs may resume study drug after resolution of the AE; they may either maintain the same dose level or have doses of study drug reduced by at least 1 dose level (dose reduction allowed only for TAK-659). When a dose reduction of TAK-659 occurs, the TAK-659 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation, or at a 20 mg increment (Table 9.a). During Part 2, depending on the MTD/RP2D determined during Part 1, TAK-659 dose reduction will follow, in general, an increment of 20 mg, or up to a 50% reduction from the previous dose, depending on the RP2D as determined in Part 1 (Table 9.b). For example, if 100 mg QD is the RP2D, the first dose reduction will lower the dose to 80 mg QD. If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 can be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of TAK-659 (eg, 60 mg, if 100 mg QD is the RP2D). Based on the data and experience gathered from the Part 1 dose escalation, alternative dose reduction levels could be determined if deemed more appropriate

following discussions between investigators and the sponsor, and will be communicated via a protocol amendment. Up to 2 dose level reductions of TAK-659 due to AEs are generally recommended. If more than 2 dose reductions of TAK-659 are needed to manage TAK-659-related AEs, discontinuation of treatment should be considered unless the treating physician considers that the patient may benefit from continued study treatment, after resolution of AEs to <Grade 1 or baseline, and consults with the sponsor.

If 1 study drug is delayed because of toxicity attributed to its use, the other study drug is to be administered as scheduled unless otherwise specified. If that study drug is either held or missed because of an AE, please refer to the CRF completion guidelines and the SOE for details of cycle length and requirements for the start of a new cycle.

During dose escalation, the Cycle 1 DLT-evaluation period typically will be 28 days. However, in the event of a nivolumab dosing interruption, a cycle length may be extended. If the second dose of nivolumab planned for Cycle 1 Day 15 is held and then dosed within the original 28-day cycle, the dose will be considered the second dose of Cycle 1, leading to a cycle with a maximum total of 42 days. The actual doses of TAK-659 received during this 28- to 42-day DLT-evaluation period will be assessed against the planned doses of TAK-659 (daily dose × cycle days) to determine whether the patient has received at least 75% of planned doses of TAK-659 to be DLT evaluable. When the second dose is administered, procedures at the original scheduled visit (ie, Cycle 1 Day 15) should be performed. If the second dose of nivolumab is interrupted for a period of time that extends beyond the original 28-day cycle, this dose will be considered missed. In this case, independent of whether the patient has received 75% planned dose of TAK-659, the patient will receive only one of the 2 nivolumab doses planned for Cycle 1 and, therefore, is not evaluable for DLT.

In Cycle 2 and beyond (during both the dose escalation and dose expansion phases of the study), if a nivolumab dose is delayed because of AEs, when the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if nivolumab is delayed past the next scheduled time point per protocol and TAK-659 dosing is also interrupted, the next scheduled time point will be delayed until dosing with either drug resumes.

Table 9.b Planned Dose Levels of TAK-659 in the Expansion Phase

Dose Reduction Levels	TAK-659	TAK-659 (if RP2D=100 mg [c])
RP2D	RP2D TBD (a)	100 mg
(–) 1 dose level	RP2D-20 mg (b)	80 mg
(–) 2 dose level	RP2D-40 mg (b)	60 mg

(a) TBD=to be determined during dose escalation.
(b) TAK-659 dose reduction will follow, in general, a decrement of 20 mg, or up to a 50% reduction from the previous dose, depending on the RP2D as determined in dose escalation.
(c) Dose reduction levels are listed if the RP2D for TAK-659 in combination with nivolumab is 100 mg QD.

9.5.1 Part 1 Intrapatient Dose Escalation

Once the RP2D of TAK-659 is determined when administered in combination with nivolumab, all patients in Part 1 actively receiving TAK-659 at a dose lower than the RP2D for a minimum of 2 cycles, in the absence of PD or unacceptable treatment-related toxicity per the investigator, may dose escalate to the RP2D at the investigator's discretion and with the sponsor's approval. Patients in whom an increase in the dose of TAK-659 is being considered must have treatment-related AEs resolved to ≤Grade 1 or baseline, or to a level that is acceptable to the investigators (non-hematologic toxicity must be ≤Grade 2).

9.5.2 Dose Modification for Hematologic and Nonhematologic Toxicity: TAK-659 and Nivolumab

A decision regarding dose modification of study drug(s) will be dependent upon the toxicity and its onset, severity, and time course. The causal relationship of any reported events (AEs or SAEs) should be assessed by the investigator in relation to TAK-659, nivolumab, or both. Dose modification of study drug(s) is required only when the toxicity is attributed to study drug(s) based on the investigator's assessment. Study drug(s) can be held at the investigator's discretion for high-grade, non-drug-related toxicities if it is viewed to be necessary in the clinical management of the event. However, when study drug(s) resumes after resolution of the non-drug-related event, no dose reduction of study drug(s) is needed. If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines and the causal relationship to 1 or both study drugs. Guidelines for dose modifications for hematologic and nonhematologic toxicity are presented in Table 9.c and Table 9.d, respectively.

When the dose of study drug(s) is withheld based on the criteria in Table 9.c and Table 9.d, clinical and laboratory re-evaluation should be repeated at least weekly or more frequently until the toxicity resolves to ≤Grade 1 or baseline, or to an acceptable level according to the investigator's assessment. Upon recovery, study drug(s) may be reinitiated either at the same dose level or at a reduced dose level (dose reduction for TAK-659 only). When a dose reduction of TAK-659 is required, no re-escalation of dose will be permitted.

For treatment-related, Grade 4, nonhematologic toxicities, dose reduction of TAK-659 by more than 2 dose levels or treatment delay for >6 weeks for either or both drugs will, in general, require that study treatment be permanently discontinued. If, in the opinion of the investigator and the sponsor (project clinician or designee), it is in the patient's best interest to continue study treatment, then the study drug(s) can be resumed at a reduced dose of TAK-659 by at least 1 dose level and/or at the same dose and schedule of nivolumab after recovery of the toxicity or toxicities in question to Grade 1 or baseline. However, no exceptions should be made in the case of adverse reactions that result in nivolumab discontinuation as required per the most recent nivolumab USPI [17] or SmPC [18]. In particular, the study discontinuation required due to the immune-related AEs or infusion reactions associated with the use of nivolumab should not be overridden.

For transient lab value abnormalities that, based on investigator assessment, are not clinically significant or are most probably related to disease and not the drug, continuation of therapy

without following the dose modification guidelines is permissible upon discussion with the sponsor.

Table 9.c Guidelines for TAK-659 and Nivolumab Dose Modifications for Hematologic Toxicity

NCI CTCAE Grade	TAK-659 Dose Modification	Nivolumab Dose Modification
Neutrophil Count (ANC) Decreased		
Grade 1 & 2 (1000/mm^3 to <LLN)	• Continue TAK-659 at same dose.	• Continue nivolumab at same dose and schedule.
Grade 3 (500 to <999/mm^3)	• Hold TAK-659 until resolved to ≥1500/mm^3 or baseline: • If resolved ≤7 days, same dose. • If resolved >7 days, reduce by 1 dose level. • If recurrence, reduce by 1 dose level.	• Continue nivolumab at same dose and schedule.
Grade 4 (<500/mm^3)	• Hold TAK-659 until resolved to ≥1500/mm^3 or baseline, then reduce by 1 dose level.	• Hold nivolumab until resolution to ≥1500/mm^3 or baseline, then resume at same dose and schedule. • If resolved >7 days after start of event and the causality is solely attributed to nivolumab, discontinuation of nivolumab should be considered.
Febrile neutropenia (<1000/mm^3; fever ≥38.5°C)	• Hold TAK-659 until resolved to ≥1500/mm^3 or baseline, and fever/infection recovered, then reduce by 1 dose level.	• Hold nivolumab until resolution to ≥1500/mm^3 or baseline and resolution of fever/infection.
Platelet Count Decreased		
Grade 1 & 2 (50,000/mm^3 to <LLN)	• Continue TAK-659 at same dose.	• Continue nivolumab at same dose and schedule.
Grade 3 (25,000-49,999/mm^3)	• Hold TAK-659 until resolved to ≤Grade 1 (≥75000/mm^3 or baseline, then: ○ If resolved ≤7 days, same dose. ○ If resolved >7 days, reduce by 1 dose level.	• Hold nivolumab until resolution to ≥75000/mm^3 or baseline, then resume at same dose and schedule. • If resolved in >7 days and the causality is solely attributed to nivolumab, discontinuation of nivolumab should be considered.
Grade 4 (<25,000/mm^3)	• Hold TAK-659 until resolved to ≤Grade 1 or baseline, then reduce by 1 dose level.	• Hold nivolumab until resolution to ≥75000/mm^3 or baseline, then resume at same dose and schedule. • If resolved in >7 days and the causality is solely attributed to nivolumab, discontinuation of nivolumab should be considered.

Table 9.c Guidelines for TAK-659 and Nivolumab Dose Modifications for Hematologic Toxicity (continued)

NCI CTCAE Grade	TAK-659 Dose Modification	Nivolumab Dose Modification
Anemia		
Grade 3	• Hold TAK-659 until resolved to ≤Grade 1 or baseline, then: ○ If resolved ≤7 days, same dose. ○ If resolved >7 days, reduce by 1 dose level.	• Hold nivolumab until resolution to ≤Grade 1 or baseline, then resume at same dose and schedule.
Grade 4	Consider permanently discontinuing study treatment based on causality determination except when the investigator determines that the patient is obtaining clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued:	
	• Hold TAK-659 until resolved to ≤Grade 1 or baseline, then reduce by 1 dose level.	• Hold nivolumab until resolution to ≤Grade 1 or baseline, then resume at same dose and schedule. • If resolved in >7 days and the causality is solely attributed to nivolumab, discontinuation of nivolumab should be considered

LLN=lower limit of normal.

Table 9.d Guidelines for TAK-659 and Nivolumab Dose Modifications for Nonhematologic Toxicity

NCI CTCAE Grade (in Alphabetic Order)	TAK-659 Dose Modification (a)	Nivolumab Dose Modification
Adrenal Insufficiency		
Moderate symptoms; medical intervention indicated (Grade 2)	• Continue TAK-659 at same dose.	• Hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule.
Severe symptoms; hospitalization indicated; or life threatening (Grade 3 or 4)	• Hold TAK-659 until resolution, then resume TAK-659 at the same dose and schedule.	• Discontinue nivolumab.
Colitis		
With moderate or severe symptoms (Grade 2 or 3 diarrhea)	• If Grade 2, optimize antidiarrheal therapy and continue TAK-659 at same dose. • If Grade 3, follow guidelines under Other Nonhematologic Toxicities.	• If Grade 2, hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule. • If Grade 3, discontinue nivolumab
With Grade 4 symptoms (Grade 4 diarrhea)	• Follow guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Encephalitis		
Moderate or severe symptoms; neurologic signs or symptoms (Grade 2 or 3)	• If unrelated to TAK-659 or Grade 2, continue TAK-659 at same dose. • If possibly related to TAK-659 and Grade 3, follow guidelines under Other Nonhematologic Toxicities.	• If Grade 2, hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule. • If Grade 3, discontinue nivolumab-
Immune mediated encephalitis (Grade 4)	• If unrelated to TAK-659, hold until resolution to Grade 0 or 1, then continue TAK-659 at same dose. • If related to TAK-659, follow guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.

Table 9.d Guidelines for TAK-659 and Nivolumab Dose Modifications for Nonhematologic Toxicity (continued)

NCI CTCAE Grade (in Alphabetic Order)	TAK-659 Dose Modification (a)	Nivolumab Dose Modification
Hepatotoxicity/Hepatitis		
ALT and/or AST >3×ULN to ≤5×ULN (Grade 2)	• Continue TAK-659 at the same dose.	• Hold nivolumab until both ALT and AST ≤1.5×ULN, then resume nivolumab at the same dose and schedule.
ALT and/or AST >5×ULN to ≤20×ULN (Grade 3)	• Follow TAK-659 guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Bilirubin >1.5×ULN to 3×ULN (Grade 2)	• Continue TAK-659 at the same dose.	• Hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule.
Bilirubin >3×ULN (Grade 3)	• Follow TAK-659 guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Hypophysitis		
Grade 2 or 3	• Continue TAK-659 at the same dose.	• Hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule.
Grade 4	• If unrelated to TAK-659, hold until resolution to Grade 0 or 1, then continue TAK-659 at same dose. • If related to TAK-659, follow guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Nephritis and Renal Dysfunction		
Serum creatinine >1 to 1.5×ULN to 6.0×ULN (Grades 1-3)	• If unrelated to TAK-659, continue TAK-659 at same dose. • If related to TAK-659, follow guidelines under Other Nonhematologic Toxicities.	• If Grade 1, continue nivolumab but monitor creatinine weekly. If Grade 2-3, hold nivolumab until Grade 1, then resume nivolumab at the same dose and schedule.
Serum creatinine >6.0×ULN (Grade 4)	• If unrelated to TAK-659, hold TAK-659 until resolution to <Grade 1, then continue TAK-659 at same dose. • If related to TAK-659, follow guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.

Table 9.d Guidelines for TAK-659 and Nivolumab Dose Modifications for Nonhematologic Toxicity (continued)

NCI CTCAE Grade (in Alphabetic Order)	TAK-659 Dose Modification (a)	Nivolumab Dose Modification
Pneumonitis		
Symptomatic, medical intervention, limiting instrumental ADL (Grade 2)	• Hold TAK-659 until resolution to ≤Grade 1 or baseline, then resume TAK-659 at same dose.	• Hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule.
Severe – requiring oxygen support; or life threatening requiring urgent intervention (Grade 3 or 4)	• Follow TAK-659 guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Rash		
Rash covering >30% body surface area (Grade 3)	• Follow TAK-659 guidelines under Other Nonhematologic Toxicities.	• Hold nivolumab until Grade 0 or 1, then resume nivolumab at the same dose and schedule.
Rash requiring antibiotics; life threatening (Grade 4)	• Follow TAK-659 guidelines under Other Nonhematologic Toxicities.	• Discontinue nivolumab.
Other Nonhematologic Toxicities		
All other Grade 3 nonhematologic toxicities with the exception of: • Grade 3 nausea, vomiting, and diarrhea resolved to ≤Grade 1 or baseline within 2 days with optimal antiemetics and antidiarrheals following SOC. • Transient Grade 3 fatigue (lasting <3 days). • Asymptomatic lipase elevation (<Grade 4) in the absence of significant amylase elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators. • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3) considered not dose limiting following agreement between sponsor and investigators	Hold TAK-659 until resolution to ≤Grade 1 or baseline. Reduce TAK-659 by 1 dose level. For the exceptions, maintain the dose level.	Hold nivolumab if determined to be related to nivolumab until resolution to Grade 0 or 1, then resume nivolumab at same dose. Permanent discontinuation should be considered for: • Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period OR requires systemic treatment • Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation • Recurrence of same Grade 3 toxicity. • Grade 3 toxicities and dose interruptions that persist for ≥6 weeks.

Table 9.d Guidelines for TAK-659 and Nivolumab Dose Modifications for Nonhematologic Toxicity (continued)

NCI CTCAE Grade (in Alphabetic Order)	TAK-659 Dose Modification (a)	Nivolumab Dose Modification
Other Nonhematologic Toxicities (continued)		
• Grade 3 hypophosphatemia resolved to Grade ≤1 or baseline value within 72 hours with phosphate repletion. • Other Grade 3 asymptomatic enzyme elevations not considered clinically significant following agreement between sponsor and investigator.		• Toxicities that require 10 mg per day or greater prednisone or equivalent for >12 weeks.
All other Grade 4 nonhematologic toxicities	Consider permanently discontinuing TAK-659 based on causality determination except when the investigator determines that the patient is obtaining a clinical benefit and has discussed this with the project clinician or designee. If the patient is not discontinued, TAK-659 dose will be reduced to at least 1 dose level lower when toxicity resolves to ≤Grade 1 or baseline.	Consider permanently discontinuing nivolumab based on causality determination.

ADL=activities of daily living, SOC=standard of care.

In general, the study drug(s) will resume only after the resolution of AEs to ≤Grade 1 or baseline or as specified in these dose modification guidelines. However, retreatment with study drug(s) could start when the AEs are resolved to a level deemed acceptable by the investigator based on consideration of the individual patient situation and discussions/agreement with the sponsor project clinician.

The recommendations in these dose modification guidelines and in the current nivolumab USPI [17] and SmPC [18] should be strictly followed. However, in individual patient cases, following discussion and agreement between the investigator and the Millennium project clinician, alternative dose modifications may be recommended to maximize exposure to study treatment while protecting patient safety. However, nivolumab discontinuation as required per the most recent nivolumab USPI [17] or SmPC [18] should not be overridden.

9.6 Concomitant Medications and Procedures

During the course of the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken while on study. All concomitant medications (defined as any medication given during

the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the informed consent form (ICF) through 28 days after the last dose of study drug. However, if a patient experiences immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocriopathies, nephritis, rash, and encephalitis as described in the nivolumab USPI [17]), they will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first. During this AE follow-up period, concomitant medications and procedures should also be collected.

The following restrictions apply during the study:

- Any antineoplastic therapy other than TAK-659 is prohibited on study. If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD) is not permitted during study. Palliative radiotherapy for local pain/symptom control in a preexisting nontarget lesion, if required, may be considered after discussion with the sponsor's clinical representative. Details of the palliative radiotherapy should be documented in the source records and eCRF, including dates of treatment, anatomical site, dose administered and fractionation schedule, and associated AEs.
- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) is not recommended at the study start. Patients who experience severe and/or febrile neutropenia during the study can be managed with growth factor support if needed, including prophylactic use of growth factor, in accordance with American Society of Clinical Oncology (ASCO) guidelines.
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications required as an ongoing therapy is not permitted with the following exceptions and clarification:
  - Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
  - Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone or equivalents.
  - A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy or prevention of infusion reactions) or for treatment of non-autoimmune conditions (eg, allergic reaction caused by contact allergen or drug-related nausea and/or vomiting) are permitted.
- Non-oncology vaccine therapies for prevention of infectious diseases (eg, HPV vaccine) within 4 weeks of study drug administration.
  - The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction.

  - Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted but must be discussed with the sponsor's medical monitor and may require a washout period before and after administration of vaccine.

- Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A should be avoided in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix G for a nonexhaustive list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA Draft DDI Guidance.
  - Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole.
  - Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin.
  - Antimycobacterials: rifabutin, rifampin, rifapentine.
  - Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone.
  - Antidepressant: nefazodone.
  - Immunosuppressant: cyclosporine.
  - Calcium channel blockers: diltiazem, felodipine, mibefradil, verapamil.
  - Antiarrhythmics: amiodarone, dronedarone, quinidine.
  - Antiplatelet: ticagrelor.
  - Antilipid: avasimibe.
  - Other cardiovascular: captopril, carvedilol, ranolazine.
  - Vasopressin antagonist: conivaptan.
  - Food/Herbals/Supplements: grapefruit-containing food and beverages, St. John's wort, quercetin.

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and in Appendix G may be used for AE management provided there is no appropriate alternative treatment available per the investigator's judgment and the dosing is not concurrent with TAK-659. This situation requires discussion between the investigator and the sponsor's medical monitor, and the discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

Note that medications used to treat HIV or hepatitis C infection are not listed above or in Appendix G because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the

list above and in Appendix G, then its use must be discussed with the medical monitor or designee to assess the relative benefit and risk.

9.7 Precautions and Restrictions

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

It is not known what effects TAK-659 has on human pregnancy or development of the embryo or fetus; therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception throughout defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice one highly effective method of contraception and one additional effective (barrier) method (see Appendix H) at the same time, from the time of signing of the informed consent form through 180 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9.8 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, G-CSF, blood products (red blood cell [RBC] and platelet transfusions), and pain

medications are permitted as needed per American Society of Hematology (ASH)/ASCO guidelines or local institutional practice. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation. Nivolumab is associated with immune-related AEs, which may be managed per clinical judgment of the investigator in accordance with the institutional guideline and the most recent nivolumab USPI [17] and SmPC [18]. Additional treatment algorithms for use in conjunction with clinical judgment are provided below. If dose modification of study drug(s) is necessary as a result of the events detailed below, please refer to Section 9.5.

9.8.1 Nausea and/or Vomiting

This study will not initially employ prophylactic anti-emetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea and/or vomiting will be actively managed by employing optimal antiemetic treatment based on local standard practice. Additionally, anti-emetics may be used prophylactically as clinically indicated following the occurrence of a first event of study drug-related or possibly related nausea and/or vomiting. An optimal antiemetic regimen is defined as one that employs both a 5-HT_3 antagonist and a corticosteroid given in standard doses and according to standard schedules.

9.8.2 Anemia, Thrombocytopenia, and/or Neutropenia

Hemoglobin and blood counts should be monitored regularly as outlined in Appendix A with additional testing obtained according to standard clinical practice. Administration of TAK-659 and nivolumab should be modified per dose modification guidance in the protocol when anemia, thrombocytopenia, or neutropenia occur (see Table 9.c). RBC transfusion and use of erythropoietin to manage severe anemia, platelet transfusion to prevent and minimize bleeding in case of severe thrombocytopenia, and myeloid growth factor (eg, G-CSF, GM-CSF) support to treat severe and/or febrile neutropenia are permitted per ASH/ASCO guidelines, as necessary. However, it should be noted that prophylactic use of myeloid growth factors should be avoided during the first cycle of dose escalation (see Section 9.6).

9.8.3 Diarrhea

Prophylactic antidiarrheals will not be used in this study; however, patients should be instructed to take loperamide or comparable antidiarrheal medication according to institutional or local practice, once infectious causes are ruled out. Adequate fluid intake should be maintained to avoid dehydration, and any fluid deficit should be corrected before initiation of treatment with study drug and during treatment. Refer to Section 9.8.8.2 for management of diarrhea if immune-mediated colitis occurs during treatment.

9.8.4 Edema (Including Periorbital)

Peripheral and periorbital edema have been observed in patients treated with TAK-659. Management of the event, if it occurs, should follow the standard local practice, and dose modification should proceed following the dose modification guidelines in Table 9.d.

9.8.5 Rash With or Without Pruritus

Prophylactic measures should be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤10 mg per day or equivalent) is permitted. Refer to dose modification guidelines in Table 9.d for occurrence of Grade 3 or 4 rash. Refer to Section 9.8.8.8 for management of rash if immune-mediated dermatitis occurs during treatment.

9.8.6 Hypophosphatemia

Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise, refer to dose modification guidelines in Table 9.d.

9.8.7 Enzyme Elevations

9.8.7.1 Transaminase, Amylase, Lipase, and CPK Elevations

Elevations of transaminases, amylase, lipase, and CPK have been observed in patients treated with TAK-659. Events are generally asymptomatic and reversible with dose interruption. See dose modification guidelines in Table 9.d.

9.8.7.2 Lactate Dehydrogenase Elevations

Lactate dehydrogenase (LDH) elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic, and their clinical significance is unknown. No action, such as dose interruption, has been taken as a result of increased LDH; however, LDH elevation is reversible on the basis of experience in patients who had TAK-659 interrupted for other reasons.

9.8.8 Immune-Mediated Adverse Reactions

Immune-mediated AEs can occur with nivolumab, both during treatment and following discontinuation. For any suspected immune-mediated AEs, other causes should be excluded. Based on the severity of the adverse reaction, nivolumab should be permanently discontinued or withheld, high-dose corticosteroids should be administered, and if appropriate, hormone-replacement therapy should be initiated. Upon improvement to Grade 1 or less, a corticosteroid taper should be initiated and continued over at least 1 month. Consideration should be given to restarting nivolumab after completion of the corticosteroid taper based on the severity of the event. Recommendations for dose modification of TAK-659 during the occurrence of immune-mediated AEs are provided in Section 9.5.

9.8.8.1 Immune –Mediated Pneumonitis

Immune-mediated pneumonitis can occur with nivolumab treatment. Patients on study will be monitored closely. Oxygen saturation will be monitored and recorded at the frequency specified in the Schedule of Events (Appendix A).

If immune-mediated pneumonitis occurs, nivolumab should be permanently discontinued for a severe (Grade 3) or life-threatening (Grade 4) event and withheld until resolution for a moderate (Grade 2) event. Corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater pneumonitis. For Grade 3 or Grade 4, non-corticosteroid immunosuppressive medication can be added if symptoms do not improve or if they worsen after 2 days of corticosteroid treatment. Bronchoscopy, lung biopsy, and prophylactic antibiotics for opportunistic infection should be considered. When the event resolves to baseline, the corticosteroid should be tapered over at least 1 month. For Grade 2 pneumonitis responsive to corticosteroids, nivolumab can be resumed after the taper. However, if Grade 2 pneumonitis does not improve after 2 weeks of corticosteroid treatment or worsens, nivolumab should be permanently discontinued.

9.8.8.2 Immune-Mediated Colitis

Immune-mediated colitis can occur with nivolumab treatment. Patients on study will be monitored for diarrhea and symptoms suggestive of immune-mediated colitis. The severity levels should be graded as below based on the NCI CTCAE criteria for diarrhea and colitis:

Grade 1: diarrhea: increase of <4 stools/day over baseline; colitis: asymptomatic and clinical or diagnostic observations only, intervention not indicated.

Grade 2: diarrhea: increase of 4-6 stools/day over baseline; IV fluids indicated for <24 hours; not interfering with activities of daily living (ADL). Colitis: abdominal pain; mucus or blood in stool.

Grade 3: diarrhea: increase of ≥7 stools/day over baseline; IV fluids indicated for ≥24 hours; interfering with ADL. Colitis: severe abdominal pain; medical intervention indicated, peritoneal signs.

Grade 4: diarrhea and colitis: life threatening; urgent intervention indicated.

If immune-mediated colitis occurs, nivolumab should be permanently discontinued for a life-threatening (Grade 4) event, and withheld until resolution for a moderate (Grade 2) or severe (Grade 3) event. Serial stool cultures should be performed to rule out bacterial infections. For Grade 2 events, antidiarrheals and other symptomatic treatment should be administered. If symptoms persist for >5 days or recur, corticosteroids should be administered at a dose of 0.5 to 1 mg/kg/day prednisone equivalents; if worsening or no improvement occurs despite initiation of corticosteroids, the dose should be increased to 1 to 2 mg/kg/day prednisone equivalents. For Grade 3 or Grade 4, corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents. If Grade 4 persists for 3 to 5 days or recurs, non-corticosteroid immunosuppressive medication can be added. (Of note, the use of anti-tumor necrosis factor-α therapy should be avoided in the setting of perforation or sepsis.) Lower endoscopy and prophylactic antibiotics for opportunistic infection should be considered in the management of the event.

When symptoms improve to ≤Grade 1, study treatment can resume for Grade 2 or Grade 3 after at least 1 month of corticosteroid tapering. If Grade 3 persists for >3 to 5 days despite active clinical

intervention or if it recurs, nivolumab should be permanently discontinued. Dose modification of TAK-659 during the event will follow the guidelines in Section 9.5.

9.8.8.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis can occur with nivolumab treatment. Patients on study will be monitored for immune-mediated hepatitis by liver function tests performed at a frequency specified in the Schedule of Events (Appendix A). Severity levels are graded as below based on transaminase elevations, with or without concomitant elevation in total bilirubin:

Grade 1: AST or ALT >ULN to 3×ULN and/or total bilirubin >ULN to 1.5×ULN.

Grade 2: AST or ALT >3 to 5×ULN and/or total bilirubin >1.5 to 3×ULN.

Grade 3 or 4: AST or ALT >5×ULN and/or bilirubin >3×ULN; life-threatening consequences for Grade 4.

If immune-mediated hepatitis occurs, nivolumab should be withheld for moderate (Grade 2) and permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis. The frequency of the liver function test monitoring should increase to every 3 days for Grade 2 and every 1 to 2 days for Grade 3/4 events. Corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 3/4 or Grade 2 if it persists for >5 to 7 days or worsens. Study treatment can resume after at least 1 month of corticosteroid tapering when liver function test elevation returns to ≤Grade 1 or baseline. Prophylactic antibiotics should be considered for opportunistic infection when retreatment starts. Dose modification of TAK-659 during the event will follow the guidelines in Section 9.5.

9.8.8.4 Immune-Mediated Hypophysitis

Immune-mediated hypophysitis can occur with nivolumab treatment. If it occurs, corticosteroids should be administered at a dose of 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or greater hypophysitis. Nivolumab should be withheld for moderate (Grade 2) or severe (Grade 3) hypophysitis and permanently discontinued for life-threatening (Grade 4) hypophysitis.

9.8.8.5 Immune-Mediated Thyroid Disorders

Thyroid disorders, including hypothyroidism and hyperthyroidism, can occur with nivolumab treatment. If it occurs, hormone-replacement therapy for hypothyroidism should be administered. Medical management should be initiated for control of hyperthyroidism. There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism.

9.8.8.6 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus can occur with nivolumab treatment. If it occurs, insulin should be administered, and nivolumab should be withheld in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Nivolumab should be permanently discontinued for life-threatening (Grade 4) hyperglycemia.

9.8.8.7 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis can occur with nivolumab treatment. Patients on study will be monitored for immune-mediated nephritis by serum creatinine test as indicated in the Schedule of Events (Appendix A). If it occurs, other causes of creatinine elevation should be excluded. Severity levels should be graded as below:

Grade 1: creatinine >ULN and >baseline but ≤1.5×baseline.

Grade 2: moderate: creatinine >1.5 to 3×baseline; >1.5 to 3×ULN.

Grade 3: severe: creatinine >3×baseline; >3 to 6×ULN.

Grade 4: life threatening: creatinine >6×ULN.

Nivolumab should be withheld for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, and corticosteroids should be administered at a dose of 0.5 to 1 mg/kg/day prednisone equivalents. If the event is resolved to ≤Grade 1 in response to corticosteroids, nivolumab can resume after the corticosteroid has been tapered for at least 1 month. If worsening or no improvement occurs within 7 days of corticosteroid initiation, the dose of corticosteroids should be increased to 1 to 2 mg/kg/day prednisone equivalents, and nivolumab should be permanently discontinued. Nivolumab should be permanently discontinued and corticosteroids administered at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid tapering for life-threatening (Grade 4) increased serum creatinine. Renal biopsy and prophylactic antibiotics for opportunistic infection should be considered during the management of the event.

9.8.8.8 Immune-Mediated Dermatitis

Immune-mediated dermatitis can occur with nivolumab treatment. Low grade rashes (<Grade 3) have also been reported with administration of TAK-659. Patients should avoid excessive exposure to sunlight and should use a broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a sun protection factor >15. Should a Grade 2 or 3 rash occur, photographic documentation is recommended.

For Grade 1 (mild) or Grade 2 (moderate) dermatitis, such as rash (covering ≤30% of body surface area) and pruritus, antihistamines and topical steroids should be used as symptomatic treatment. If rash persists for >1 to 2 weeks or recurs, nivolumab should be withheld, and corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents should be considered. For Grade 3 (severe) or Grade 4 (life-threatening) dermatitis, corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents. Skin biopsy and prophylactic antibiotics for opportunistic infection should be considered. Nivolumab should be withheld for severe (Grade 3) rash and permanently discontinued for life-threatening (Grade 4) rash. When dermatitis of ≤Grade 3 resolves to ≤Grade 1, nivolumab treatment can resume after a corticosteroid taper of ≥1 month. Dose modification of TAK-659 during the event will follow the guidelines in Section 9.5.

9.8.8.9 Immune-Mediated Encephalitis

Immune-mediated encephalitis can occur with nivolumab treatment. If it occurs, nivolumab should be withheld in patients with new-onset moderate to severe neurologic signs or symptoms, and patients should be evaluated to rule out infectious or other causes of moderate to severe neurologic deterioration. Evaluation may include, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other etiologies are ruled out, corticosteroids should be administered at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid tapering. Nivolumab should be permanently discontinued for immune-mediated encephalitis.

In addition to the immune-mediate toxicities addressed above, the following clinically significant, immune-mediated adverse reactions have occurred in less than 1.0% of patients receiving nivolumab as a single agent or in combination with ipilimumab in clinical trials (n=1261): uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, motor dysfunction, vasculitis, and myasthenic syndrome.

9.8.9 Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of nivolumab as a single agent. Although these reactions have been observed at a low incidence, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the medical monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4.03 guidelines [35].

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate.

For Grade 1 symptoms: mild reaction; infusion interruption not indicated; intervention not indicated.

Bedside monitoring of the patient should be provided until recovery from symptoms. For future infusions, prophylactic premedications such as diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be considered at least 30 minutes before additional administrations.

For Grade 2 symptoms: moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≥24 hours.

Nivolumab infusion should be stopped. The patient should be given IV infusion normal saline, and diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered. Close bedside monitoring should be provided until symptoms resolve. Corticosteroid or bronchodilator therapy may also be administered as appropriate. When

symptoms resolve, the infusion can be restarted at 50% of the original infusion rate, which can then increase to 100% of the original rate if no further complications ensue after 30 minutes. If symptoms recur, nivolumab will not be administered at that visit. Diphenhydramine 50 mg IV should be re-administered, and the patient should be closely monitored until symptoms resolve. The amount of study drug infused must be recorded on the eCRF. For future infusions, prophylactic premedications such as diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be considered at least 30 minutes before additional administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: severe reaction, Grade 3: prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: life threatening; pressor or ventilatory support indicated.

Infusion should be discontinued immediately. The patient should be given IV infusion with normal saline, and the following medications are recommended: 1) a bronchodilator such as epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration; and/or 2) diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. The patient should be closely monitored until recovery of symptoms. The patient will be permanently discontinued from the trial. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

9.9 Blinding and Unblinding

This is an open-label study.

9.10 Description of Investigational Agents

9.10.1 TAK-659

TAK-659 has been formulated into immediate-release film-coated tablets for use in phase 1 clinical studies via a common granulation process. Three different tablet dosage strengths, 20 mg, 60 mg, and 100 mg, were formulated. The formulation contains compendial excipients that include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. Tablets were coated with Opadry® film coat.

Additional dose strength tablets, either higher or lower than the currently available tablets (20 mg, 60 mg, 100 mg) may also be developed to appropriately identify an RP2D that offers the maximal benefit balancing safety, tolerability, PK, and potential efficacy.

9.10.2 Nivolumab

Nivolumab is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the most recent nivolumab USPI [17] or SmPC [18].

9.11 Preparation, Reconstitution, and Dispensation

9.11.1 TAK-659

Detailed instructions for the dispensing of TAK-659 immediate-release film-coated tablets are provided in the Pharmacy Manual.

TAK-659 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-659.

9.11.2 Nivolumab

Nivolumab is a commercially available drug supplied as a solution for injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the most recent nivolumab USPI [17] or SmPC [18].

9.12 Packaging and Labeling

9.12.1 TAK-659

TAK-659 20 mg, 60 mg, 100 mg, and additional dose strength tablets will be packaged into round, white, high-density polyethylene bottles with induction seals, desiccant packs, and polypropylene child resistant caps. Each bottle of TAK-659 will be labeled with either a single-panel or multi-language label containing pertinent study information, country-specific requirements, and a caution statement.

9.12.2 Nivolumab

Nivolumab will be supplied to the site from commercial sources. Please refer to the most recent nivolumab USPI [17] or SmPC [18].

9.13 Storage, Handling, and Accountability

9.13.1 TAK-659

TAK-659 tablets should be stored in the original dispensing bottles at 1°C to 25°C (33.8°F-77°F) with excursions permitted to 30°C (86°F) as long as they do not exceed 7 days. All temperature excursions of the tablets must be reported back to the sponsor for assessment and determination for continued use. Please refer to the Pharmacy Manual for additional information. The TAK-659 tablets must be used before the retest date that is indicated on the label and/or accompanying documentation. Throughout the duration of the clinical trial, the stability of the drug product will be monitored. TAK-659 tablets should remain in the original bottle provided to the investigational

site and patients. Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily.

Because TAK-659 is an investigational agent, it should be handled with due care. In the case of broken tablets, raising dust should be avoided during the clean-up operation. Damaged tablets may be harmful by inhalation, ingestion, or skin and/or eye contact. In the case of contact of damaged tablets with the eyes or skin, there should be immediate and thorough flushing and washing for at least 15 minutes with water (and soap for skin). Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of TAK-659, including that TAK-659 is to be taken as intact tablets. Patients will receive diary cards to record dosing compliance of TAK-659. Patients will be instructed to return any unused study drug in the original packaging along with their completed diary cards at the appropriate visits.

9.13.2 Nivolumab

Nivolumab should be stored according to instructions provided in the manufacturer's USPI [17] or SmPC [18].

10.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Council for Harmonisation (ICH) guidelines.

10.1 Study Personnel and Organizations

The contact information for the Millennium Study Monitor for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and the contract research organization (CRO) may be found in the Study Manual. A full list of investigators is available in the sponsor's or CRO's investigator database.

10.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

10.3 Treatment Group Assignments

This is a phase 1 study that incorporates a dose escalation phase and a dose expansion phase at the MTD/RP2D. In the dose escalation phase, the patient population will consist of all-comer patients with advanced solid tumors for whom 1 or more prior lines of therapy have failed and who have no effective therapeutic options available based on investigator assessment. The dose expansion phase will include 3 cohorts: 1) patients with metastatic TNBC who have had ≥1 prior line of chemotherapy; 2) patients with locally advanced or metastatic NSCLC that has progressed on or after a prior platinum-based chemotherapy; and 3) patients with locally advanced or metastatic HNSCC that has progressed or recurred within 6 months of the last platinum-based chemotherapy. Thirty response-evaluable patients will be enrolled in each expansion cohort. Each expansion cohort will include 24 patients who are naïve to anti-PD-1/anti-PD-L1 therapy and 6 patients who are relapsed/refractory to prior anti-PD-1/anti-PD-L1 therapy. Ten response-evaluable patients in each cohort will receive 2 weeks of single-agent TAK-659 at its RP2D before starting combination therapy and will provide serial tumor biopsies during this period; these patients can be either naïve to or relapsed/refractory to anti-PD1/anti-PDL1 therapy. After completion of 2 weeks of single-agent TAK-659, these patients will receive TAK-659 at its RP2D in combination with nivolumab from Week 3 onward. Twenty response-evaluable patients in each cohort will receive TAK-659 at its RP2D in combination with nivolumab, from Day 1 Week 1.

10.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, and End of Treatment (EOT). Evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Procedures

conducted during the Screening period that are performed within 3 days of Cycle 1 Day 1 may also be used as the predose evaluation and do not need to be repeated, unless otherwise specified.

Unless otherwise noted, evaluations during the Treatment period must occur before study drug administration on scheduled visits. Tests and procedures should be performed on schedule for all visits. The timing of PK and pharmacodynamic assessments is specified in the Schedule of Events (Appendix A) and is not flexible. Laboratory assessments and procedures may occur up to 3 days before the scheduled day due to extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).

Refer to the Schedule of Events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

10.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Informed consent may be captured before the Screening period (ie, 28 days before Cycle 1 Day 1).

10.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during Screening.

10.4.3 Medical History

During the Screening period, a complete medical history (including smoking history) will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and will include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 10.4.9. During dose expansion, medical history will also include baseline disease characteristics such as staging, risk/prognostic index, and other individual prognostic evaluations.

10.4.4 Physical Examination

A physical examination (PE) will be conducted per standard of care and will include a neurological examination at the times specified in the Schedule of Events (Appendix A). During dose escalation, complete PEs will be performed at Screening, Day 1 of each cycle of treatment, and EOT. Symptom- or finding-directed PEs will be performed at Day 8, 15, and 22 of Cycle 1 and Day 15 of Cycle 2. During dose expansion, complete PEs will be performed at Screening only, and post-Screening PEs will be symptom- or finding-directed PEs.

10.4.5 Patient Height and Weight

Height will be measured only during Screening (within 28 days before the first dose of TAK-659).

Weight will be measured during the times specified in the Schedule of Events (Appendix A).

10.4.6 Vital Signs

Vital sign measurements include diastolic and systolic blood pressure, heart rate, and temperature, and will be assessed as specified in the Schedule of Events (Appendix A). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for approximately 5 minutes. Oxygen saturation will also be measured when vital signs are taken.

Pulse oximetry should be obtained before each dose of nivolumab and any time a patient has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator but should remain consistent for each individual patient throughout the study. If the patient's status changes, the investigator can alter the extent of exertion per their medical judgment. If a patient shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity.

10.4.7 ECOG Performance Status

ECOG performance status is to be assessed at the times specified in the Schedule of Events (Appendix A).

10.4.8 ECG

A 12-lead singlet ECG will be performed and interpreted locally at the time points specified in the Schedule of Events (Appendix A). The ECG schedule is more intensive for patients enrolled in the dose escalation cohorts.

All scheduled ECGs should be performed predose, unless otherwise specified in Table A, and after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

Confirmation that the machine estimates of the rate-corrected QT interval (milliseconds) of electrocardiograph (QTc) are accurate using the appropriate QT correction formula (QTcF or Bazett corrected QT interval [QTcB]) should be performed. Estimates of QTc for study eligibility should use QTcF. If a QTcF value confirmed by a qualified reader is >475 msec for a woman or >450 msec for a man, an evaluation to determine etiology should be conducted. If the prolonged QTc finding can be corrected with medication and/or correction of electrolyte abnormalities, and a repeat ECG meets eligibility requirements, the patient may enroll in the study upon review and agreement by the sponsor's clinician.

Following initiation of treatment, if a QTc value is confirmed by a qualified reader as >500 msec or >60 msec elevated from baseline for any ECG, the following will occur:

- The sponsor's clinician will be promptly notified.

- Study treatment should be held, and an evaluation should be conducted to correct other possible causes (eg, electrolyte disturbance, concomitant medication).
- A formal consult by a cardiologist should be considered. Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.

The decision to reinitiate study treatment with or without dose reduction (dose reduction applicable to TAK-659 only) and additional monitoring in those patients who had asymptomatic prolonged QTc >500 msec or >60 msec from baseline (Grade 3) that has reverted to an acceptable interval, have previously tolerated study treatment, and appear to have benefited from study treatment with either disease control or response will be agreed to by the investigator and the sponsor's clinician on a case-by-case basis.

The ECGs performed should be reviewed by the investigator or delegate before the patient leaves the clinic on visit days.

10.4.9 Concomitant Medications and Procedures

Concomitant medications and procedures will be recorded in the eCRF from the time of signing of the ICF through 28 days after the last dose of study drug. However, if a patient experiences immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocriopathies, nephritis, rash, and encephalitis as described in the nivolumab USPI [17]), they will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first. During this AE follow-up period, concomitant medications and procedures should also be collected.

See Section 9.6 for a list of medications and procedures that should be avoided during the study unless otherwise specified.

10.4.10 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events (Appendix A). Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

10.4.11 Enrollment

A patient is considered to be enrolled in the study when the first dose of study drug has been administered.

Procedures for completing enrollment information are described in the Study Manual.

10.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the Study and Laboratory Manuals. Clinical laboratory evaluations will be performed as outlined in the following sections.

10.4.12.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematological parameters shown in Table 10.a and urine samples for analysis of the parameters shown in Table 10.b will be obtained as specified in the Schedule of Events (Appendix A).

Creatinine clearance should be calculated according to the Cockcroft-Gault equation (Appendix E).

Table 10.a Clinical Chemistry and Hematology Tests

Hematology		Serum Chemistry
Hematocrit	Albumin	Creatinine
Hemoglobin	Alkaline phosphatase (ALP)	γ-glutamyl transferase (GGT)
Leukocytes with differential	Alanine aminotransferase (ALT)	Glucose
Neutrophils (ANC)	Aspartate aminotransferase (AST)	Lactate dehydrogenase (LDH)
Platelet (count)	Amylase	Lipase
	Bilirubin (total)	Magnesium
	Blood urea nitrogen (BUN)	Phosphate
	Calcium	Potassium
	CO_2	Sodium
	Chloride	Total protein
	Creatine phosphokinase (CPK)	Cardiac Troponin I and Troponin T (cTnI and cTnT)
		Urate

Table 10.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

10.4.12.2 Immune Safety Tests

Blood samples for immune safety tests will be collected at the time points specified in the Schedule of Events (Appendix A) and analyzed for the immune safety parameters shown in Table 10.c. Serum for additional immune safety testing (if needed) will be obtained and sent to the study sponsor. Refer to the laboratory manual for details on collecting, processing, storage, and shipment of serum samples to the study sponsor.

Table 10.c Immune Safety Tests

Immune Safety Tests	
Adrenocorticotropic hormone	Free T4 level
Antinuclear antibody	Rheumatoid factor
C-reactive protein	Thyroid-stimulating hormone

Additional tests may be ordered at the investigator's discretion in case of abnormal immunologic or endocrine findings. Additional endocrine testing may require an endocrinologist consult.

10.4.13 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine or serum pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose may be administered. If the serum pregnancy test is performed within 3 days before the first dose and the result is negative, the urine pregnancy test on Cycle 1 Day 1 may be waived.

10.4.14 Ophthalmic Exam

A slit lamp eye examination will be performed by an ophthalmologist at Screening; on Cycle 2 Day 1; on Cycle 7 Day 1; every 6 cycles thereafter (±2 weeks); and at EOT. Based on the nonclinical toxicology findings with TAK-659 in rats, slit lamp examinations should focus on detecting any posttreatment changes in the ocular lens. Examination and photographing of the retina will be performed at Baseline but not during the study unless it is clinically indicated. Additional eye exams may also be performed, as required. Patients will be carefully monitored for eye complaints at each visit and instructed to report visual symptoms as soon as they occur.

10.4.15 Disease Assessment

Patients will undergo CT with contrast or MRI, x-ray, and/or bone scanning as appropriate at Screening/Baseline (within 28 days before the first study drug administration), the end of Cycles 2, 4, and 6 (between Days 22 and 29 [predose]), and every 3 cycles thereafter (ie, Cycle 9, 12, etc) to monitor and assess response status using RECIST version 1.1 [1]. Follow-up CT scans will encompass the known sites of disease. Disease sites that cannot be adequately imaged by CT may be documented by MRI. Target and nontarget measurable lesions will be evaluated at Baseline and each subsequent evaluation using an imaging modality consistent with that used at Screening. A

confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all patients with an objective response of PR or better.

- Verification of response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no sooner than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.
- Verification of progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the patient is considered to not have PD.

Note that patients with nonmeasurable tumor lesions are also eligible for enrollment to dose escalation.

When assessing response, special consideration should be given to the tumor response characteristics associated with immunotherapy:

1. Measurable tumor size reduction may take longer treatment duration with immunotherapy than with a cytotoxic regimen.
2. Response to immunotherapy may occur after appearance of PD, as assessed per conventional RECIST version 1.1. In particular, small, new lesions may appear in the presence of other responsive target lesions (pseudo-progression).
3. Durable SD may represent antitumor activity of immunotherapy.

The sponsor may consider an exploratory independent central review of the study imaging data using immune-related RECIST if deemed necessary.

Pseudo-progression has been described during treatment with nivolumab in multiple indications. Therefore, discontinuation of study treatment is not recommended unless PD (at least 20% increase in tumor burden compared with nadir at any single point during study treatment) has been confirmed in 2 consecutive imaging assessment 8 weeks apart or more conveniently at the next scheduled imaging time point. However, when the objectively assessed PD per imaging is accompanied by rapid clinical deterioration, immediate study drug discontinuation is indicated. Refer to Section 10.4.16 for details regarding treatment beyond PD.

In the event of antitumor response, the sponsor may request electronic images of scans performed on study to be collected for central storage. Determination of disease status will be based on local investigator assessment. The collection and central storage of scans are planned in the event that more detailed analysis of imaging data, as determined by the sponsor, is needed.

Tumor assessments for all patients should continue per protocol even if dosing is interrupted.

10.4.16 Treatment Beyond Disease Progression

Contemporary immunotherapy protocols generally allow patients to continue treatment beyond initial radiographic evidence of PD following further investigation, as accumulating data indicates

it is possible that some patients treated with immunotherapy may derive clinical benefit beyond initial RECIST-defined PD, which may not be captured by radiographic assessments. [36,37]In this study, patients treated TAK-659 in combination with nivolumab will be permitted to continue treatment beyond initial RECIST 1.1-defined PD if the following criteria are met:

1. Investigator-assessed overall clinical benefit from continued treatment with nivolumab and/or TAK-659.
2. Tolerance of study drug(s).
3. Stable performance status.
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (eg, CNS metastases).
5. Patient provides written informed consent before receiving additional nivolumab or TAK-659 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial RECIST 1.1-defined progression should be discussed with the Takeda medical monitor and documented in the study records. Then, the patient may remain on the study and continue to receive monitoring according to the protocol-defined Schedule of Events.

A radiographic assessment/scan should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD.

For the patients who continue study therapy beyond progression, further progression is defined as an additional ≥20% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and is therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Treatment should be discontinued permanently upon documentation of further PD. If the patient experiences rapid PD (such as global deterioration as perceived by the investigator) before radiographic assessment within 8 weeks of original PD, the investigator can discontinue the study treatment without objective evidence of disease progression and report it as “symptomatic deterioration”.

For statistical analyses, patients who continue study therapy beyond initial RECIST 1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

10.4.17 Tumor Biopsies

Serial tumor biopsies will be obtained from approximately 10 patients enrolled in each expansion cohort at Screening, after 2 weeks of TAK-659 single-agent treatment, and after 6 weeks of the combination treatment as indicated in the Schedule of Events (Appendix A). An additional, optional biopsy sample may be taken upon PD if the patient consents. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an aPTT and PT based on site's institutional standard; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure. The tumor biopsy procedure will be performed by core needle, under radiological guidance if indicated, or surgically if the site of disease is superficial and palpable or visible. CCI [redacted]

10.4.18 Banked Tumor Specimen Measurements

If archival tumor tissue is available, it will be collected for all patients for biomarker analysis at any time during the treatment, except for patients who undergo serial biopsies. CCI [redacted]

10.4.19 Analysis of PBMCs

Blood samples will be collected from all patients enrolled in the expansion phase of the study as indicated in the Schedule of Events (Appendix A) for immune cell profiling to investigate the pharmacodynamic effect of TAK-659 as a single agent and in combination with nivolumab.

10.4.20 Cytokine/Chemokine Measurements

Blood samples will be collected from all patients enrolled in the expansion phase of the study as indicated in the Schedule of Events (Appendix A) for analysis of cytokines and chemokines. Serum will be extracted from blood samples and subjected to analysis of a panel of cytokines and chemokines using a multiplex platform.

10.4.21 Analysis of ctDNA

Blood samples will be collected from all patients enrolled in the expansion phase of study as indicated in the Schedule of Events (Appendix A), and plasma will be extracted to obtain ctDNA. Changes in the amount of purified ctDNA may be quantified and monitored during the course of

treatment. In addition, ctDNA may be subjected to analysis of mutations using an appropriate platform such as next-generation sequencing.

10.4.22 PK Measurements

The primary aim of PK sampling in this study is to measure the plasma concentrations of TAK-659. However, pending technical feasibility, plasma samples for TAK-659 PK assessments may additionally be used for exploratory identification and profiling of TAK-659 metabolites to increase understanding of TAK-659 metabolism and clearance. If technically feasible, these plasma samples also could be used for exploratory measurement of nivolumab concentrations if an investigation into the effect of TAK-659 co-administration on nivolumab PK is warranted based on emerging study findings. Details on the collection, storage, processing, handling, and shipping of the PK samples are provided in the Laboratory Manual.

Dose Escalation Cohorts

Blood samples for determination of TAK-659 plasma concentrations will be obtained during Cycle 1 on Days 1, 2, 15, and 16 at the times indicated in Table A. For clinic visits where predose PK samples are scheduled, patients will be instructed to refrain from taking their TAK-659 dose at home before the clinic visit.

The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on days of PK sample collection (Days 1, 2, 15, and 16). In addition, the dates and exact times of TAK-659 dosing (from patient diaries) will be recorded in the eCRF for the 2 doses administered before the day of PK sample collection.

Dose Expansion Cohorts

Blood samples for determination of TAK-659 plasma concentrations will be obtained during Cycles 1 through 4 at the times indicated in Table B. For clinic visits where predose samples are scheduled, patients should be instructed to refrain from taking their TAK-659 dose at home before the clinic visit. For the Cycle 1 Day 8 visits, patients should be instructed to take their TAK-659 dose at home before the clinic visit; PK samples can be collected at any time during this clinic visit. A distribution of clinic visit times during the day across patients is to be encouraged to provide a range of postdose sampling times across the study population.

The dates and exact times of TAK-659 dosing and PK sample collection will be recorded in the eCRF on days of PK sample collection. In addition, the dates and exact times of TAK-659 dosing (from patient diaries) will be recorded in the eCRF for the 2 doses administered before the day of PK sample collection.

For both the dose escalation and dose expansion cohorts, the timing of blood sampling for plasma PK may be changed if emerging data indicate that an alteration in the sampling scheme is needed for optimal characterization of TAK-659 PK. However, the number of PK samples collected and the volume of blood drawn for these samples will not increase.

10.4.23 DNA Measurements

CCI

[redacted]

10.5 Completion of Treatment

Patients will be treated until PD, occurrence of unacceptable toxicities, withdrawal due to other reasons, or the study is terminated by the sponsor. Study treatment can continue beyond initial RECIST 1.1 progression as specified in Section 10.4.16.

10.6 Completion of Study

Patients will be considered to have completed the study if:

- They are followed until death before the end of the survival follow-up window (up to 12 months after discontinuation of study drug for any reason).
- They remain on study treatment free of PD at the close of the study at least 1 year after their first dose of study treatment.
- They continue on to the follow-up for survival after discontinuation of the study drug and reach the end of the 12-month OS follow-up window.
- They discontinue study treatment while in CR and continue on to the follow-up for progression and either experience PD before the end of the 12-month follow-up period or reach the end of the follow-up period.
- The sponsor terminates the study.

10.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Treatment with study drug may be discontinued for any of the following reasons:

- AE, including patients who experience a DLT (during escalation) or DLT-like toxicity (during expansion) during the first cycle, and patients with other drug-related AEs that require study drug discontinuation per dose modification guidelines in Section 9.5 and the current USPI [17] and SmPC [18] for nivolumab. Discontinuation of treatment occurs only when both study drugs are required to be discontinued due to AEs.
- Protocol violation.
- PD: as noted previously, PD per RECIST 1.1 should be confirmed in 2 subsequent scans 8 weeks apart before treatment discontinuation is considered unless there are clear signs of

rapid clinical progression. In addition, in rare situations, patients with confirmed PD may remain on study, after discussion between the investigator and the sponsor clinician, if it is felt that they are deriving a clinical benefit from doing so.

- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

During the dose escalation phase, patients who are withdrawn from treatment during Cycle 1 for reasons other than DLT will be replaced. During the expansion phase, patients who do not meet the response-evaluable criteria will be replaced.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

10.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- AE.
- Protocol violation.
- PD.
- Symptomatic deterioration (at investigator's discretion).
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

10.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. Patients will be given a diary to record TAK-659 dosing. The

dosing diary will provide supporting information, if necessary. The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.

Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. The timing of PK (and pharmacodynamic) assessments as specified in the Schedule of Events (Appendix A) is not flexible. If extenuating circumstances prevent a patient from beginning treatment or completing a planned procedure or assessment within 3 days of the scheduled time, the patient may continue the study at the discretion of the investigator and after consultation with the Millennium clinician or designee.

If a dose of TAK-659 is held for up to 21 days for reasons unrelated to toxicity, the patient may be discontinued from the study following a discussion between the investigator and the sponsor.

10.10 Posttreatment Follow-up Assessments (PFS and OS)

Patients who stop treatment for any reason other than PD will continue to have PFS follow-up visits. The PFS follow-up visit should be conducted at the site every 2 months (up to 6 months after the first dose of study drug) or 3 months from the last dose of study drug until PD for a maximum of 6 months from the date of the last dose of study drug. After the occurrence of PD, patients will continue to have OS follow-up visits. The OS information will be collected every 2 months until 12 months from the date of the last dose of study drug. Patients who discontinue the study, regardless of reasons for discontinuation, will be followed for survival every 2 months until death, loss to follow-up, or withdrawal of consent to further follow-up for up to 12 months after discontinuation of the study drug.

Survivor information may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieval from online or other databases (eg, social security indexes). In addition, the start of another anticancer therapy will be collected.

NOTE: Related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 PTE Definition

A PTE is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

11.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 11.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

development of drug dependency or drug abuse. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010 [35]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

11.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 11.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 11.1) must be reported (see Section 11.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Cognizant

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: takedaoncocases@cognizant.com

All Other Countries (Rest of World)

Fax #: 1-202-315-3560

E-mail: takedaoncocases@cognizant.com

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE version 4.03, effective 14 June 2010 [35]. The criteria are provided in the Study Manual.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

11.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from signing of the ICF through 28 days after administration of the last dose of study drug and recorded in the eCRFs. However, immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis as described in nivolumab USPI) will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug and will be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 28 days after administration of the last dose of study drug and recorded in the eCRF. After this period,

only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor also must be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.5 Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the Medical Information Call Center/Dohmen Life Science Services and report the complaint. The contact information is as follows:

Medical Information Center:	Dohmen Life Science Services
Phone:	1-844-ONC-TDKA (1-844-662-8532)
Fax:	1-800-881-6092
E-mail:	GlobalOncologyMedinfo@takeda.com
Hours:	Monday-Friday, 9 AM–7 PM, ET

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Cognizant (refer to Section 11.2)

11.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 calendar days for fatal and life-threatening events and 15 calendar days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues

where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

12.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

13.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

13.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of

a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

14.0 STATISTICAL METHODS

14.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

14.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population: the Safety population is defined as all patients who receive at least 1 dose of study drug. Patients will be analyzed according to the actual treatment they received.
- Response-Evaluable population: the Response-Evaluable population is defined as patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have at least 1 post-Baseline disease assessment.
- PK-Evaluable population: the PK-Evaluable population is defined as patients with sufficient concentration-time and dosing data to reliably estimate PK parameters. This population will be used for analyses of PK parameters.
- DLT-Evaluable population: the DLT-Evaluable population is defined as patients who have met the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 1. The minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1) plus 2 doses of nivolumab, and observed for ≥28 days (unless DLT occurs before the end of the 28- to 42-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur.

14.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively, including sex, age, race, weight, height, and other parameters as appropriate. No inferential statistics will be carried out.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

14.1.3 Efficacy Analysis

Summary tabulations will be presented by treatment and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. For time to event data, Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable) will also be provided.

The SAP will be developed and finalized by the sponsor, or its designee, before final database lock. The SAP will outline all data handling conventions and specify all statistical methods to be used for safety and efficacy analyses. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

All efficacy analyses will be based on investigator assessments. Any sensitivity analysis will be specified in the SAP.

14.1.3.1 Analyses of Primary Efficacy Endpoints

The primary endpoint for efficacy for the dose expansion phase is ORR. A responder is defined as a patient who has either CR or PR. ORR will be summarized using the Response-Evaluable population, in the following groups:

- By expansion cohort.
- Within each expansion cohort, by anti-PD1/PD-L1 naïve and anti-PD1/PD-L1 relapsed/refractory subgroup.
- Across all expansion cohorts in the anti-PF1/PD-L1 relapsed/refractory patients.

14.1.3.2 Analyses of Secondary Efficacy Endpoints

Disease control rate is the proportion of patients who had CR, PR, or SD in the Response-Evaluable population. Duration of response, PFS, and OS will be analyzed by a Kaplan-Meier approach using the Safety population. Rate of PD at 6 months is the proportion of patients who progressed by 6 months. All secondary efficacy endpoints will be summarized using the Response-Evaluable population, in the following groups:

- By expansion cohort.
- Within each expansion cohort, by anti-PD1/PD-L1 naïve and anti-PD1/PD-L1 relapsed/refractory subgroup.
- Across all expansion cohorts in the anti-PF1/PD-L1 relapsed/refractory patients.

14.1.4 PK Analysis

The PK population will be used for the description of the plasma PK profile of TAK-659 and for the estimation of plasma PK parameters of TAK-659. Plasma concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods.

For dose escalation cohorts, plasma TAK-659 concentrations will be summarized by time postdose and grouped by dose group and dosing cycle and day. Mean and individual plasma TAK-659 concentration data will be plotted over time and grouped by dose group and dosing cycle and day. Plasma concentration-time data will be used to calculate single-dose (Cycle 1 Day 1) and multiple-dose (Cycle 1 Day 15) plasma PK parameters of TAK-659 by noncompartmental methods. These parameters will include, but not be limited to, C_{max}, T_{max}, C_{trough}, AUC_{τ}, CL/F,

PTR, and Rac. Estimation of plasma PK parameters of the terminal disposition phase, such as $t_{1/2}$ and area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}), will depend on an adequate representation of the terminal disposition phase during the period of PK sampling. Plasma PK parameters of TAK-659 will be summarized using descriptive statistics by dose group and by dosing cycle and day.

For dose expansion cohorts, plasma concentrations of TAK-659 will be listed by cohort, nominal and actual time point, and dosing cycle and day.

TAK-659 plasma PK data from dose escalation and expansion cohorts, along with data from other studies, may contribute to population PK analyses and exposure-response analyses for pharmacodynamic, safety, and efficacy endpoints. If applicable, the specifics of the population PK and exposure-response analyses will be described in separate analysis plans, and results will be reported separately from the clinical study report.

14.1.5 Pharmacodynamic Analysis

Individual data at each time point will be summarized in a table describing changes in the course of treatment per patient. Individual and summary data also will be presented graphically for each marker. If sufficient data are generated, data may be summarized by cohort or by indication as appropriate. Descriptive statistics, graphical methods, and statistical modeling will be used as appropriate to explore the relationship between response and the levels of various biomarkers. In addition, the relationship between PK and pharmacodynamics changes may be evaluated as permitted by the data.

14.1.6 Biomarker Analyses

CCI [redacted]

14.1.7 Pharmacogenomic Analyses

CCI [redacted]

14.1.8 Safety Analyses

The Safety population will be used for all safety analyses.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, ECOG performance status, ECG results, and clinical laboratory results. Exposure to study drug and reasons for discontinuation will be tabulated.

All treatment-emergent AEs (TEAEs) will be tabulated. A TEAE for tabulation is defined as: 1) any AE that occurs after administration of the first dose of study drug and up through 30 days after the last dose of study drug; 2) any event that is considered drug related regardless of the start date of the event; or 3) any event that is present at the Baseline assessment but worsens in severity after the assessment or is subsequently considered drug related by the investigator. AEs will be tabulated according to the MedDRA by system organ class, high-level term, and preferred term, and will include the following categories:

- TEAEs.
- Grade 3, 4, and 5 TEAEs (presented by grade and overall).
- Drug-related TEAEs.
- Drug-related, Grade 3, 4, and 5 TEAEs (presented by grade and overall).
- TEAEs resulting in study drug discontinuation.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- Treatment-emergent SAEs.
- Nonserious TEAEs.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values (and/or changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the safety profile of TAK-659 in combination with nivolumab.

Descriptive statistics for the actual values and changes from baseline ECGs will be tabulated by time point, including any unscheduled measurements.

All concomitant medications collected from Screening through the study period will be classified to preferred terms according to the WHO drug dictionary.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and further define the safety profile of TAK-659 plus nivolumab.

14.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

14.3 Determination of Sample Size

During the dose escalation phase, dose escalation will be conducted according to a standard 3+3 dose escalation schema, and approximately 12 to 18 DLT-evaluable patients will be enrolled (including a possible 3 to 6 patients in the nivolumab fixed dose evaluation cohort). The MTD/RP2D cohort will have at least 6 patients.

The sample sizes for each expansion cohort are estimated using a 1-sided exact binomial test at a significance level of α=0.1 with a power of 80%. Each cohort uses a null hypothesis of response rate ≤20%, versus an alternative hypothesis of response rate ≥40% for patients who are naïve to anti-PD/PD-L1 and any other immune-directed antitumor therapies. Therefore, approximately 24 response-evaluable patients for each cohort will be needed. In addition, 6 response-evaluable patients with prior exposure to a PD-1 or PD-L1 inhibitor will be enrolled in each expansion cohort. In total, 30 response-evaluable patients for each cohort and 90 response-evaluable patients in total (~108 patients based on 15% drop out) will be needed.

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 15.1.

16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

16.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, patient recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives [drug/notification] no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

16.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The patient must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the patient determines he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient at the time of consent and prior to the patient entering into the study. Patients should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and prior to patient entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

16.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 16.2).

Copies of any patient source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, patient name, address, and other identifier fields not collected on the patient's eCRF).

16.4 Publication, Disclosure, and Clinical Trial Registration Policy

16.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

16.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda

contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once patients receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

16.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws, and/or regulations.

16.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

17.0 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
2. IARC. The global and regional burden of cancer. In: Stewart BW, Wild CP, editors. World Cancer Report 2014: World Health Organization Press; 2014; 1.1.
3. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol 2012;23 Suppl 6:vi7-12.
4. Solin LJ, Hwang WT, Vapiwala N. Outcome after breast conservation treatment with radiation for women with triple-negative early-stage invasive breast carcinoma. Clinical Breast Cancer 2009;9(2):96-100.
5. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, van Geel AN, Tilanus-Linthorst MM, Bartels CC, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. Ann Surg Oncol 2007;14(12):3335-44.
6. Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006;24(36):5652-7.
7. Freedman GM, Anderson PR, Li T, Nicolaou N. Locoregional recurrence of triple-negative breast cancer after breast-conserving surgery and radiation. Cancer 2009;115(5):946-51.
8. Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol 2006;24(34):5381-7.
9. Andre F, Zielinski CC. Optimal strategies for the treatment of metastatic triple-negative breast cancer with currently approved agents. Ann Oncol 2012;23 Suppl 6:vi46-51.
10. Sarris EG, Saif MW, Syrigos KN. The Biological Role of PI3K Pathway in Lung Cancer. Pharmaceuticals (Basel) 2012;5(11):1236-64.
11. Joseph AW, D'Souza G. Epidemiology of human papillomavirus-related head and neck cancer. Otolaryngol Clin North Am 2012;45(4):739-64.
12. Parfenov M, Pedamallu CS, Gehlenborg N, Freeman SS, Danilova L, Bristow CA, et al. Characterization of HPV and host genome interactions in primary head and neck cancers. Proc Natl Acad Sci U S A 2014;111(43):15544-9.
13. O'Rorke MA, Ellison MV, Murray LJ, Moran M, James J, Anderson LA. Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis. Oral Oncol 2012;48(12):1191-201.
14. Rousseau A, Badoual C. Head and Neck: Squamous cell carcinoma: an overview. Atlas of Genetics and Cytogenetics in Oncology and Haematology 2011;16(2):145-55.

15. Keating GM. Nivolumab: A Review in Advanced Squamous Non-Small Cell Lung Cancer. Drugs 2015;75(16):1925-34.
16. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252-64.
17. OPDIVO (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb, 2016.
18. OPDIVO 10 mg/mL concentrate for solution for infusion (nivolumab) [Summary of Product Characteristics].
19. Luangdilok S, Box C, Patterson L, Court W, Harrington K, Pitkin L, et al. Syk tyrosine kinase is linked to cell motility and progression in squamous cell carcinomas of the head and neck. Cancer Res 2007;67(16):7907-16.
20. Dawson CW, Port RJ, Young LS. The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC). Semin Cancer Biol 2012;22(2):144-53.
21. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513(7517):202-9.
22. Zhang J, Benavente CA, McEvoy J, Flores-Otero J, Ding L, Chen X, et al. A novel retinoblastoma therapy from genomic and epigenetic analyses. Nature 2012;481(7381):329-34.
23. Katz E, Dubois-Marshall S, Sims AH, Faratian D, Li J, Smith ES, et al. A gene on the HER2 amplicon, C35, is an oncogene in breast cancer whose actions are prevented by inhibition of Syk. Br J Cancer 2010;103(3):401-10.
24. Muellner MK, Mair B, Ibrahim Y, Kerzendorfer C, Lechtermann H, Trefzer C, et al. Targeting a cell state common to triple-negative breast cancers. Mol Syst Biol 2015;11(1):789.
25. Lechner MG, Megiel C, Russell SM, Bingham B, Arger N, Woo T, et al. Functional characterization of human Cd33+ and Cd11b+ myeloid-derived suppressor cell subsets induced from peripheral blood mononuclear cells co-cultured with a diverse set of human tumor cell lines. J Transl Med 2011;9:90.
26. Cotechini T, Medler TR, Coussens LM. Myeloid Cells as Targets for Therapy in Solid Tumors. Cancer J 2015;21(4):343-50.
27. DiLillo DJ, Yanaba K, Tedder TF. B cells are required for optimal CD4+ and CD8+ T cell tumor immunity: therapeutic B cell depletion enhances B16 melanoma growth in mice. J Immunol 2010;184(7):4006-16.
28. Schalper KA, Brown J, Carvajal-Hausdorf D, McLaughlin J, Velcheti V, Syrigos KN, et al. Objective measurement and clinical significance of TILs in non-small cell lung cancer. J Natl Cancer Inst 2015;107(3).

29. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2015.

30. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med 2015;21(8):938-45.

31. Segal NH, Parsons DW, Peggs KS, Velculescu V, Kinzler KW, Vogelstein B, et al. Epitope landscape in breast and colorectal cancer. Cancer Res 2008;68(3):889-92.

32. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372(26):2509-20.

33. Gebhardt C, Sevko A, Jiang H, Lichtenberger R, Reith M, Tarnanidis K, et al. Myeloid Cells and Related Chronic Inflammatory Factors as Novel Predictive Markers in Melanoma Treatment with Ipilimumab. Clin Cancer Res 2015;21(24):5453-9.

34. Gray ES RH, Reid AL, Boyd SC, Pereira MR, et al. Circulating tumor DNA to monitor treatment response and detect acquired resistance in patients with metastatic melanoma. Oncotarget 2015.

35. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v4.03. June 14, 2010. Publication No. 09-5410.

36. Weinstock C, Maher V, Zhang L, XU J, Tang S, Sridhara R, et al. FDA analysis of treatment beyond progression disease (PD) in patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab vs. everolimus. J Clin Oncol (ASCO Annual Meeting Proceedings) 2016;34(suppl). 4508.

37. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375(19):1856-67.

Appendix A Schedules of Events

Schedule of Events for Dose Escalation (28-Day Cycle)

	Screening (a)	Cycle 1						Cycle 2 and Beyond			EOT (b) (+10 Days)	Survival Follow-up	
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Days 22-29		PFS (c)	OS (d)
Informed consent (e)	X												
Inclusion/exclusion criteria	X												
Demographics and disease characteristics	X												
Complete medical history (f)	X	X											
Physical examination (f)	X	X		X	X		X	X	X		X		
Height	X												
Weight (g)	X	X						X			X		
Vital signs (h)	X	X		X	X		X	X	X		X		
ECOG performance status	X	X						X			X		
12-lead ECG (i)	X	X			X			X			X		
Monitoring of concomitant medications and procedures (j)	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first												
AE reporting (j)	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first												
	Serious adverse events (k) will be reported from signing of the ICF through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy.												
Dosing													
TAK-659 administration (l)		TAK-659 is dosed PO QD every day.											
Nivolumab administration (m)		Nivolumab is dosed every 2 weeks on Days 1 and 15 of each treatment cycle.											
Patient diary review (n)		X		X	X		X	X	X	X	X		

Footnotes are on last table page.

Schedule of Events for Dose Escalation (28-Day Cycle) (continued)

	Screening (a)	Cycle 1						Cycle 2 and Beyond			EOT (b) (+10 Days)	Survival Follow-up	
		Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 1	Day 15	Days 22-29		PFS (c)	OS (d)
Imaging/Response Assessments													
Tumor assessment for solid tumors by RECIST version 1.1 (CT scan/MRI) (o)	X									X		X (c)	
Sample/Laboratory Assessments													
Hematology/chemistry (p, q)	X	X		X	X		X	X	X		X		
Urinalysis (for hematuria and proteinuria evaluation) (q,r)	X				X			X					
Immune safety tests (q)	X	X		X	X		X	X	X		X		
Pregnancy test (s)	X	X						X					
Ophthalmic exam (t)	X							X			X		
CCI [redacted]													
Blood samples for PK (v)		X	X		X	X							
CCI [redacted]													
Survival follow-up contact													X (d)

(a) Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.
(b) The EOT visit will occur 28 days (+10 days) after the last dose of study drug or before the start of subsequent anticancer therapy if that occurs sooner.
(c) All patients, including those patients no longer on treatment, will be assessed for survival. Patients who stop treatment for any reason other than PD will continue to have follow-up visits for PFS. The PFS follow-up visit should be conducted at the site every 2 months from the last dose of study drug until PD for a maximum of 6 months from the date of the first dose of study drug or 3 months from the last dose of study drug until PD for a maximum of 6 months from the last dose of study drug. Information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who discontinue study treatment before PD, investigator response assessments based upon available local data will also be collected during the survival follow-up period.

(d) After the occurrence of PD, patients will continue to have follow-up visits for OS. The OS information will be collected every 2 months until 12 months from the date of the last dose of study drug.
(e) Informed consent may be captured before the Screening period (28 days before first dose).
(f) The Cycle 1 Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1 Day 1). Complete physical examinations (including smoking history) will be performed during Screening and will include a neurological exam. Complete physical exams will also be performed on Day 1 of each cycle, and at EOT. Symptom- or finding-directed physical examinations will be performed on Days 8, 15, and 22 of Cycle 1 and on Day 15 of Cycles 2, 3, and 4.
(g) Weight should be obtained at Screening, on Day 1 predose of each cycle, and at EOT.
(h) Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1 and 3 (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.
(i) 12-lead ECGs will be performed as detailed in Section 10.4.8.
(j) If a patient experiences immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocriopathies, nephritis, rash, and encephalitis), they will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first. During this AE follow-up period, concomitant medications and procedures should also be collected.
(k) Including serious PTEs; see Section 11.0.
(l) TAK-659 will be administered PO QD for 28-day cycles. The option to modify the schedule of drug administration to include alternative schedules will be based on the review of the available PK, safety, and other clinical data by the investigators and the sponsor. On days when nivolumab infusions are administered, the dose of TAK-659 should be taken first and is to be taken in the clinic.
(m) Nivolumab is to be administered at 3 mg/kg or 240 mg IV as a 60-minute infusion on Days 1 and 15 of each 28-day cycle. Nivolumab should be administered after the dose of TAK-659 is taken, and the infusion should start within 30 minutes after the dose of TAK-659 is administered.
(n) The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.
(o) Response assessments for solid tumors, including CT scan with contrast (or MRI if clinically indicated) of the chest, abdomen, pelvis, and other known sites of disease (eg, head and neck), relevant tumor markers (eg, CA125, PSA, CA19.9, CEA), and physical assessment of the disease will be performed at Screening, between Days 22 and 29 (predose) of Cycles 2, 4, and 6, and between Days 22 and 29 (predose) of every 3 cycles thereafter (ie, Cycle 9, 12, etc). The same imaging modality (CT scan with contrast or MRI) and/or the same methods for disease measurement must be used throughout the study. If the patient has had an appropriate CT scan or MRI performed within 28 days before Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at Screening. See Section 10.4.15 for details.
(p) The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated on Cycle 1 Day 1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (white blood cell [WBC] count), differential WBC count, and platelets. The chemistry panel consists of the following: sodium, potassium, CO_2, chloride, BUN, creatinine, bilirubin, ALP, AST, ALT, LDH, GGT, albumin, glucose, urate, calcium, phosphate, magnesium, amylase, lipase, total protein, cardiac troponin I and T (cTnI and cTnT), and CPK.
(q) Laboratory assessments can be conducted within -3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise noted. Day 1 visits of Cycle 2 and beyond may be modified by up to 3 days for extenuating circumstances (ie, inclement weather, holidays, vacations, or other

administrative reasons).
(r) Urinalysis samples will be collected predose and analyzed at the site's local laboratory.
(s) A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine or serum pregnancy test must be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 is administered for that cycle. If a serum pregnancy test is performed within 3 days of dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1.
(t) An ophthalmic exam should be performed at Screening, on Cycle 2 Day 1, on Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 10.4.14 for details.
CCI [redacted]
(see Section 10.4.18). Suitable specimens are either a tumor block or a minimum of 10 unstained slides.
(v) Blood samples for plasma PK analysis will be collected as specified in Table A.
CCI [redacted]

Table A Dose Escalation ECG and PK Schedule: Cycle 1

	Cycle 1					
	Day 1		Day 2	Day 15		Day 16
	Single ECG	PK	PK	Single ECG	PK	PK
Predose (within 1 hour before dosing on all days) (a,b)	X	X	X (24 h after Day 1 dose ±1 h)	X	X	X (24 h after Day 15 dose ±1 h)
0.5 hour postdose (±10 min)		X			X	
1 hours postdose (±10 min)		X			X	
2 hours postdose (±10 min)	X	X		X	X	
4 hours postdose (±30 min)		X			X	
8 hours postdose (±30 min)		X			X	

When the timing of a PK, pharmacodynamic, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.
(a) On days when predose samples are collected, patients will be instructed to arrive at the clinic in the morning without taking their TAK-659 dose at home. The TAK-659 dose will be administered in the clinic after collection of all predose samples.
(b) The timing of the predose PK sample on Days 2, 15, and 16 should be encouraged to occur at approximately the same time as the TAK-659 dosing times on the previous days of the cycle to ensure that samples represent trough samples.

Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle)

	Screening (a)	Cycle 1				Cycle 2 and Beyond			EOT (b) (+10 Days)	Survival Follow-up	
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Days 22-29		PFS (c)	OS (d)
Informed consent (e)	X										
Inclusion/exclusion criteria	X										
Demographics and disease characteristics	X										
Complete medical history (f)	X	X									
Physical examination (f)	X	X	X	X	X	X	X		X		
Height	X										
Weight (g)	X	X				X			X		
Vital signs (h)	X	X	X	X	X	X	X		X		
ECOG performance status	X	X				X			X		
12-lead ECG (i)	X	X				X			X		
Monitoring of concomitant medications and procedures (j)	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first										
AE reporting (j)	Recorded from signing of the ICF through 28 days after the last dose of study drug or to the start of subsequent anticancer therapy, whichever occurs first										
	Serious adverse events (k) will be reported from signing of the ICF through 28 days after the last dose of study drug even if the patient starts nonprotocol therapy.										

Footnotes are on last table page.

Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle) (continued)

	Screening (a)	Cycle 1				Cycle 2 and Beyond			EOT (b) (+10 Days)	Survival Follow-up	
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Days 22-29		PFS (c)	OS (d)
Dosing											
TAK-659 administration (l,v)		TAK-659 is dosed PO QD every day beginning on Cycle 1 Day 1.									
Nivolumab administration (m,v)		TAK-659 single-agent treatment window; no nivolumab administered		Nivolumab is dosed every 2 weeks, starting on Cycle 1 Day 15, and on Days 1 and 15 for every cycle thereafter.							
TAK-659 administration (n)		TAK-659 is dosed PO QD every day.									
Nivolumab administration (n)		Nivolumab is dosed every 2 weeks on Days 1 and 15 of each treatment cycle.									
Patient diary review (m)		X	X	X	X	X	X	X	X		
Imaging/Response Assessments											
Tumor assessment for solid tumors by RECIST version 1.1 (CT scan/MRI) (p)	X							X		X (c)	
Sample/Laboratory Assessments											
Hematology/chemistry (q,r)	X	X	X	X	X	X	X		X		
Urinalysis (for hematuria and proteinuria evaluation) (r,s)	X			X		X					
Immune safety tests (r)	X	X	X	X	X	X	X		X		
Pregnancy test (t)	X	X				X					
Ophthalmic exam (u)	X					X			X		

Footnotes are on last table page.

Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle) (continued)

	Screening (a)	Cycle 1				Cycle 2 and Beyond			EOT (b) (+10 days)	Survival Follow-up	
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Days 22-29		PFS (c)	OS (d)
Tumor biopsy for pharmacodynamic assessment (v)	X			X		X (w)			X (y)		
CCI											
Blood sample for PBMCs (z)	X			X		X (w)			X (y)		
Blood sample for cytokine/chemokine measurement (aa)	X			X		X (w)			X (y)		
Blood sample for ctDNA (bb)	X			X		X (w)			X (y)		
Blood samples for PK (cc)		X	X	X		X					
Blood samples for pharmacogenetic studies	X (dd)										
Survival follow-up contact											X (d)

(a) Screening assessments are performed within 28 days before the Cycle 1 Day 1 dose. Screening assessments performed no more than 3 days before Day 1 will qualify as baseline assessments and need not be repeated, unless otherwise specified.
(b) The EOT visit will occur 28 days (+10 days) after the last dose of study drug or before the start of subsequent anticancer therapy if that occurs sooner.
(c) All patients, including those patients no longer on treatment, will be assessed for survival. Patients who stop treatment for any reason other than PD will continue to have follow-up visits for PFS. The PFS follow-up visit should be conducted at the site every 2 months from the last dose of study drug until PD for a maximum of 6 months from the date of the first dose of study drug or 3 months from the last dose of study drug until PD for a maximum of 6 months from the last dose of study drug. Information on any subsequent anticancer therapies will be collected during the survival follow-up period. For patients who discontinue study treatment before PD, investigator response assessments based upon available local data will also be collected during the survival follow-up period.
(d) After the occurrence of PD, patients will continue to have follow-up visits for OS. The OS information will be collected every 2 months until 12 months from the date of the last dose of study drug.
(e) Informed consent may be captured before the Screening period (28 days before the first dose).
(f) The Cycle 1 Day 1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 3 days before administration of the first dose of study drug (Cycle 1 Day 1). Complete physical examinations (including smoking history) will be performed

during Screening and will include a neurological exam. Complete physical exams will also be performed on Day 1 of each cycle and at the EOT visit. Symptom- or finding-directed physical examinations will be performed on Days 8, 15, and 22 of Cycle 1 and on Day 15 of Cycles 2, 3, and 4.
(g) Weight should be obtained at Screening, on Day 1 predose of each cycle, and at EOT.
(h) Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1 and 3 (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.
(i) 12-lead ECGs will be performed as detailed in Section 10.4.8.
(j) If a patient experiences immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocriopathies, nephritis, rash, and encephalitis), they will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first. During this AE follow-up period, concomitant medications and procedures should also be collected.
(k) Including serious PTEs; see Section 11.0.
(l) TAK-659 will be administered PO QD during 28-day cycles commencing on Cycle 1 Day 1 for patients in the single-agent treatment window. On days when nivolumab infusions are administered, the dose of TAK-659 should be taken first and is to be taken in the clinic.
(m) Nivolumab is to be administered either at 3 mg/kg or 240 mg IV as a 60-minute infusion starting on Cycle 1 Day 15 and on Days 1 and 15 of each 28-day cycle thereafter for patients in the single-agent treatment window. The dose of nivolumab will be consistent for all patients in the expansion cohorts and will be either 3 mg/kg or 240 mg IV. Nivolumab should be administered after the dose of TAK-659 is taken, and the infusion should start within 30 minutes after the dose of TAK-659 is administered.
(n) TAK-659 will be administered PO QD during 28-day cycles commencing on Cycle 1 Day 1 for patients not participating in the single-agent treatment window. Nivolumab is to be administered at 3 mg/kg or 240 mg IV as a 60-minute infusion on Days 1 and 15 of each 28-day cycle for patients not participating in the single-agent treatment window. The dose of nivolumab will be consistent for all patients in the expansion cohorts and will be either 3 mg/kg or 240 mg IV. On days when nivolumab infusions are administered, the dose of TAK-659 should be taken first and is to be taken in the clinic. The nivolumab infusion should start within 30 minutes after the dose of TAK-659 is administered.
(o) The study center staff will check the patient drug diary versus the patient's supply of TAK-659 tablets to assess compliance.
(p) Response assessments for solid tumors, including CT scan with contrast (or MRI if clinically indicated) of the chest, abdomen, pelvis, and other known sites of disease (eg, head and neck), relevant tumor markers (eg, CA125, PSA, CA19.9, CEA) and physical assessment of the disease, will be performed at Screening, between Days 22 and 29 (predose) of Cycles 2, 4, and 6, and between Days 22 and 29 (predose) of every 3 cycles thereafter (ie, Cycle 9, 12, etc). The same imaging modality (CT scan with contrast or MRI) and/or the same methods for disease measurement must be used throughout the study. If the patient has had an appropriate CT scan or MRI performed within 28 days before Cycle 1 Day 1, the results of that scan may be used for tumor lesion measurements at Screening. See Section 10.4.15 for details.
(q) The hematology and chemistry blood samples for Cycle 1 Day 1 may be collected within 3 days before dosing to ensure patient eligibility on study Day 1. If screening clinical laboratory testing was performed within 3 days before the Cycle 1 Day 1 dose, it need not be repeated on Cycle 1 Day 1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (white blood cell [WBC] count), differential WBC count, and platelets. The chemistry panel consists of the following: sodium, potassium, CO_2, chloride, BUN, creatinine, bilirubin, ALP, AST, ALT, LDH, GGT, albumin, glucose, urate, calcium, phosphate, magnesium, amylase, lipase, total protein, cardiac troponin I and T (cTnI and cTnT), and CPK.
(r) Laboratory assessments can be conducted within -3 days of the scheduled visit, with the exception of PK/pharmacodynamic assessments or unless otherwise

noted. Day 1 visits of Cycle 2 and beyond may be modified by up to 3 days for extenuating circumstances (ie, inclement weather, holidays, vacations, or other administrative reasons).
(s) Urinalysis samples will be collected predose and analyzed at the site's local laboratory.
(t) A serum pregnancy test will be performed for women of childbearing potential at Screening. A urine or serum pregnancy test must be performed predose on Day 1 of all cycles with negative results available before the first dose of TAK-659 is administered for that cycle. If a serum pregnancy test is performed within 3 days of dosing and the result is negative, the urine pregnancy test may be waived on Cycle 1 Day 1.
(u) An ophthalmic exam should be performed at Screening, on Cycle 2 Day 1, on Cycle 7 Day 1, every 6 cycles thereafter (±2 weeks), and at EOT. See Section 10.4.14 for details.
(v) Serial tumor biopsies will be obtained from approximately 10 patients enrolled in each expansion cohort at Screening, after 2 weeks of TAK-659 single-agent therapy, and after 6 weeks of the combination treatment. An additional, optional biopsy sample may be taken upon PD if the patient consents. Coagulation testing, consisting of PTT and PT, should be performed and assessed in advance of performing any tumor biopsy procedures.
(w) Only on Cycle 3 Day 1.
CCI

(y) Optional sample collection at time of relapse.
(z) Peripheral blood samples will be collected from all patients enrolled in the expansion phase at Screening and predose on Cycle 1 Day 15 and Cycle 3 Day 1 for pharmacodynamic assessment and their potential association with clinical activity of TAK-659 or in combination with nivolumab. Samples will be subjected to flow cytometry analysis to evaluate changes in immune cell populations.
(aa) Peripheral blood samples will be collected at Screening and predose on Cycle 1 Day 15 and Cycle 3 Day 1 for pharmacodynamic assessment and their potential association with clinical activity of TAK-659 or in combination with nivolumab. Samples will be assayed to measure a panel of cytokines and chemokines.
(bb) Peripheral blood samples will be collected at Screening and predose on Cycle 1 Day 15 and Cycle 3 Day 1 for identification of candidate biomarker(s) predictive of clinical activity of the combination of TAK-659 and nivolumab. ctDNA will be purified from collected samples from analysis including, but not limited to, sequencing.
(cc) Blood samples for plasma PK analysis will be collected as specified in Table B during Cycles 1-4.
(dd) A peripheral blood sample will be obtained at Screening for the purpose of genotyping patients for certain polymorphisms in genes that may be involved in the metabolism and/or clearance of TAK-659 (eg, CYP2D6). This sample may be collected during the course of the study if the sample cannot be collected at Screening.

Table B Dose Expansion PK Schedule: Cycles 1 through 4

	Cycle 1			Cycle 2	Cycle 3	Cycle 4
	Day 1	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**Day 1**
Predose (within 1 hour before dosing on all days) (a, b)			X	X	X	X
1 hour postdose (±10 minutes)	X					
2-4 hours postdose	X		X			
At time of clinic visit		X (c)				

When the timing of a PK, pharmacodynamic, or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood samples.
(a) On days on which predose samples are collected, patients will be instructed to arrive at the clinic in the morning without taking their TAK-659 dose at home. The TAK-659 dose will be administered in the clinic after collection of all predose samples.
(b) The timing of the predose PK samples should be encouraged to occur at approximately the same time as TAK-659 dosing times on previous days to ensure that samples represent trough samples.
(c) For the Cycle 1 Day 8 visit, patients will be instructed to take their TAK-659 dose at home before their clinic visit. The PK sample can be collected at any time during the clinic visit. A distribution of clinic visit times during the day across patients is to be encouraged to provide a range of postdose sampling times across the study population.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential patients, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. If trial-related duties and functions are assigned to any individual or party, ensure that this individual or party is qualified to perform those trial-related duties and functions, and implements procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH. and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D ECOG Scale for Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

Appendix E Cockcroft-Gault Equation

For male patients:

$$\text{Creatinine clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For female patients:

$$\text{Creatinine clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix F New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix G Medications, Supplements, and Food Products that are Strong CYP3A and/or P-gp Inhibitors or Inducers

Medication, Supplement, or Food Product (a,b)	Required Washout Period Before First Dose
Strong CYP3A Reversible Inhibitors and/or P-gp Inhibitors	
amiodarone azithromycin captopril carvedilol cyclosporine diltiazem dronedarone erythromycin felodipine ketoconazole itraconazole nefazodone posaconazole quercetin quinidine ranolazine ticagrelor verapamil voriconazole	5 times the inhibitor half-life (if a reasonable half-life estimate is known), or 7 days (if a reasonable half-life estimate is unknown)
Strong CYP3A Mechanism-based Inhibitors	
clarithromycin (c) conivaptan (c) mibefradil (c,d) telithromycin	7 days, or 5 times the inhibitor half-life, whichever is longer
grapefruit-containing foods and beverages	5 days
Strong CYP3A Inducers and/or P-gp Inducers	
avasimibe (e) carbamazepine phenobarbital phenytoin primidone rifabutin rifapentine rifampin St. John's wort	7 days, or 5 times the inducer half-life, whichever is longer

Footnotes are on the following page.

(a) Note that the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ DrugInteractionsLabeling/ucm080499.htm). If a medication, supplement, or food/beverage is suspected or known to be a P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer but is not on the list, then its use must be discussed on a case-by-case basis with the medical monitor or designee to assess the relative benefit and risk.
(b) Note that medications used to treat HIV or hepatitis C infection that are strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.
(c) Also inhibitor of P-gp.
(d) Withdrawn from the US market due to safety reasons.
(e) Not marketed in the US.

Appendix H Methods of Contraception Considered to be Effective

Acceptable Methods Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable 2
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence [4]

Methods that are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

1. Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
2. Contraception methods that in the context of this guidance are considered to have low user dependency.
3. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.
4. In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
5. A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Appendix I Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

All sites of disease, target and nontarget lesions must be assessed at Baseline. Objective disease status is to be recorded at each evaluation using the response categories and **definitions provided in this section.**

All sites of measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at Baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target site of measurable lesions.

Disease Response Criteria for Target and Nontarget Lesions

Evaluation of Target Lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
Evaluation of nontarget lesions	
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[39]
Abbreviation: LD = longest diameter.

The following table summarizes the overall response status calculation at each time point for patients who have measurable disease per RECIST at baseline.

Time Point Response: Patients With Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47. [39]
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

The following table summarizes the overall response status calculation at each time point for patients who have nonmeasurable (therefore nontarget) disease at baseline.

Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[34]
Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for nontarget disease because SD is increasingly used as endpoint for assessment of efficacy in some trial so to assign this category when no lesions can be measured is not advised.

Appendix J Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Update approved indications for nivolumab.

The primary change occurs in Section 4.1.2.2 Nivolumab:

Added text: Nivolumab is approved in the European Union (EU) for advanced melanoma. Following initial approval in melanoma, nivolumab was approved the US for the treatment of metastatic NSCLC after prior chemotherapy and in the **European Union** for the treatment of squamous cell NSCLC after prior chemotherapy. It is also approved in the U**nited** S**tates** for the treatment of advanced renal cell carcinoma in patients who have received prior anti-angiogenic therapy **and for the treatment of patients with metastatic or recurrent HNSCC following progression on platinum-based therapy. More recently, the US Food and Drug Administration (FDA) granted accelerated approval for nivolumab for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy. See the current versions of the Opdivo United States Prescribing Information [USPI] [17] and Summary of Product Characteristics [SmPC] [18] for further details on indications approved in the United States and European Union, respectively.**

Rationale for Change:

To provide updated information.

Change 2: Update information regarding nonclinical studies of TAK-659 in combination with anti-programmed cell death protein 1 therapy.

The primary change occurs in Section 4.1.3 Nonclinical Experience:

Initial wording:	Preclinical studies show that SYKi results in loss of myeloid-derived suppressor cells (MDSCs) and activation of T-cell response both in vitro and in vivo. Although TAK-659 did not impact T cell function directly, a synergistic activity is expected with a PD-1 inhibitor in combination with TAK-659 in tumors where SYK-mediated MDSC or B-cell immunosuppression is active. The synergistic benefit of administering an anti-PD-1 with TAK-659 has been observed preclinically, and this effect could be indirectly attributed to the decrease in CD11b+ MDSC or B220+ B cells in the tumor-infiltrating lymphocytes (TILs) of TAK-659-treated tumors.
Amended or new wording:	~~Pre~~**Non**clinical studies show that ~~SYKi~~ **SYK inhibition** results in loss of myeloid-derived suppressor cells (MDSCs) and activation of T-cell response both in vitro and in vivo. ~~Although TAK-659 did not impact T cell function directly, a~~

~~synergistic activity is expected with a PD-1 inhibitor in combination with TAK-659~~ **TAK-659 in combination with anti-PD-1 therapy has shown regulation of B cells, NK cells, and macrophages in syngeneic nonclinical mouse models. The combination effects in immune cells are model and context dependent, and combination activity would be greatest** in tumors where SYK-mediated MDSC or B-cell immunosuppression is active. ~~The synergistic benefit of administering an anti-PD-1 with TAK-659 has been observed preclinically, and~~ **The** ~~pre~~**nonclinical combination treatment of TAK-659 and anti-PD-1 therapy provides therapeutic advantage over single-agent treatment with durable tumor growth inhibition, maintained complete responses (CRs), and a vaccinal memory effect.** ~~t~~This effect could be indirectly attributed to the decrease in CD11b+ MDSC or B220+ B cells in the tumor-infiltrating lymphocytes (TILs) of TAK-659-treated tumors.

Rationale for Change:

To provide updated information.

Section 4.2 Rationale for the Proposed Study also contains this change.

Change 3: Update summaries of TAK-659 clinical experience and risks and benefits.

The primary change occurs in Section 4.1.4 Clinical Experience:

Description of Change: Replaced previous text with updated safety, efficacy, and PK (where available) data from Studies C34001, C34002, and C34003.

Rationale for Change:

To provide updated information.

The following sections also contain this change:

- Section 4.1.5 Risks and Benefits.
- Section 4.2.1 Rationale for Dose and Schedule Selection.

Change 4: Add an option to conduct a nivolumab fixed-dose evaluation cohort.

The primary change occurs in Section 7.1 Overview of Study Design:

Added text: **After the RP2D of TAK-659 has been identified, on the basis of evaluation of the combination with a weight-based dose of nivolumab (3 mg/kg), this RP2D of TAK-659 may be evaluated in combination with a fixed dose of 240 mg IV nivolumab following discussion between the investigator and sponsor. For single-agent nivolumab, the fixed dose is expected to have equivalent exposure, safety, and efficacy as the weight-based (3 mg/kg) dose. If the nivolumab fixed dose is evaluated in combination with the TAK-659 RP2D, 3 patients will be initially enrolled into the cohort. Following evaluation of the safety, efficacy, and any available PK data, along with discussions between the investigator and**

sponsor, 3 additional patients may be enrolled into the cohort for a total of 3 to 6 patients. If ≥1 out of 6 patients experiences dose-limiting toxicity (DLT) during Cycle 1, or significant safety issues are seen in Cycle 2 and beyond, re-evaluation of the TAK-659 RP2D when administered with a fixed dose of nivolumab is permitted

The dose of nivolumab in the expansion cohorts will be either 3 mg/kg or 240 mg IV, dependent on whether the 240 mg fixed-dose cohort is evaluated. If the 240 mg fixed-dose cohort is evaluated and deemed safe and tolerable, the dosing regimen may switch to 240 mg, on the basis of change in clinical practice and discussion between the investigator and sponsor. If the nivolumab fixed-dose evaluation cohort is not run, the dose of nivolumab for all patients in the dose expansion phase will be 3 mg/kg.

Rationale for Change:

To evaluate the dose regimen recently approved by the US FDA.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 4.1.2.2 Nivolumab.
- Section 4.2.1 Rationale for Dose and Schedule Selection.
- Section 7.2 Number of Patients.
- Section 9.1.2 Nivolumab.
- Section 9.4 Dose Escalation Rules.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnotes m and n.

Change 5: Identify how a study cycle is defined and the requirement for the start of a new cycle in the event of a study drug interruption, and provide a source of further guidance on calculating cycle length.

The primary change occurs in Section 7.1 Overview of Study Design:

Added text: **During dose escalation, the Cycle 1 DLT-evaluation period typically will be 28 days. However, in the event of a nivolumab dosing interruption, a cycle length may be extended. If the second dose of nivolumab planned for Cycle 1 Day 15 is held and then dosed within the original 28-day cycle, the dose will be considered the second dose of Cycle 1, leading to a cycle with a maximum total of 42 days. The actual doses of TAK-659 received during this 28- to 42-day DLT-evaluation period will be assessed against the planned doses of TAK-659 (daily dose × cycle days) to determine whether the patient has received at least 75% of planned**

doses of TAK-659 to be DLT evaluable. When the second dose is administered, procedures at the original scheduled visit (ie, Cycle 1 Day 15) should be performed. If the second dose of nivolumab is interrupted for a period of time that extends beyond the original 28-day cycle, this dose will be considered missed. In this case, independent of whether the patient has received 75% of the planned doses of TAK-659, the patient will receive only one of the 2 nivolumab doses planned for Cycle 1 and, therefore, is not evaluable for DLT.

In Cycle 2 and beyond, during escalation and during the expansion phase of the study, if a nivolumab dose is delayed because of AEs, when the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point per protocol. However, if nivolumab is delayed past the next scheduled time point per protocol and TAK-659 dosing is also interrupted, the next scheduled time point will be delayed until dosing with either drug resumes.

Rationale for Change:

To ensure that patients receive appropriate monitoring and that treatment cycles are clinically meaningful.

Section 9.5 Dose Modification Guidelines also contains this change.

Change 6: Clarify that the maximum tolerated dose/maximally administered dose/recommended phase 2 dose will be determined using weight-based nivolumab dosing.

The primary change occurs in Section 7.1 Overview of Study Design:

Initial wording:	The dose of nivolumab will be 3 mg/kg IV.
Amended or new wording:	**While the MTD/maximally administered dose (MAD)/RP2D of TAK-659 are being determined, ~~T~~**the **starting** dose of nivolumab will be 3 mg/kg IV.

Rationale for Change:

To provide clarification.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 4.2.1 Rationale for Dose and Schedule Selection.
- Section 9.4 Dose Escalation Rules.

Change 7: Clarify the use of blood samples for biomarker analysis.

The primary change occurs in Section 7.1 Overview of Study Design:

Initial wording:	In addition to analysis of tumor biopsy samples as described above for a subset of patients in each expansion cohort, blood samples will be collected from all patients enrolled in the expansion phase of the study and analyzed for changes in immune cell populations in the course of treatment, levels of cytokines and chemokines known for or deemed relevant to tumor growth or antitumor activity of TAK-659 or the combination, and ctDNA. The result will be compared with that obtained from the analysis of biopsied tumor samples and used to identify a biomarker(s) that would enable monitoring the activity of TAK-659 and the combination in future studies using peripheral blood samples. In addition, a biomarker(s) or assay may be developed for selecting patients who would benefit the most from treatment with the combination of TAK-659 and nivolumab.
Amended or new wording:	In addition to analysis of tumor biopsy samples as described above for a subset of patients in each expansion cohort, blood samples will be collected from all patients enrolled in the expansion phase of the study and analyzed for **posttreatment** changes in immune cell populations in the course of treatment, levels of cytokines and chemokines known for or deemed relevant to tumor growth or antitumor activity of TAK-659 or the combination, and ctDNA **quantity and characteristics.** The result will be compared with that obtained from the analysis of **paired** ~~biopsied~~ tumor **biopsy** samples and used to identify a biomarker(s) that would enable monitoring the activity of TAK-659 and the combination in future studies using peripheral blood samples. In addition, **postdose change of** a biomarker(s) ~~or assay~~ may be ~~developed~~ **evaluated** for ~~selecting patients who would benefit the most from treatment with the combination of TAK-659 and nivolumab~~ **its (their) association with clinical responses from treatment with TAK-659 in combination with nivolumab.**

Rationale for Change:

Required additional information.

Change 8: Update the estimated number of patients in the study.

The primary change occurs in Section 7.2 Number of Patients:

Initial wording:	It is expected that approximately 120 patients will be enrolled in the study from approximately 25 study centers in North America and Europe: approximately 9 to 12 patients in the dose escalation cohort and approximately 36 patients (30 evaluable patients+15% dropout) in each of the 3 dose expansion cohorts. Enrollment is defined as the time of the initiation of the first dose of study drug.

Amended or new wording:	It is ~~expected~~ **estimated** that ~~approximately 120~~**126** patients will be enrolled in the study from approximately 25 study centers in North America and Europe: approximately 9 to 12 patients ~~in~~**among** the dose escalation cohort**s evaluating weight-based dosing of nivolumab, 3 to 6 patients in the possible nivolumab fixed-dose evaluation cohort,** and approximately 36 patients (30 evaluable patients+15% dropout) in each of the 3 dose expansion cohorts. Enrollment is defined as the time of the initiation of the first dose of study drug.

Rationale for Change:

To reflect additional patients in the new, optional nivolumab fixed-dose evaluation cohort.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 7.1 Overview of Study Design.
- Section 14.3 Determination of Sample Size.

Change 9: Update the inclusion criterion regarding minimum creatinine clearance laboratory value for entry into the study.

The primary change occurs in Section 8.1 Inclusion Criteria, criterion 6:

Initial wording:	• Serum creatinine must be ≤1.5×ULN or creatinine clearance or calculated creatinine clearance must be >50 mL/minute (See Appendix E).
Amended or new wording:	• ~~Serum c~~**C**reatinine **clearance** must be ~~≤1.5×ULN or creatinine clearance or calculated creatinine clearance must be >50~~ **≥60** mL/minute **as estimated by the Cockcroft Gault equation** (~~S~~see Appendix E) **or based on urine collection (12 or 24 hours).**

Rationale for Change:

To be consistent with other TAK-659 protocols.

The following sections also contain this change:

- Section 4.1.4.1 Clinical Pharmacokinetics of TAK-659
- Section 10.4.12.1 Clinical Chemistry, Hematology, and Urinalysis

Change 10: Update the inclusion criterion regarding minimum hemoglobin laboratory value for entry into the study.

The primary change occurs in Section 8.1 Inclusion Criteria, criterion 6:

Initial wording:	• Hemoglobin must be ≥8 g/dL, absolute neutrophil count (ANC) must be ≥1500/μL, and platelet count must be ≥75,000/μL.

Amended or new wording:	• Hemoglobin must be ≥~~8~~**9** g/dL, absolute neutrophil count (ANC) must be ≥1500/µL, and platelet count must be ≥75,000/µL.

Rationale for Change:

To be consistent with other TAK-659 protocols.

Change 11: Update the inclusion criteria regarding permitted lipase and amylase concentrations values for entry into the study.

The primary change occurs in Section 8.1 Inclusion Criteria, criterion 6:

Added text:	• **Lipase must be ≤1.5×ULN and amylase ≤1.5×ULN with no clinical symptoms suggestive of pancreatitis and cholecystitis.**

Rationale for Change:

Required additional information.

Change 12: Update the inclusion criterion regarding permissible blood pressure in hypertensives patients for entry into the study.

The primary change occurs in Section 8.1 Inclusion Criteria, criterion 6:

Added text:	• **Blood pressure ≤Grade 1 (hypertensive patients are permitted if their blood pressure is controlled to ≤Grade 1 by hypotensive medications and glycosylated HbA1C ≤6.5%).**

Rationale for Change:

Required additional information.

Change 13: Clarify that patients in the non-small cell lung cancer cohort with epidermal growth factor receptor or anaplastic lymphoma kinase genomic alternation should have had progressive disease (PD) on United States Food and Drug Administration–approved therapy.

The primary change occurs in Section 8.1 Inclusion Criteria, criterion 10:

Initial wording:	• Patients with EGFR or ALK genomic alternations should have PD on prior therapy for these aberrations.
Amended or new wording:	• Patients with EGFR or ALK genomic alternations should have PD on prior **US FDA-approved** therapy for these aberrations.

Rationale for Change:

Required additional information.

Change 14: Update exclusion criteria regarding patients with history of autoimmune disease, type I diabetes mellitus, childhood asthma, and thyroid disorders.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 2:

Initial wording:	Active, known, or suspected autoimmune disease.
Amended or new wording:	**Active~~, known,~~ or suspected autoimmune disease or a history of known autoimmune disease, with the exception of:** • **Patients with vitiligo, type I diabetes mellitus, resolved childhood asthma/atopy, residual hypothyroidism due to autoimmune condition requiring only hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.**

Rationale for Change:

Required additional information.

Section 2.0 STUDY SUMMARY also contains this change.

Change 15: Update the restrictions on corticosteroid-based medication.

The primary change occurs in Section 8.2 Exclusion Criteria, criteria 3 and 14:

Initial wording:	3. Diagnosis of immunodeficiency or any condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of treatment. … 14. Treatment with high-dose corticosteroids for anticancer purposes within 14 days before the first dose of TAK-659; daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.
Amended or new wording:	3. ~~Diagnosis or immunodeficiency or any~~**Any** condition requiring systemic treatment with ~~either~~ corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days ~~of treatment~~**before first dose of study drug.** • **Corticosteroids for topical use or in nasal spray are allowed, as are inhaled steroids and adrenal replacement steroid doses >10 mg daily in the absence of active autoimmune disease.** … ~~14. Treatment with high-dose corticosteroids for anticancer purposes within 14 days~~

~~before the first dose of TAK-659; daily dose equivalent to 10 mg oral prednisone or less is permitted. Corticosteroids for topical use or in nasal spray or inhalers are allowed.~~

Rationale for Change:

Required additional information.

Section 9.6 Concomitant Medications and Procedures also contains this change.

Change 16: Clarify exclusion criterion regarding previous anticancer treatments.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 10:

Initial wording:	Systemic anticancer treatment or radiotherapy less than 2 weeks before the first dose of study treatment (≤4 weeks for monoclonal antibodies with evidence of PD) or not recovered from acute toxic effects from prior chemotherapy and radiotherapy.
Amended or new wording:	Systemic anticancer treatment **(including investigational agents)** or radiotherapy ~~less than~~ <2 weeks before the first dose of study treatment (≤4 weeks for ~~monoclonal antibodies with evidence of PD~~ **antibody-based therapy including unconjugated antibody, antibody-drug conjugate, and bi-specific T-cell engager agents; ≤8 weeks for cell-based therapy or antitumor vaccine) or have** not recovered from acute toxic effects from prior chemotherapy and radiotherapy.

Rationale for Change:

To be consistent with other TAK-659 protocols.

Change 17: Update exclusion criterion regarding patients with another malignancy.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 16:

Initial wording:	Active secondary malignancy that requires treatment. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.
Amended or new wording:	~~Active secondary malignancy that requires treatment.~~ **Patients with another malignancy within 2 years of study start.** Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection and are considered disease-free at the time of study entry.

Rationale for Change:

To be consistent with other TAK-659 protocols.

Change 18: Update the restrictions on the use of non-oncology vaccine therapies.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 19:

Added text:
- **Non-oncology vaccine therapies for prevention of infectious diseases (eg, human papillomavirus [HPV] vaccine) within 4 weeks of study drug administration. The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction. Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted but must be discussed with the sponsor's medical monitor and may require a washout period before and after administration of vaccine.**

Rationale for Change:

Required additional information.

Section 9.6 Concomitant Medications and Procedures also contains this change.

Change 19: Update language regarding use of P-glycoprotein and/or strong cytochrome P450 3A inhibitors or inducers and clarify exceptions to their use for treatment of an AE requiring a TAK-659 hold.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 19:

Initial wording:
- Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. The use of these agents is not permitted during the study. See Appendix G for a list of prohibited strong CYP3A reversible inhibitors and/or P-gp inhibitors based on the US FDA draft DDI guidance.
- Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. The use of these agents is not permitted during the study. See Appendix G for a list of prohibited strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the US FDA draft DDI guidance.

Amended or new wording:
- Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. **In general,** ~~T~~**t**he use of these agents is not permitted during the study **(see Section 9.6 for details)**. See Appendix G for a **nonexhaustive** list of ~~prohibited~~ strong CYP3A reversible

inhibitors and/or P-gp inhibitors based on the US FDA draft DDI guidance.

- Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. **In general,** ~~T~~the use of these agents is not permitted during the study **(see Section 9.6 for details)**. See Appendix G for a **nonexhaustive** list of ~~prohibited~~ strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers based on the US FDA draft DDI guidance.

Rationale for Change:

To be consistent with other TAK-659 protocols.

The following sections also contain this change:

- Section 9.6 Concomitant Medications and Procedures.
- Appendix G Medications, Supplements, and Food Products that are Strong CYP3A and/or P-gp Inhibitors or Inducers

Change 20: Update the language for dose-expansion patients regarding activated partial thromboplastin time or plasma thromboplastin.

The primary change occurs in Section 8.2 Exclusion Criteria, criterion 20:

Initial wording:	• Activated partial thromboplastin time (aPTT) or plasma thromboplastin (PT) outside the normal range.
Amended or new wording:	• Activated partial thromboplastin time (aPTT) or plasma thromboplastin (PT) outside the ~~normal range~~**institution's standard of care**.

Rationale for Change:

Required additional information.

Change 21: Provide additional instruction on how to address missed doses of study drug.

The primary change occurs in Section 9.2 Missed Doses and Infusion Delays:

Added text:

9.2 Missed Doses and Infusion Delays

If a patient does not take the TAK-659 dose at his/her scheduled dosing time (±6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments on that day or subsequent days to account for the missed dose, for example, by taking a double dose of TAK-659 on the following day. Patients should record any skipped doses in their dosing diaries (see the Study Manual) and resume

dosing at the next scheduled time with the prescribed dosage.

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after TAK-659 ingestion, patients should not re-dose following emesis and should record the time of the emesis in his/her dosing diary (see the Study Manual). Patients should resume dosing at the next scheduled time with the prescribed dosage.

Patients with nivolumab infusion delays of greater than 6 weeks should normally discontinue treatment and enter the Follow-up period, with the exception of cases where benefit-risk may justify continued study therapy (eg, patient deriving clinical benefit who requires prolonged steroid taper for management of non-DLT AEs). These situations require consultation and agreement between the investigator and medical monitor.

Rationale for Change:

Required additional information.

Change 22: Update dose-limiting toxicity evaluation period.

The primary change occurs in Section 9.4 Dose Escalation Rules:

Initial wording:	The minimum treatment and safety evaluation requirements are met if, in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1) plus 2 doses of nivolumab, and observed for ≥28 days (unless DLT occurs before the end of the 28-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur.
Amended or new wording:	The minimum treatment and safety evaluation requirements are met if~~,~~ in Cycle 1, the patient has been treated with TAK-659 for ≥21 days (receiving at least 75% of planned doses of TAK-659 in Cycle 1~~)~~ **(depending on cycle length)** plus 2 doses of nivolumab, and observed for ≥28 **to 42** days (unless DLT occurs before the end of the 28~~-~~ **to 42**-day evaluation period) following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and investigators to conclude that a DLT did not occur.

Rationale for Change:

To account for time that may result due to a dose delay.

The following sections also contain this change:

- Section 7.1 Overview of Study Design.
- Section 9.3 Definitions of DLT.
- Section 14.1.1 Analysis Sets.

Change 23: Update the guidelines for TAK-659 and nivolumab dose modifications for hematologic and nonhematologic toxicity.

The primary change occurs in Section 9.5.2 Dose Modification for Hematologic and Nonhematologic Toxicity: TAK-659 and Nivolumab:

Description of Change:

- Table 9.c: updated or added nivolumab dose modifications for the following:
  - Grade 4 neutrophil count (ANC) decreased.
  - Febrile neutropenia.
  - Grade 3 and 4 platelet count decreased.
  - Grade 3 and 4 anemia.
- Table 9.d: updated or added nivolumab dose modifications for the following:
  - Grade 2 or 3 colitis.
  - Grade 2 or 3 encephalitis.
  - Grade 1-3 serum creatinine.
  - Grade 2 or 3 drug-related uveitis.
  - Grade 3 drug-related pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction.
  - Grade 3 hypophosphatemia.
  - Grade 3 asymptomatic enzyme elevations.

Rationale for Change:

Corrected for accuracy.

Change 24: Clarify use of concomitant medications and procedures.

The primary change occurs in Section 9.6 Concomitant Medications and Procedures (formerly Section 9.5 Excluded Concomitant Medications and Procedures):

Initial wording:

9.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any antineoplastic therapy other than TAK-659. This includes chronic use of corticosteroids at daily doses greater than the equivalent of 10 mg of prednisone as part of any anticancer treatment regimens. If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD). Palliative radiotherapy for pain control in a pre-existing lesion may

be considered after discussion with the sponsor's clinical representative.

- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) in Cycle 1 during dose escalation. Patients who experience severe and/or febrile neutropenia can be managed with growth factor support if needed in accordance with American Society of Clinical Oncology (ASCO) guidelines.
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications required as an ongoing therapy is not permitted with the following exceptions and clarification:
  - Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
  - Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone or equivalents.
  - A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy or prevention of infusion reactions) or for treatment of non-autoimmune conditions (eg, allergic reaction caused by contact allergen or drug-related nausea and/or vomiting) are permitted.

Systemic treatment with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A is not permitted in this study because in vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix G for excluded medications, supplements, and food products; Appendix G also provides the required washout period for these substances before the first dose of study drug. Note that medications used to treat HIV or hepatitis C infection are not listed below or in Appendix G because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a or P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list below and in Appendix G, then its use must be approved on a case-by-case basis by the medical monitor after consultation with the clinical pharmacologist and assessment of the relative benefit and risk.

Amended or new wording:

9.5~~6~~ ~~Excluded~~ Concomitant Medications and Procedures

During the course of the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood

transfusions, should be recorded from signing of the informed consent form (ICF) through 28 days after the last dose of study drug. However, if a patient experiences immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocriopathies, nephritis, rash, and encephalitis as described in the nivolumab USPI [17]), they will be followed to resolution or stabilization, the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first. During this AE follow-up period, concomitant medications and procedures should also be collected.

The following ~~medications and procedures are prohibited~~ **restrictions apply** during the study:

- Any antineoplastic therapy other than TAK-659 **is prohibited on study.** ~~This includes chronic use of corticosteroids at daily doses greater than the equivalent of 10 mg of prednisone as part of any anticancer treatment regimens.~~ If alternative therapy is required for treatment of the patient's tumor, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD) **is not permitted during study**. Palliative radiotherapy for **local** pain**/symptom** control in a preexisting **nontarget** lesion**, if required,** may be considered after discussion with the sponsor's clinical representative. **Details of the palliative radiotherapy should be documented in the source records and eCRF, including dates of treatment, anatomical site, dose administered and fractionation schedule, and associated AEs.**
- Prophylactic use of myeloid growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF]) ~~in Cycle 1 during dose escalation~~ **is not recommended at the study start.** Patients who experience severe and/or febrile neutropenia during the study can be managed with growth factor support if needed**, including prophylactic use of growth factor,** in accordance with American Society of Clinical Oncology (ASCO) guidelines.
- Systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications required as an ongoing therapy is not permitted with the following exceptions and clarification:
  - ~~Subjects~~**Patients** are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
  - Physiologic replacement doses of systemic corticosteroids are permitted, even

if >10 mg/day prednisone or equivalents.

- A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy or prevention of infusion reactions) or for treatment of non-autoimmune conditions (eg, allergic reaction caused by contact allergen or drug-related nausea and/or vomiting) are permitted.

- **Non-oncology vaccine therapies for prevention of infectious diseases (eg, HPV vaccine) within 4 weeks of study drug administration.**
  - **The inactivated seasonal influenza vaccine can be given to patients before treatment and while on therapy without restriction.**
  - **Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella) may be permitted but must be discussed with the sponsor's medical monitor and may require a washout period before and after administration of vaccine.**
- ~~Systemic treatment~~ **Concurrent systemic administration of TAK-659** with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A ~~is not permitted~~ **should be avoided** in this study~~. because i~~**I**n vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix G for ~~excluded~~ **a nonexhaustive list of** medications, supplements, and food products~~; Appendix G also provides the required washout period for these substances before the first dose of study drug.~~ **that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA Draft DDI Guidance.**
  - Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole.
  - Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin.
  - Antimycobacterials: rifabutin, rifampin, rifapentine.
  - Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone.
  - Antidepressant: nefazodone.
  - Immunosuppressant: cyclosporine.
  - Calcium channel blockers: diltiazem, felodipine, mibefradil, verapamil.
  - Antiarrhythmics: amiodarone, dronedarone, quinidine.
  - Antiplatelet: ticagrelor.
  - Antilipid: avasimibe.
  - Other cardiovascular: captopril, carvedilol, ranolazine.
  - Vasopressin antagonist: conivaptan.

– Food/Herbals/Supplements: grapefruit-containing food and beverages, St. John's wort, quercetin.

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and in Appendix G may be used for AE management provided there is no appropriate alternative treatment available per the investigator's judgment and the dosing is not concurrent with TAK-659. This situation requires discussion between the investigator and the sponsor's medical monitor, and the discussion will be documented in the study file. Patients should be closely monitored for potential toxicities.

Note that medications used to treat HIV or hepatitis C infection are not listed ~~below~~ **above** or in Appendix G because patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. In addition, oncology medications are not listed because they are prohibited during the study. If a medication, supplement, or food/beverage is suspected or known to be a ~~or~~ P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer, but is not on the list ~~below~~ **above** and in Appendix G, then its use must be ~~approved on a case-by-case basis by~~ **discussed with** the medical monitor **or designee** ~~after consultation with the clinical pharmacologist and assessment of~~ **to assess** the relative benefit and risk.

Rationale for Change:

Required additional information.

The following sections also contain this change:

- Section 10.4.9 Concomitant Medications and Procedures.
- Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote j.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote j.
- Appendix G Medications, Supplements, and Food Products that are Strong CYP3A and/or P-gp Inhibitors or Inducers.

Change 25: Add information on the management of diarrhea, edema, rash, hypophosphatemia, and enzyme elevations.

The primary change occurs in new Sections 9.8.3 Diarrhea through 9.8.7 Enzyme Elevations:

Added text: **9.8.3 Diarrhea**

Prophylactic antidiarrheals will not be used in this study; however, patients should be instructed to take loperamide or comparable antidiarrheal medication according to institutional or local practice, once infectious causes are ruled out.

Adequate fluid intake should be maintained to avoid dehydration, and any fluid deficit should be corrected before initiation of treatment with study drug and during treatment. Refer to Section 9.8.8.2 for management of diarrhea if immune-mediated colitis occurs during treatment.

9.8.4 Edema (Including Periorbital)

Peripheral and periorbital edema have been observed in patients treated with TAK-659. Management of the event, if it occurs, should follow the standard local practice, and dose modification should proceed following the dose modification guidelines in Table 9.d.

9.8.5 Rash With or Without Pruritus

Prophylactic measures should be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤10 mg per day or equivalent) is permitted. Refer to dose modification guidelines in Table 9.d for occurrence of Grade 3 or 4 rash. Refer to Section 9.8.8.8 for management of rash if immune-mediated dermatitis occurs during treatment.

9.8.6 Hypophosphatemia

Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise, refer to dose modification guidelines in Table 9.d.

9.8.7 Enzyme Elevations

9.8.7.1 Transaminase, Amylase, Lipase, and CPK Elevations

Elevations of transaminases, amylase, lipase, and CPK have been observed in patients treated with TAK-659. Events are generally asymptomatic and reversible with dose interruption. See dose modification guidelines in Table 9.d.

9.8.7.2 Lactate Dehydrogenase Elevations

Lactate dehydrogenase (LDH) elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic, and their clinical significance is unknown. No action, such as dose interruption, has been taken as a result of increased LDH; however, LDH elevation is reversible on the basis of experience in patients who had TAK-659 interrupted for other reasons.

Rationale for Change:

Required additional information.

Change 26: Clarify that smoking history should be collected with medical history.

The primary change occurs in Section 10.4.3 Medical History:

Initial wording:	During the Screening period, a complete medical history will be compiled for each patient.
Amended or new wording:	During the Screening period, a complete medical history **(including smoking history)** will be compiled for each patient.

Rationale for Change:

Required additional information.

The following sections also contain this change:

- Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote f.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote f.

Change 27: Include pulse oximetry in the collection of vital signs.

The primary change occurs in Section 10.4.6 Vital Signs:

Added text: **Pulse oximetry should be obtained before each dose of nivolumab and any time a patient has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator but should remain consistent for each individual patient throughout the study. If the patient's status changes, the investigator can alter the extent of exertion per their medical judgment. If a patient shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity.**

Rationale for Change:

Required additional information.

Change 28: Update list of laboratory tests to include creatine phosphokinase and cardiac troponin I and troponin T.

The primary change occurs in Section 10.4.12.1 Clinical Chemistry, Hematology, and Urinalysis:

Description of change: Added creatine phosphokinase (CPK) and cardiac troponin I and troponin T to Table 10a.

Rationale for Change:

Added because of elevations in CPK observed in patients treated with TAK-659 and elevations of troponin observed in patients treated with TAK-659 100 mg cohort in combination with nivolumab (3mg/kg) who developed cardiac toxicity.

The following sections also contain this change:

- Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote p.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote q.

Change 29: Update pregnancy testing to include both urine and serum pregnancy testing.

The primary change occurs in Section 10.4.13 Pregnancy Test:

Initial wording:	A urine pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose may be administered.
Amended or new wording:	A urine **or serum** pregnancy test will be performed predose on Day 1 of all cycles with negative results available before the first dose may be administered.

Rationale for Change:

Required additional information.

The following sections also contain this change:

- Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote s.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote t.

Change 30: Update the disease assessment criteria regarding verification of response and verification of progression.

The primary change occurs in Section 10.4.15 Disease Assessment:

Added text:

- **Verification of response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed no sooner than 28 days after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.**
- **Verification of progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression**

should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the patient is considered to not have PD.

Rationale for Change:

Required additional information.

Change 31: Update how pseudo disease progression is defined.

The primary change occurs in Section 10.4.15 Disease Assessment:

Initial wording:	Pseudo-progression has been described during treatment with nivolumab in multiple indications. Therefore, discontinuation of study treatment is not recommended unless PD (at least 25% increase in tumor burden compared with nadir at any single point during study treatment) has been confirmed in 2 consecutive imaging assessment at least 4 weeks apart. However, when the objectively assessed PD per imaging is accompanied by rapid clinical deterioration, immediate study drug discontinuation is indicated.
Amended or new wording:	Pseudo-progression has been described during treatment with nivolumab in multiple indications. Therefore, discontinuation of study treatment is not recommended unless PD (at least ~~25%~~ **20%** increase in tumor burden compared with nadir at any single point during study treatment) has been confirmed in 2 consecutive imaging assessment ~~4~~ **8** weeks apart **or more conveniently at the next scheduled imaging time point**. However, when the objectively assessed PD per imaging is accompanied by rapid clinical deterioration, immediate study drug discontinuation is indicated. **Refer to Section 10.4.16 for details regarding treatment beyond PD.**

Rationale for Change:

Corrected for accuracy.

Change 32: Clarify that tumor assessments should be collected for patients who have interruption(s) in study drug administration.

The primary change occurs in Section 10.4.15 Disease Assessment:

Added text:	**Tumor assessments for all patients should continue per protocol even if dosing is interrupted.**

Rationale for Change:

Required additional information.

Change 33: Indicate that additional exploratory independent review of study imaging data may occur if deemed necessary.

The primary change occurs in Section 10.4.15 Disease Assessment:

Added text: **The sponsor may consider an exploratory independent central review of the study imaging data using immune-related RECIST if deemed necessary.**

Rationale for Change:

Required additional information.

Change 34: Add section about treatment beyond disease progression.

The primary change occurs in new Section 10.4.16 Treatment Beyond Disease Progression:

Added text: **10.4.16 Treatment Beyond Disease Progression**

Contemporary immunotherapy protocols generally allow patients to continue treatment beyond initial radiographic evidence of PD following further investigation, as accumulating data indicates it is possible that some patients treated with immunotherapy may derive clinical benefit beyond initial RECIST-defined PD, which may not be captured by radiographic assessments. [36,37]In this study, patients treated TAK-659 in combination with nivolumab will be permitted to continue treatment beyond initial RECIST 1.1-defined PD if the following criteria are met:

1. **Investigator-assessed overall clinical benefit from continued treatment with nivolumab and/or TAK-659.**
2. **Tolerance of study drug(s).**
3. **Stable performance status.**
4. **Treatment beyond progression will not delay an imminent intervention to prevent serious complications of PD (eg, CNS metastases).**
5. **Patient provides written informed consent before receiving additional nivolumab or TAK-659 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.**

The decision to continue treatment beyond initial RECIST 1.1-defined progression should be discussed with the Takeda medical monitor and documented in the study records. Then, the patient may remain on the study and continue to receive monitoring according to the protocol-defined Schedule of Events.

A radiographic assessment/scan should be performed within 8 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD.

For the patients who continue study therapy beyond progression, further progression is defined as an additional ≥20% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and is therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

Treatment should be discontinued permanently upon documentation of further PD. If the patient experiences rapid PD (such as global deterioration as perceived by the investigator) before radiographic assessment within 8 weeks of original PD, the investigator can discontinue the study treatment without objective evidence of disease progression and report it as "symptomatic deterioration".

For statistical analyses, patients who continue study therapy beyond initial RECIST 1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

Rationale for Change:

Required additional information.

Change 35: Clarify timing of tumor biopsy sampling.

The primary change occurs in Section 10.4.17 Tumor Biopsies:

Initial wording:	The biopsy sample at Screening must be obtained at least 2 days after the last dose of any prior anticancer therapy and before the first dose of study drug treatment. Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an aPTT and PT within the normal range; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure.
Amended or new wording:	~~The biopsy sample at Screening must be obtained at least 2 days after the last dose of any prior anticancer therapy and before the first dose of study drug treatment.~~ Patients undergoing tumor biopsy procedures must have a platelet count >75,000/mm^3 and an aPTT and PT ~~within the normal range~~**based on site's institutional standard**; must not have an ECOG performance status >1; must not be receiving any anticoagulant therapy or antiplatelet agents; and must not have any other known coagulation abnormalities that would contraindicate the tumor biopsy procedure.

Rationale for Change:

Required additional information.

Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote v, also contains this change.

Change 36: Specify that cytokine/chemokine measurements will be taken from serum.

The primary change occurs in Section 10.4.20 Cytokine/Chemokine Measurements:

Initial wording:	Plasma will be extracted from blood samples and subjected to analysis of a panel of cytokines and chemokines using a multiplex platform.
Amended or new wording:	~~Plasma~~**Serum** will be extracted from blood samples and subjected to analysis of a panel of cytokines and chemokines using a multiplex platform.

Rationale for Change:

Required additional information.

Change 37: Clarify study drug dosing instructions on days when predose pharmacokinetic (PK) samples are scheduled.

The primary change occurs in Section 10.4.22 PK Measurements, Dose Escalation Cohorts subsection:

Initial wording:	**Dose Escalation Cohorts** Blood samples for determination of TAK-659 plasma concentrations will be obtained during Cycle 1 on Days 1, 2, 15, and 16 at the times indicated in Table A. The samples obtained on Days 2 and 16 should be obtained before TAK-659 dosing on those days. On those days, patients should be instructed to refrain from taking their TAK-659 dose at home before the clinic visit.
Amended or new wording:	**Dose Escalation Cohorts** Blood samples for determination of TAK-659 plasma concentrations will be obtained during Cycle 1 on Days 1, 2, 15, and 16 at the times indicated in Table A. ~~The samples obtained on Days 2 and 16 should be obtained before TAK-659 dosing on those days. On those days,~~ **For clinic visits where predose PK samples are scheduled,** patients ~~should~~ **will** be instructed to refrain from taking their TAK-659 dose at home before the clinic visit.

Rationale for Change:

To ensure that patients do not take study drug at home on any day when predose PK samples are scheduled.

Change 38: Add to the PK measurements section a rationale for conducting PK sampling at any time during the clinic visit on Cycle 1 Day 8 during dose expansion.

The primary change occurs in Section 10.4.22 PK Measurements, Dose Expansion Cohorts subsection:

Added text: **A distribution of clinic visit times during the day across patients is to be encouraged to provide a range of postdose sampling times across the study population.**

Rationale for Change:

To ensure consistency of PK-related information between the PK measurements section and Table B.

Change 39: Update reasons for completion of treatment.

The primary change occurs in Section 10.5 Completion of Treatment:

Initial wording:	Patients will be considered to have completed study treatment if they have an opportunity to complete 6 cycles of study treatment, if they achieve a CR, or if they experience PD.
Amended or new wording:	~~Patients will be considered to have completed study treatment if they have an opportunity to complete 6 cycles of study treatment, if they achieve a CR, or if they experience PD.~~**Patients will be treated until PD, occurrence of unacceptable toxicities, withdrawal due to other reasons, or the study is terminated by the sponsor. Study treatment can continue beyond initial RECIST 1.1 progression as specified in Section 10.4.16.**

Rationale for Change:

To be consistent with other TAK-659 protocols.

Section 2.0 STUDY SUMMARY also contains this change.

Change 40: Indicate that the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, not modified RECIST version 1.1, will be used to measure PD.

The primary change occurs in Section 10.7 Discontinuation of Treatment With Study Drug and Patient Replacement:

Initial wording:	• PD: as noted previously, PD per RECIST should be confirmed in 2 subsequent scans at least 4 weeks apart before treatment discontinuation is considered unless there are clear signs of rapid clinical progression. In addition, in rare situations, patients with confirmed PD may remain on study, after discussion between the investigator and the sponsor clinician, if it is felt that they are deriving a clinical benefit from doing so.
Amended or new wording:	• PD: as noted previously, PD per RECIST **1.1** should be confirmed in 2 subsequent scans ~~at least 4~~**8** weeks apart before treatment discontinuation is considered unless there are clear signs of rapid clinical progression. In addition, in rare situations, patients with confirmed PD may remain on study, after discussion between the investigator and the sponsor clinician, if it is felt that they are deriving a clinical benefit from doing so.

Rationale for Change:

To correct for accuracy.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Section 10.4.15 Disease Assessment.

Change 41: Update procedures for monitoring AEs and the period of observation.

The primary change occurs in Section 11.3 Monitoring of AEs and Period of Observation:

Added text:	• AEs will be reported from signing of the ICF through 28 days after administration of the last dose of study drug and recorded in the eCRFs. **However, immune-mediated toxicities that either result in discontinuation of nivolumab or both study treatments or occur during the 28-day AE follow-up period (including immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis as described in nivolumab USPI) will be followed to resolution or stabilization, or the start of alternative therapy, or a minimum of 100 days after last dose of study treatment, whichever occurs first.**

Rationale for Change:

Required additional information.

The following sections also contain this change:

- Section 7.3 Duration of Study. also contains this change.
- Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote j.
- Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote j.

Change 42: Clarify that PK parameters will be summarized using descriptive statistics.

The primary change occurs in Section 14.1.4 PK Analysis:

Initial wording:	Plasma PK parameters of TAK-659 will be summarized by dose group and by dosing cycle and day.
Amended or new wording:	Plasma PK parameters of TAK-659 will be summarized **using descriptive statistics** by dose group and by dosing cycle and day.

Rationale for Change:

Required additional information.

Section 2.0 STUDY SUMMARY also contains this change.

Change 43: Indicate that the relationship between PK and pharmacodynamics changes may be evaluated.

The primary change occurs in Section 14.1.5 Pharmacodynamic Analysis:

Added text: **In addition, the relationship between PK and pharmacodynamics changes may be evaluated as permitted by the data.**

Rationale for Change:

Required additional information.

Change 44: Update language regarding informed consent forms.

The primary change occurs in Section 16.2 Patient Information, Informed Consent, and Patient Authorization (formerly titled Subject Information, Informed Consent, and Subject Authorization):

Initial wording:	The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations. The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. … All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent.

Amended or new wording:

The ICF, ~~subject~~ **patient** authorization form (if applicable), and ~~subject~~ **patient** information sheet (if applicable) must be written in a language fully comprehensible to the prospective ~~subject~~ **patient**. It is the responsibility of the investigator to explain the detailed elements of the ICF, ~~subject~~ **patient** authorization form (if applicable), and ~~subject~~ **patient** information sheet (if applicable) to the ~~subject~~ **patient**. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. ~~In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.~~

The ~~subject~~ **patient**~~, or the subject's legally acceptable representative,~~ must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the ~~subject~~ **patient**~~, or the subject's legally acceptable representative,~~ determines he or she will participate in the study, then the ICF and ~~subject~~ **patient** authorization form (if applicable) must be signed and dated by the ~~subject~~ **patient**~~, or the subject's legally acceptable representative,~~ at the time of consent and prior to the ~~subject~~ **patient** entering into the study. ~~The subject~~**Patients** ~~or the subject's legally acceptable representative,~~ should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink.

…

All revised ICFs must be reviewed and signed by relevant ~~subjects~~ **patients** ~~or the relevant subject's legally acceptable representative~~ in the same manner as the original informed consent.

Rationale for Change:

Added to comply with International Council for Harmonisation (ICH) Section 4.2.6.

Appendix B Responsibilities of the Investigator also contains this change.

Change 45: Clarify language regarding study-site monitoring visits.

The primary change occurs in Section 15.1 Study-Site Monitoring Visits:

Deleted text:

All aspects of the study and its documentation will be subject to review by the sponsor or designee ~~(as long as blinding is not jeopardized)~~, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents.

Rationale for Change:

Corrected for accuracy.

Change 46: Remove time-bound references to the nivolumab USPI.

The primary change occurs in Section 17.0 REFERENCES:

Initial wording:	17. OPDIVO (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb, 2016.
Amended or new wording:	17. OPDIVO (nivolumab) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb, ~~2016~~ **dailymed.nlm.nih.gov/dailymed/.**

Rationale for Change:

To reflect the latest version of the prescribing information.

The following sections also contain this change:

- Section 4.1.5 Risks and Benefits.
- Section 9.5.2 Dose Modification for Hematologic and Nonhematologic Toxicity: TAK-659 and Nivolumab.
- Section 10.7 Discontinuation of Treatment With Study Drug and Patient Replacement.

Change 47: Update the Schedule of Events to include additional tests when nivolumab is dosed.

The primary change occurs in Appendix A Schedules of Events:

Description of Change:	Removed "Cycle 5, 6, and beyond" column and updated "Cycles 2, 3, and 4" column to indicate "Cycle 2 and beyond".

Rationale for Change:

To ensure appropriate monitoring of laboratory tests prior to nivolumab dosing on Day 15 of study cycles.

Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), also contains this change.

Change 48: Update timing of vital sign measurements for Cycle 1 Day 1.

The primary change occurs in Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote h:

Initial wording:	(h) Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1, 3, and 8 (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.

Amended or new wording:	(h) Measure vital signs before dosing. On Cycle 1 Day 1 only, also measure vital signs at 1 **and** 3~~, and 8~~ (±10 minutes) hours postdose. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes. Oxygen saturation will also be measured when vital signs are taken.

Rationale for Change:

Reduce unnecessary measurements.

Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote h, also contains this change.

Change 49: Clarify language regarding disease response assessments to include all relevant sites of disease.

The primary change occurs in Appendix A Schedules of Events, Schedule of Events for Dose Escalation (28-Day Cycle), footnote o:

Initial wording:	(n) Response assessments for solid tumors, including CT scan with contrast (or MRI if clinically indicated) of the chest, abdomen, and pelvis, relevant tumor markers (eg, CA125, PSA, CA19.9, CEA), and physical assessment of the disease will be performed at Screening, between Days 22 and 29 (predose) of Cycles 2, 4, and 6, and between Days 22 and 29 (predose) of every 3 cycles thereafter (ie, Cycle 9, 12, etc).
Amended or new wording:	(n) Response assessments for solid tumors, including CT scan with contrast (or MRI if clinically indicated) of the chest, abdomen, ~~and~~ pelvis, **and other known sites of disease (eg, head and neck),** relevant tumor markers (eg, CA125, PSA, CA19.9, CEA), and physical assessment of the disease will be performed at Screening, between Days 22 and 29 (predose) of Cycles 2, 4, and 6, and between Days 22 and 29 (predose) of every 3 cycles thereafter (ie, Cycle 9, 12, etc).

Rationale for Change:

Reduce unnecessary measurements.

Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnote p, also contains this change.

Change 50: Clarify language regarding purpose of pharmacodynamic assessments.

The primary change occurs in Appendix A Schedules of Events, Schedule of Events for Expansion TNBC, HNSCC, and NSCLC (28-Day Cycle), footnotes z, aa, and bb:

Initial wording:	(y) Peripheral blood samples will be collected at Screening, Cycle 1 Day 15, and Cycle 3 Day 1 for pharmacodynamic assessment and development of a biomarker(s) predictive of clinical activity of the combination of TAK-659 and nivolumab. Samples will be subjected to flow cytometry analysis to evaluate changes in immune cell populations. (z) Peripheral blood samples will be collected at Screening, Cycle 1 Day15, and Cycle 3 Day 1 for pharmacodynamic assessment and development of a biomarker(s) predictive of clinical activity of the combination of TAK-659 and nivolumab. Samples will be assayed to measure a panel of cytokines and chemokines known for or deemed relevant to tumor growth and antitumor activity of TAK-659 and the combination with nivolumab.
Amended or new wording:	(y) Peripheral blood samples will be collected **from all patients enrolled in the expansion phase** at Screening~~,~~ **and predose on** Cycle 1 Day 15~~,~~ and Cycle 3 Day 1 for pharmacodynamic assessment and ~~development of a biomarker(s) predictive of~~ **their potential association with** clinical activity of ~~the~~ **TAK-659 or in** combination ~~of TAK-659 and~~**with** nivolumab. Samples will be subjected to flow cytometry analysis to evaluate changes in immune cell populations. (z) Peripheral blood samples will be collected at Screening~~,~~ **and predose on** Cycle 1 Day 15~~,~~ and Cycle 3 Day 1 for pharmacodynamic assessment and ~~development of a biomarker(s) predictive of~~ **their potential association with** clinical activity of ~~the~~ **TAK-659 or in** combination ~~of TAK-659 and~~**with** nivolumab. Samples will be assayed to measure a panel of cytokines and chemokines ~~known for or deemed relevant to tumor growth and antitumor activity of TAK-659 and the combination with nivolumab~~.

Rationale for Change:

Required additional information.

Change 51: Update responsibilities of investigator.

The primary change occurs in Appendix B Responsibilities of the Investigator:

Added text: **5. If trial-related duties and functions are assigned to any individual or party, ensure that this individual or party is qualified to perform those trial-related duties and functions, and implements procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.**

Rationale for Change:

Added to comply with International Council for Harmonisation (ICH) Section 4.2.6.

Change 52: Add RECIST version 1.1 as appendix.

The primary change occurs in Appendix I Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1):

Description of change: Added RECIST Version 1.1 as new appendix.

Rationale for Change:

Required additional information.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	28-Apr-2017 23:12 UTC