Clinical Study Protocol

NCT Number: NCT05070247

Title: An Open-label, Dose Escalation and Expansion, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of TAK-500, a Novel Stimulator of Interferon Genes Agonist, as a Single Agent and in Combination With Pembrolizumab in Adult Patients With Select Locally Advanced or Metastatic Solid Tumors

Study Number: TAK-500-1001

Document Version and Date: Amendment 3, 13 Jun 2023

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PROTOCOL

An Open-label, Dose Escalation and Expansion, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of TAK-500, a Novel Stimulator of Interferon Genes Agonist, as a Single Agent and in Combination With Pembrolizumab in Adult Patients With Select Locally Advanced or Metastatic Solid Tumors

Phase 1/2 Study of TAK-500 as a Single Agent and in Combination With Pembrolizumab in Patients With Select Locally Advanced or Metastatic Solid Tumors

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Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 Please note: Takeda Development Center Americas, Inc. may be referred to in this protocol as "sponsor" or "Takeda."
Study Number:	TAK-500-1001
EU Clinical Trial Number:	2023-505374-15
Compound:	TAK-500
Date:	13 June 2023 **Amendment Number:** 3

Amendment History:

Date	Amendment Number	Region
13 June 2023	Amendment 3	Global
25 October 2022	Amendment 2	United States
21 September 2021	Amendment 1	United States
15 July 2021	Initial Protocol	United States

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list, for relevant contract research organization and sponsor contacts, will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, 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.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

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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 Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): 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.

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[redacted], MD, PhD Date
[redacted]
Clinical Science Oncology

[redacted], PhD Date
[redacted]
Statistical and Quantitative Sciences

[redacted], PhD Date
[redacted]
Quantitative Clinical Pharmacology

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, prescribing information, 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 patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

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

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Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 3 Summary of Changes

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2.

The primary reasons for this amendment are to:

- Describe the study design for the phase 2 dose expansion phase of the study, as summarized in Figure 6.b.
- Add the respective inclusion criteria for the single indication cohorts of the dose expansion phase.
- Adapt the objectives and endpoints to include the phase 2 dose expansion phase.
- Update the sample size calculation for the expansion phase.
- [redacted].
- [redacted]

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Study Protocol Title	Changed phase 1a/1b to phase 1/2.	Updated to reflect objectives and endpoints specific to phase 1 dose escalation and phase 2 dose expansion.
2.	Title page 2.0 STUDY SUMMARY	Added European Union (EU) clinical trial number	Added according to EU Clinical Trial Regulation (CTR) guidelines.
3.	2.0 STUDY SUMMARY, Study Design, TAK-500 SA Dose Escalation, and Dose Levels(s) 6.1.2 TAK-500 Dose Escalation Appendix F BOIN Design	Added intermediary dose level of 24 µg/kg.	Updated to reflect intermediary dose level added for use in the phase 1 dose escalation.

Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	2.0 STUDY SUMMARY, Study Design 6.1 Overview of Study Design 6.1.3 TAK-500 Dose Expansion and Randomized Dose Comparison 6.1.3.1 Expansion Cohort Tumor Type Selection 6.1.3.2 Dose Expansion in Nonsquamous NSCLC 6.1.3.3 TAK-500 SA and in Combination With Pembrolizumab Dose Expansion in 2L Pancreatic Adenocarcinoma 6.1.3.4 Combination TAK-500 With Pembrolizumab Dose Expansion in 3L RCC	Updated with all study design details of dose expansion, including the 3 cancer types selected for dose expansion; updated Figure 6.a Overview of Study Design – Dose Escalation; and added Figure 6.b Schematic of Study Design – Dose Expansion.	Protocol updated to reflect planned dose expansion in 3 indications, including nonsquamous non-small cell lung cancer (NSCLC), renal clear cell carcinoma (RCC), and pancreatic adenocarcinoma. This replaces the prior language around potential planned expansion in triple-negative breast cancer. Dose expansion plans now include potential for randomized dose comparison (dose optimization) in 2 different dose levels.
5.	2.0 STUDY SUMMARY, Primary and Secondary Objectives and Endpoints 5.1.1 Primary Objectives 5.1.2 Secondary Objectives 5.2.1 Primary Endpoints 5.2.2 Secondary Endpoints		Updated to reflect objectives and endpoints specific to phase 2 expansion. These include evaluation of preliminary antitumor activity of TAK-500 SA and combination with pembrolizumab and identification of the dose for further development. Primary and secondary endpoints adjusted include overall response rate, progression-free survival, and overall survival (OS).
6.	2.0 STUDY SUMMARY 6.1.2.1 TAK-500 SA Dose Escalation 6.1.2.2 TAK-500 in Combination With Pembrolizumab Dose Escalation	Updated wording around pharmacologically active dose (PAD) determination.	Clarified circumstances under which a dose level meets the PAD when a response is observed, and proceedings when the minimum PAD is confirmed.

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Protocol Amendment 3			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7.	2.0 STUDY SUMMARY, Number of Patients, Number of Sites 6.2 Number of Patients	Updated to include all patients in the dose expansion phase of this study.	Numbers now include all patients in planned phase 2 escalation and expansion phase of protocol. This is increased according to the inclusion of multiple single-indication expansion cohorts.
8.	2.0 STUDY SUMMARY, Period of Evaluation 6.3.4 Total Study Duration	Updated overall study duration, including definition of study start and study end.	Study duration now includes dose escalation and multiple expansion cohorts, and timing has been adjusted to take into consideration additional length of recruitment and treatment of the additional patients associated with expansion cohorts.
9.	2.0 STUDY SUMMARY, Inclusion Criteria 7.1 Inclusion Criteria	Updated inclusion criterion #3 to include the eligibility requirements for the patients from the 3 indications and other dose expansion phase details.	Details the criteria around eligibility of patients for the nonsquamous NSCLC, RCC, and pancreatic adenocarcinoma expansion cohorts.
10.	2.0 STUDY SUMMARY, Inclusion Criteria 7.1 Inclusion Criteria 8.8 Precautions and Restrictions	Updated inclusion criteria #12 and #13 and section on precautions and restrictions. Contraception duration was updated from 120 to 180 days.	Change to be consistent with prior requests from EU regulatory authorities.
11.	2.0 STUDY SUMMARY	Added potential risks and benefits summary to the protocol summary.	Added according to EU CTR guidelines.
12.	2.0 STUDY SUMMARY Exclusion Criteria 7.2 Exclusion Criteria	Removed exclusion criteria #6 and #7.	Patients who smoke or use vaping products will not be excluded from this study, as there has been no evidence of pneumonitis from administration of TAK-500 or the small molecule STING payload TAK-676.
13.	2.0 STUDY SUMMARY, Exclusion Criteria 7.2 Exclusion Criteria	Updated exclusion criterion #9 to include more detailed specifications for excluding patients with a history of leptomeningeal disease and brain metastases.	Patients with leptomeningeal disease excluded due to concern for rapid progression and lack of evidence regarding blood-brain barrier penetration of TAK-500.

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Protocol Amendment 3			
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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
14.	2.0 STUDY SUMMARY, Sample Size Justification 13.3 Determination of Sample Size	Updated to include sample size calculation for the expansion phase of the study.	Numbers now include all patients in planned escalation and expansion phase of protocol. This is increased according to the inclusion of multiple single-indication expansion cohorts. Dropout rate changed to 10% from 15% to reflect current assumptions for enrollment.
15.	2.0 STUDY SUMMARY, Study Design, Determination of PAD 8.4 Definition of PAD	[redacted]	[redacted]
16.	4.2 Rationale for the Proposed Study 4.2.1.2 Pancreatic Adenocarcinoma 4.2.1.4 Nonsquamous NSCLC 4.2.1.8 RCC	Updated to include paragraph on dose expansion, and updated background information on the 3 indications NSCLC, pancreatic adenocarcinoma, and RCC.	Expanded rationale for selection of expansion indications included for better background and understanding.
17.	4.2.3 Rationale for European Union Auxiliary Medicinal Products for CRS Mitigation	Added rationale for use of auxiliary medicinal products (AxMP).	Added according to EU CTR guidelines.
18.	4.2.4.1 Tumor Biopsies	Clarified the evaluation of immune cell infiltration within the tumor (secondary endpoint).	Clarified that secondary endpoint includes changes in immune cell infiltration.
19.	4.3.4 Risks Associated With the AxMPs	Added section on risks and benefits of AxMP.	Added according to EU CTR guidelines.

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
20.	5.1.3 Exploratory Objectives 5.2.3 Exploratory Endpoints	[redacted]	[redacted]
21.	6.1.1 Premedication Appendix A SOEs	Updated text and moved premedication section to Section 6.1.1 because it applies to both the dose escalation and the dose expansion part of this study.	[redacted] Moved to earlier section to clarify that premedication applies to both SA and combination arms.
22.	8.1.1 TAK-500	Added text on premedication use.	Clarification.
23.	8.1.4 List of European Union Auxiliary Medicinal Products Table 8.a	Added justification for AxMPs and details on their use.	Added according to EU CTR guidelines.
24.	9.4.6 Vital Signs 9.4.6.3 [redacted] Appendix A SOEs	[redacted]	[redacted]
25.	9.4.14.2 Tumor Biopsies	Updated to include a possible waiver for the mandatory paired biopsies.	Updated to allow possible exception to mandatory biopsies outside of safety concerns as long as there is initial discussion and approval with sponsor.

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
26.	9.4.19 Collection, Storage, and Future Use of Biological Samples From Clinical Trial Subjects	Text was added describing the collection, storage, and future use of biological samples.	Added according to EU CTR guidelines.
27.	9.4.20 [redacted] 9.4.20.1 [redacted] 9.4.20.2 [redacted] 9.4.20.3 [redacted] 9.4.20.4 [redacted] Appendix A SOEs	[redacted]	[redacted]
28.	9.9 Completion of Study (for Individual Patients)	Updated to include paragraph on dose expansion.	Clarifies that for expansion, patients will be followed through end of life for evaluation of OS.
29.	10.1.4 Special Situation Report Definition	Added definitions for special situation reports.	Added according to EU CTR guidelines.
30.	10.2.1 Recording and Reporting AEs and SAEs Related to AxMPs	Added reporting requirements for AEs and SAEs (serious adverse events) that are considered related to AxMP(s) by the investigator.	Added according to EU CTR guidelines.
31.	10.5 Procedures for Reporting Product Complaints or SSRs	Clarified and updated product complaints and special situation reporting.	Added according to EU CTR guidelines.
32.	13.1.3 Efficacy Analysis	Added the definition for OS.	Definition for OS.
33.	13.1.11 [redacted]	[redacted]	[redacted]
34.	13.1.12 [redacted] 13.1.12.1 [redacted] 13.1.12.2 [redacted]	[redacted]	[redacted]

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Protocol Amendment 3			
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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
35.	14.2 Protocol Deviations	Clarified that it is mandatory to report serious breach of Good Clinical Practice or the protocol to regulatory authorities.	Added according to EU CTR guidelines.
36.	15.3 Patient Confidentiality	Added clarification on serious breach affecting personal data.	Added according to EU CTR guidelines.
37.	Appendix A SOEs	Added footnote to selectively decrease pharmacokinetic and pharmacodynamic biomarker samples during planned visits of the dose expansion phase.	Decreases patient burden in expansion phase.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-500
Title of Protocol: An Open-label, Dose Escalation and Expansion, Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Preliminary Antitumor Activity of TAK-500, a Novel Stimulator of Interferon Genes Agonist, as a Single Agent and in Combination With Pembrolizumab in Adult Patients With Select Locally Advanced or Metastatic Solid Tumors	**EU Clinical Trial No.: 2023-505374-15**
Study Number: TAK-500-1001	**Phase:** 1/2

Study Design:

TAK-500-1001 is a phase 1/2, open-label, dose escalation and expansion study designed to determine the safety, tolerability, antitumor activity, pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity of TAK-500, a novel Stimulator of Interferon Genes (STING) agonist, as a single agent (SA) and in combination with pembrolizumab. This information will be used to determine the pharmacologically active dose (PAD) range and the dose for further development of TAK-500 as an SA and in combination with pembrolizumab. The study will proceed in 2 main sections: (1) a phased dose escalation of each treatment arm (TAK-500 as an SA and in combination with pembrolizumab) and (2) the evaluation of TAK-500 in combination with pembrolizumab in single tumor type expansion cohorts, with possible exploration of once every 3 weeks (Q3W) versus once every 2 weeks (Q2W) administration of TAK-500. Additional expansion cohorts in the same or other select tumor types may be warranted based on safety, pharmacodynamics, and clinical activity. Approximately 313 patients in total will be enrolled in this study. In the dose escalation phase (phase 1), approximately 82 patients will be enrolled with the following 9 types of locally advanced or metastatic solid tumors: gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma (HCC), nonsquamous non–small cell lung cancer (NSCLC), squamous-cell carcinoma of the head and neck (SCCHN), mesothelioma, triple-negative breast cancer (TNBC), renal clear cell carcinoma (RCC), and nasopharyngeal carcinoma (NPC). In the dose expansion phase (phase 2), approximately 231 patients will be enrolled with the following 3 types of locally advanced or metastatic solid tumors: nonsquamous NSCLC, pancreatic adenocarcinoma, and RCC.

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TAK-500 SA Dose Escalation:

The proposed explorable dose range of TAK-500 is from 4 to 480 µg/kg (4, 8, 16, 24, 40, 80, 160, 240, 360, and 480 µg/kg) administered Q3W in a 21-day cycle. Q2W administration of TAK-500 in a 42-day cycle may also be explored once the PAD range has been established. See Figure 6.a for an overview of phase 1 dose escalation design.

All patients will be hospitalized for 24 (±4) hours (after the first 2 doses of TAK-500 (Cycle [C]1 Day [D]1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500). Regardless of the treatment cycle, if a Grade ≥2 cytokine release syndrome (CRS) or infusion-related reaction occurs during or after administration of study drug, hospitalization is required for 24 (±4) hours after the end of the next 2 TAK-500 infusions. For patients without evidence of Grade ≥2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in clinic for at least 6 hours after the end of infusion (EOI). Patients who do not experience an infusion-related reaction or Grade ≥2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour. Patient evaluation including a complete set of vital signs is required before discharge home from either the hospital or clinic.

SA dose escalation/de-escalation will continue until full determination of the PAD range. PAD determination is based on observation of peripheral pharmacodynamic activity, including, but not limited to peripheral biomarkers

evaluating both [redacted]. Although clinical activity is not necessary to confirm PAD, observation of a partial response (PR) or complete response (CR) is sufficient to declare PAD regardless of other translational data. To confirm the minimum PAD, 2 dose levels (DLs) must each meet PAD criteria, and, consequently, the minimum PAD and PAD +1 DLs may be confirmed simultaneously. In the circumstance where a radiographic response (PR or CR) is observed at a given dose level, that dose level may be declared as meeting PAD requirements without waiting for confirmation of PAD in a subsequent dose level. Once PAD is confirmed, additional patients (approximately 3 to 6 additional patients per DL) may be enrolled at the minimum PAD and PAD +1 DLs in order to establish a more robust statistical basis for comparison of pharmacodynamic biomarkers across the TAK-500 SA DLs. Additional patients may be added to other DLs above the minimum PAD as required to identify the DL with optimal pharmacodynamic activity and inform determination of the dose for further development. Backfill cohorts may or may not be enriched for specific tumor type(s) selected from those included in dose escalation.

TAK-500 SA dose escalation may continue past minimum PAD and PAD +1 DLs as dictated by the Bayesian Optimal Interval (BOIN) design until either (1) the SA maximum tolerated dose (MTD) is determined, (2) peripheral pharmacodynamic biomarkers demonstrate a marked decrease in [redacted] in comparison to prior DLs, or (3) the maximum planned DL of 480 µg/kg is completed.

In the SA arm, approximately 52 patients will be enrolled to achieve about 46 dose-limiting toxicity (DLT) evaluable patients.

TAK-500 in Combination With Pembrolizumab Dose Escalation:

While the potential explorable dose range of TAK-500 in combination with pembrolizumab is also from 4 to 480 µg/kg, by default the combination arm will begin at a TAK-500 DL of 80 µg/kg, triggered upon safety clearance of the 80 µg/kg TAK-500 SA DL. If it is determined during the conduct of the SA dose escalation that the TAK-500 SA minimum PAD is ≤40 µg/kg, the combination TAK-500 plus pembrolizumab dose escalation will begin at a dose no higher than the TAK-500 SA minimum PAD DL. The determination to initiate the combination dose escalation arm will be based on the accumulated safety and pharmacodynamic data from all TAK-500 SA cohorts available at that time. The combination dose escalation may begin at a DL of TAK-500 that is below the TAK-500 SA PAD if this is determined to be necessary from the evaluation of safety and toxicity data.

Each combination DL will enroll at least 3 patients initially. A cohort size different from 3 is permissible thereafter. There will be at least a 24-hour dosing delay between the first patient of any new combination DL and subsequent patients enrolled at the same DL. The dose escalation/de-escalation decisions will follow the same BOIN design as the TAK-500 SA arm. If a DL of TAK-500 SA is considered to be too toxic in the SA arm, it and any higher DLs will be excluded from the explorable dose range of the combination arm.

Pembrolizumab will be administered at the fixed DL of 200 mg Q3W, to be administered on the same day as TAK-500 on a Q3W schedule in a 21-day cycle, or if Q2W dosing of TAK-500 is explored, pembrolizumab will be administered on Days 1 and 22 in a 42-day cycle.

As with the TAK-500 SA arm, dose escalation/de-escalation for the combination arm will continue until determination of its minimum PAD and PAD +1 DL. Once the minimum PAD is confirmed in the combination arm, additional patients (approximately 3 to 6 additional patients per DL) may be enrolled to both the minimum PAD and PAD +1 DLs to establish a more robust statistical basis for comparison across DLs. Additional patients may be added to other DLs above the minimum PAD as required to identify the DL with optimal pharmacodynamic activity and inform determination of the dose for further development. Backfill cohorts may or may not be enriched for specific tumor type(s) selected from those included in dose escalation. The criteria for the determination of minimum PAD and PAD +1 DLs are the same for both the SA and combination arms.

In the combination arm, the number of patients will depend on the starting DL. Assuming the starting DL is 80 µg/kg, about 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients.

Determination of PAD:

Determination of the PAD dose range for TAK-500 will be used to inform decision-making regarding selection

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of the starting dose for the combination with pembrolizumab dose escalation and for dose selection for both the SA and combination dose expansion cohorts. PAD for TAK-500 is defined as any dose at which there is evidence of TAK-500–mediated pharmacodynamic effects and may include, but is not limited to:

- Evidence of [redacted] activation in peripheral blood.
- Evidence of [redacted] in peripheral blood.
  OR
- Clinical evidence of antitumor activity (eg, PR or CR) as determined by Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1.

To enhance and refine PAD and dose selection for expansion cohorts, additional peripheral and tumoral pharmacodynamic biomarkers will be assessed. Peripheral pharmacodynamic biomarkers may [redacted].

The relationship between TAK-500, total antibody, and/or deconjugated TAK-676 exposure and pharmacodynamic response ([redacted]) will be explored on an ongoing basis as PK and pharmacodynamic data become available to understand the PK-pharmacodynamic relationship of TAK-500 and to help in estimation of the PAD range.

BOIN Dose Escalation:

Except for the initial 2 TAK-500 SA 1 + 2 + 3 accelerated titration cohorts, dose escalation of TAK-500 in both the SA and combination arms will follow the BOIN design to inform dose escalation decisions and potential MTD estimation. Each DL of TAK 500 following the BOIN dose escalation will enroll at least 3 patients initially. A cohort size different from 3 is permissible thereafter per the escalation/de-escalation guidelines. There will be a 24-hour dosing delay between the first patient of any new DL and subsequent patients enrolled at the same DL. The target toxicity rate is $\phi = 0.3$. To guide dose escalation decisions, if the observed DLT rate at the current dose is ≤ 0.236, the next cohort of patients will be treated at the next higher DL; if it is ≥ 0.358, the next cohort of patients will be treated at the next lower DL; if it is within 0.236 and 0.358, additional patients will be enrolled in this DL. For the purpose of overdose control, dose j and higher levels will be eliminated from further examination if $Pr(pj > 0.3 \mid data) > 0.95$, where pj is the true DLT rate of DL j. If the lowest dose is eliminated, the dose escalation will be stopped for safety. Dose escalation will continue until either: (1) the maximum sample size is reached, or (2) the number of patients treated at the current DL reaches 9 and the recommendation is to retain at the current DL.

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In the SA dose escalation, after the BOIN escalation starts, the maximum number of DLT evaluable patients to be enrolled is 42 (40 rounded up to the nearest multiple of 3). In the combination escalation, the maximum number of DLT-evaluable patients to be enrolled depends on the starting DL. In principle, we plan an average of about 5 patients per DL from the starting DL to 480 µg/kg. For example, if the starting DL is 80 µg/kg, the maximum number of DLT-evaluable patients to be enrolled is 27 (25 rounded up to the nearest multiple of 3).

Isotonic regression will be used on the cumulative DLT rate for each DL to determine the MTD, defined as the highest TAK-500 dose as an SA or in combination with pembrolizumab that does not result in unacceptable toxicity. Note that dose escalation cohorts treated with a specific premedication regimen will be analyzed separately from cohorts treated without premedication or with other premedication regimens.

Intrapatient Dose Escalation:

Intrapatient dose escalation will not be permitted as part of the DLT-evaluable dose escalation set, but patients treated at TAK-500 SA DLs below minimum PAD will be allowed to escalate to minimum PAD once the minimum PAD DL has been confirmed and cleared from a safety perspective.

For patients to be eligible for intrapatient dose escalation, they must continue on study without interruption and without evidence of progressive disease by imaging or clinical deterioration.

<u>TAK-500 Dose Expansion and Randomized Dose Comparison</u>

In addition to TAK-500 SA and TAK-500 plus pembrolizumab combination dose escalation, the preliminary antitumor activity along with the safety, tolerability, PK, and PD of TAK-500 will be further evaluated in single-

indication expansion cohorts. Dose expansion may proceed with both TAK-500 SA and TAK-500 with pembrolizumab and include the opportunity to simultaneously explore 2 dose levels of TAK-500 (recommended dose for expansion [RDE] 1 and RDE 2) to provide additional data for identification of the dose for further development. See Figure 6.b for an overview of phase 2 dose expansion design.

As noted above, dose escalation in both the SA and pembrolizumab combination arms will proceed beyond identification of PAD, until either (1) the respective MTD is determined, (2) peripheral pharmacodynamic biomarkers demonstrate a marked decrease in [redacted] in comparison to prior DLs, or (3) the maximum planned DL of 480 µg/kg is completed. Once complete, the totality of data from dose escalation will be utilized to identify the RDE(s) and dosing schedule of TAK-500 (Q2W and/or Q3W, both in a 42-day cycle) for single-indication dose expansion cohorts. The RDE(s) of TAK-500 may be the same as the MTD or may be below the MTD if the totality of data (safety and tolerability, PK and PD, and clinical antitumor activity) suggest a lower dose is favorable. Additionally, the RDE(s) for dose expansion may or may not be different for the TAK-500 SA versus the TAK-500 plus pembrolizumab combination expansion cohorts. For all combination TAK-500 plus pembrolizumab cohorts, pembrolizumab administration will remain constant at 200 mg intravenous (IV) Q3W in a 42-day cycle.

To accommodate the possible comparison between the Q3W and Q2W schedules, all expansion cohorts will be administered in a 42-day cycle. Any Q2W DL evaluated in dose expansion must be at or below a Q2W DL previously shown to be tolerated in dose escalation.

Expansion Cohort Tumor Type Selection:

Selection of tumor types and line of therapy for single-indication dose expansion cohorts was based primarily on scientific rationale for targeting with TAK-500, including [redacted]. High unmet clinical need and clinical tractability were also considered. Based on this analysis, 3 tumor types were prioritized for initial dose expansion cohorts: **nonsquamous NSCLC, pancreatic adenocarcinoma, and RCC**. These cohorts may begin simultaneously, or one or two indications may be prioritized over the other(s). Other single indication expansion cohorts may be explored instead of, or in addition to, these indications, if anti-tumor activity is seen during dose escalation in a given tumor.

Dose Expansion in Nonsquamous NSCLC

The preliminary antitumor activity, safety, tolerability, PK, and PD of TAK-500 SA and/or in combination with pembrolizumab will be evaluated in treatment-refractory nonsquamous NSCLC patients without driver mutations in both the second-line (2L) and third-line (3L) settings.

Combination TAK-500 With Pembrolizumab Dose Expansion With Randomized Dose Comparison in 2L NSCLC

Enrollment in 2L NSCLC cohorts will include patients with treatment-refractory nonsquamous NSCLC (without targetable driver mutations) with recurrent locally advanced or metastatic disease that has previously progressed while on or following 1 prior line of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given in combination with an anti-CTLA4 antibody or chemotherapy (eg, carboplatin and pemetrexed). Patients are eligible to enroll regardless of PD-L1 status.

The combination TAK-500 plus pembrolizumab dose expansion in 2L NSCLC will proceed as outlined below with concurrent start of early randomized dose comparison.

- Expansion in 2L NSCLC will proceed simultaneously at 2 separate DLs of TAK-500 following a 2:1 randomized approach, to RDE 1 and RDE 2, respectively. The 2 DLs will be chosen such that adequate dose/response and exposure/response analyses can be performed to support the selection of the dose for further development. RDE 1 and RDE 2 selection will be made on the totality of data, including safety, antitumor activity, PK, and pharmacodynamic analysis, with both doses having a positive benefit-risk

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ratio for further study at the time of selection. Neither RDE 1 nor RDE 2 will be higher than the highest dose level assessed in the dose escalation phase or the MTD, whichever is lower.

- Approximately 59 patients will enroll in this cohort, with up to 39 patients randomized to RDE 1 (to achieve an approximate total of 35 response-evaluable patients, assuming a 10% drop-out rate) and up to 20 patients randomized to RDE 2 (to achieve an approximate total of 18 response-evaluable patients assuming a 10% drop-out rate). A futility analysis will be performed based on overall response rate (ORR) at the time when there are 21 response-evaluable patients in RDE 1 and each of these 21 patients has experienced at least 1 of the following: (1) shown a clinical response (cPR or cCR), (2) had at least 2 posttreatment response assessments, or (3) had documented PD or death. If a partial response or complete response is initially observed at the second posttreatment response assessment, a third posttreatment response assessment will be performed to confirm the response before the patient may be included in the futility analysis. If there are ≥5 responders among the first 21 response-evaluable patients treated at RDE 1, then the futility analysis is successful, and the enrollment will continue to 35 response-evaluable patients. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.
- If RDE 1 enrollment is terminated due to failing futility at the stage 1 analysis or fails to meet the number of responses needed for proof of concept at final analysis, additional patients may be enrolled to RDE 2 in a nonrandomized manner to include 21 response-evaluable patients. A futility analysis will then be performed based on ORR as described for RDE 1. If there are ≥5 responders among the first 21 response-evaluable patients treated at RDE 2, then the enrollment will continue to 35 response-evaluable patients. Otherwise, the cohort will be terminated for futility. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.

TAK-500 SA Dose Expansion With Randomized Dose Comparison in 3L NSCLC

Enrollment in 3L NSCLC cohorts will include patients with treatment-refractory nonsquamous NSCLC (without targetable driver mutations) with recurrent locally advanced or metastatic disease that has previously progressed while on or following 2 prior lines of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given in combination with an anti-CTLA4 antibody or chemotherapy (eg, carboplatin and pemetrexed). Patients must have had disease progression while on or after 1 or 2 lines of chemotherapy in the recurrent locally advanced or metastatic setting. If the anti-PD-(L)1 therapy is given in combination with chemotherapy, the patient must have progressed on an additional line of chemotherapy. Patients are eligible to enroll regardless of PD-L1 status.

- Expansion in 3L NSCLC will proceed simultaneously at two separate dose levels of TAK-500 following a 1:1 randomized approach, to RDE 1 and RDE 2, respectively. The 2 dose levels will be chosen such that adequate dose/response and exposure/response analyses can be performed to support the selection of the dose for further development. RDE 1 and RDE 2 selection will be made on the totality of data, including safety, antitumor activity, PK and pharmacodynamic analysis, with both doses having a positive benefit-risk ratio for further study at the time of selection. Neither RDE 1 nor RDE 2 will be higher than the highest dose level assessed in the dose escalation phase or the MTD, whichever is lower.
- The 3L nonsquamous NSCLC expansion cohorts will be based on a single-stage design.
- Approximately 48 patients will enroll in this cohort, with 24 patients randomized to RDE 1 and RDE 2 each (to achieve an approximate total of 21 response-evaluable patients assuming a 10% drop-out rate in each dose level).

TAK-500 SA and in Combination With Pembrolizumab Dose Expansion in 2L Pancreatic Adenocarcinoma

The preliminary antitumor activity, safety, tolerability, PK, and pharmacodynamics of TAK-500 SA or in combination with pembrolizumab will be evaluated in treatment-refractory pancreatic adenocarcinoma with 1

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prior line of therapy.

Enrollment in the 2L pancreatic adenocarcinoma expansion will include patients with treatment-refractory pancreatic adenocarcinoma with recurrent locally advanced or metastatic disease that has previously progressed while on or following 1 prior line of therapy. Patient must have had disease progression while on or following 1 prior line of fluorouracil or gemcitabine-based chemotherapy (eg, FOLFIRINOX, FOLFOX, FOLFIRI, gemcitabine/nab-paclitaxel) in the metastatic/recurrent locally advanced setting. Prior chemotherapy in the neoadjuvant/adjuvant setting does not qualify unless the patient had progression of disease within 6 months of completion of neoadjuvant/adjuvant chemotherapy. Patients cannot have had prior exposure to anti-PD-(L)1 therapy. Patients are eligible to enroll regardless of PD-(L)1 status. Patients with MSI-H/dMMR disease are not eligible.

- Expansion in 2L pancreatic adenocarcinoma will randomize TAK-500 SA and TAK-500 in combination with pembrolizumab. Both arms will include TAK-500 at the TAK-500 RDE 1 identified during combination TAK-500 plus pembrolizumab dose escalation, unless the RDE 1 for the combination is below the PAD established during the TAK-500 SA dose escalation. In this instance, the RDE 1 for TAK-500 SA would be utilized for the corresponding arm.
- The 2L pancreatic adenocarcinoma expansion cohorts will be based on Simon's 2-stage design with ORR as an endpoint and separate futility analyses for the TAK-500 SA and TAK-500 combination cohorts.
- Approximately 45 patients will be enrolled in each arm to achieve an approximate total of 40 response-evaluable patients, assuming a 10% drop-out rate per cohort. A futility analysis will be performed at the time when there are 25 response-evaluable patients. The same futility criteria will be applied for each arm. If there are ≥4 responders among the first 25 response-evaluable patients, then the futility analysis is successful, and the enrollment will continue to 40 response-evaluable patients in the respective cohort. Otherwise, the cohort will be terminated for futility. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.

Combination TAK-500 With Pembrolizumab Dose Expansion in 3L RCC

The preliminary antitumor activity, safety, tolerability, PK, and PD of TAK-500 in combination with pembrolizumab will be evaluated in treatment-refractory RCC with 2 prior lines of therapy.

Enrollment in the 3L RCC cohort will include patients with treatment-refractory RCC with recurrent locally advanced or metastatic disease that has previously progressed while on or following at least 2 prior lines of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or an anti-vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) (eg, cabozantinib). Patients must have had prior therapy with 1 or 2 lines of VEGFR TKIs in the metastatic/recurrent locally advanced setting. If anti-PD-(L)1 therapy was given in combination with a VEGFR TKI, the patient must have had progressive disease on an additional line of therapy (eg, VEGFR TKI or VEGFR TKI-containing combination). Patients are eligible to enroll regardless of PD-L1 status.

- Expansion in 3L RCC will occur at the RDE 1 of TAK-500 identified during combination TAK-500 plus pembrolizumab dose escalation.
- The 3L RCC expansion cohorts will be based on a single-stage design, with enrollment of up to approximately 34 patients to achieve a total of 30 response-evaluable patients (assuming a 10% drop-out rate).

Study Conduct:

TAK-500 administration will occur in facilities with readily available resuscitation equipment, diagnostic equipment and supportive care/medications, such as oxygen, antihistamines, acetaminophen, corticosteroids, epinephrine, anti–interleukin (IL)-6 agents, and bronchodilators.

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All patients will be hospitalized for 24 (±4) hours (after the first 2 doses of TAK-500 (C1D1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500). Regardless of the treatment cycle, if a Grade ≥2 CRS or infusion-related reaction occurs during or after administration of study drug, hospitalization is required for 24 (±4) hours after the end of the next 2 TAK-500 infusions. For patients without evidence of Grade ≥2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in clinic for at least 6 hours after the EOI. Patients who do not experience an infusion-related reaction or Grade ≥2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour. Patient evaluation including assessment of a complete set of vital signs is required before discharge home from either the hospital or clinic.

During hospitalization, vital signs will be taken no less frequently than every 6 hours until discharge. Before discharge from the hospital and/or clinic, a symptom-directed physical examination including assessment of the respiratory and neurologic systems and complete set of vital signs will be required.

At the time of discharge from the hospital, patients and their caregivers will be educated about potential symptoms including but not limited to fever, edema, lightheadedness, dizziness, tachypnea, dyspnea, confusion, aphasia, dysphasia, ataxia, or tremor. If patients develop any of these symptoms, they should be instructed to immediately contact the principal investigator, who may recommend immediate medical attention.

The required hospitalization for the phase 2 dose expansion portion of the study may be decreased or removed if an adequate safety profile is demonstrated in the dose escalation phase of the study for the dose level(s) and premedication regimen(s) included in expansion. If hospitalization is not required for dose expansion, outpatient monitoring will be required as outlined in the above paragraph.

Adverse events (AEs) will be assessed, and laboratory values, vital signs, electrocardiograms (ECGs), and other clinically indicated examinations will be obtained to evaluate the safety and tolerability of the study treatment. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. A DLT will be defined as any of the treatment-emergent adverse events (TEAEs) described in the Section 8.2 that occurs during the first 21 days on study (C1D21) and are considered by the investigator to be at least possibly related to TAK-500 alone or in combination with pembrolizumab. TEAEs meeting DLT definitions occurring in later cycles will be considered in the determination of the dose for further development of TAK 500. Radiological evaluations (computed tomographic scan and/or magnetic resonance imaging as clinically indicated) will be used to assess the status of the patient's underlying disease. [redacted] tumor tissue or a minimum number of unstained slides of the tumor tissue will be collected, if available, from all enrolled patients to assess baseline features such as [redacted]. All patients with a safely accessible lesion enrolling at or above DLs where TAK-500 has previously shown pharmacodynamic activity will have mandatory tumor biopsies performed per the schedules of events (SOEs).

Once peripheral evidence of TAK-500 pharmacodynamic modulation of the [redacted] is observed in the blood and/or clinical response (PR or CR) is observed in at least 1 patient, subsequent paired biopsies will be required for all patients with a safely accessible lesion and in whom a fresh tumor biopsy would not place the patient at an unjustifiable risk, in the opinion of the investigator.

Serial blood samples will be collected for circulating biomarkers ([redacted]). An evaluation of disease response will be performed using the RECIST v1.1 (as determined by the investigator) and per the SOEs. Clinically validated peripheral tumor markers will also be collected for patients with appropriate tumor types (AFP, CA 27.29, and CA 19-9). Serial blood samples for determination of the serum concentration of TAK-500 and related metabolites to understand TAK-500 metabolism and excretion mechanisms will be obtained at prespecified time points as described in the SOEs.

In the setting of disease progression while on TAK-500 SA, crossover to the TAK-500 with pembrolizumab combination arm is optional and at the discretion of the investigator, in agreement with the sponsor. Patients in the TAK-500 SA treatment arm with objective evidence of PD may cross over to the TAK-500 and

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pembrolizumab combination arm into the last DL that is or was accruing patients. Crossover treatment should begin within 28 days of documented disease progression and after the EOT visit; additionally, it is recommended that the first pembrolizumab dose be administered on a regularly scheduled TAK-500 dosing day. Crossover patients will proceed to a second EOT visit within 30 days of last TAK-500 dose after the combination treatment.

The sponsor may stop or halt enrollment or treatment of ongoing patients, depending on the nature and severity of a safety-related event. A final decision to terminate the study or a protocol amendment will be made only after a full review of the safety data by the sponsor's Safety Management Team and the investigators.

Primary Objectives:

The primary objective for phase 1 dose escalation phase is:

- To determine the safety and tolerability of TAK-500 administered as an SA and in combination with pembrolizumab in patients with select locally advanced or metastatic solid tumors, including gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC.

The primary objectives for phase 2 dose expansion phase are:

- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic nonsquamous NSCLC.
- To assess the preliminary antitumor activity of TAK-500 SA in 3L recurrent locally advanced or metastatic nonsquamous NSCLC.
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To assess the preliminary antitumor activity of TAK-500 SA in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 3L recurrent locally advanced or metastatic RCC.
- To determine the dose for further development of TAK-500 administered as SA and in combination with pembrolizumab.

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Secondary Objectives:

The secondary objectives for the phase 1 dose escalation are:

- To determine the RDEs of TAK-500 administered as SA and in combination with pembrolizumab.
- To characterize the single and multiple dose PK of TAK-500 administered as SA and in combination with pembrolizumab.
- To evaluate the preliminary antitumor activity of TAK-500 administered as SA and in combination with pembrolizumab.
- To evaluate the dose-responsive impact on T-cell infiltration into the tumor following TAK-500 administered as SA and in combination with pembrolizumab.
- To determine the immunogenicity of TAK-500.

The secondary objectives for the phase 2 dose expansion are:

- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic nonsquamous NSCLC.
- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To determine the safety and tolerability of TAK-500 combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic RCC.

Patient Population: Male or female patients aged 18 years or older, at the time of consent, with the following pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic solid tumors, whose disease has progressed on or are intolerant to all standard therapy: gastroesophageal (esophageal,

gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC. Patients who are intolerant to all standard therapies are those who have developed clinical or laboratory abnormalities that prevent continued drug administration as evaluated by the principal investigator at the time of screening.

Number of Patients:	**Number of Sites:**
Approximately 313 patients in total will be enrolled in this study. For the phase 1 dose escalation phase, in the SA arm, about 52 patients will be enrolled to achieve about 46 DLT-evaluable patients (includes cohorts treated with and without premedication). In the combination arm, the number of patients will depend on the starting DL. Assuming the combination starting DL is 80 µg/kg, about 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients. Additional patients may be enrolled for the evaluation of Q2W administration of TAK-500 if this schedule is explored in the dose escalation phase. For the phase 2 dose expansion phase, assuming only 1 TAK-500 administration schedule is expanded, approximately 231 patients will be enrolled to achieve a total of approximately 205 response-evaluable patients. This number may increase if more than 1 TAK-500 administration schedule is explored.	Approximately 70 sites globally.
Dose level(s): Pembrolizumab: 200 mg Q3W TAK-500: 4 to 480 µg/kg (4, 8, 16, 24, 40, 80, 160, 240, 360, and 480 µg/kg) Q3W or Q2W	**Route of Administration:** Pembrolizumab: IV infusion over 30 minutes TAK-500: IV infusion as described in pharmacy manual
Duration of Treatment: up to 1 year. Patients with demonstrated clinical benefit will continue treatment beyond this point if approved by the sponsor.	**Period of Evaluation:** It is anticipated that this study will last for approximately 50 months.

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Potential Risks and Benefits

TAK-500 is currently being evaluated in an ongoing first-in-human (FIH) phase 1/2 study in patients with solid tumors (Study TAK-500-1001) and the clinical benefits and risks have not been fully determined. Possible risks, based on nonclinical studies, include CRS, pulmonary edema, and toxicities for immune/lymphoid system, liver, and cardiovascular system.

Pembrolizumab prescribing information (USPI dated November 2020) includes warnings for severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (both before and after treatment), and embryo-fetal toxicities. In addition, the most common AEs after pembrolizumab administered as an SA, as reported in ≥20% of patients, were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. The most current prescribing information for pembrolizumab should be consulted.

[redacted]

[redacted].

Inclusion Criteria:

1. Male or female patients aged 18 years or older.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.
3. Patients with the following pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic solid tumors, whose disease has progressed on or are intolerant to standard therapy:
    a. For dose escalation with TAK-500 SA and combination TAK-500 with pembrolizumab:
        - Patients with the following pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic solid tumors, whose disease has progressed on or are intolerant to all standard therapy: gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC. Patients who are intolerant to all standard therapies are those who have developed clinical or laboratory abnormalities that prevent continued drug administration as evaluated by the principal investigator at the time of screening.

    b. For dose expansion in 2L nonsquamous NSCLC (TAK-500 plus pembrolizumab):
        - Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic nonsquamous NSCLC.
        - Patients may not have a known targetable driver mutation, rearrangement or amplification (eg, EGFR, ALK, MET, ROS1, BRAF, KRASG12C, etc.).
        - Must have had disease progression while on or following 1 prior line of therapy:
            1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting.

               OR

               Disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

               Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or chemotherapy (eg, carboplatin and pemetrexed).

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- Patients are eligible regardless of PD-L1 status.

c. For dose expansion in 3L nonsquamous NSCLC (TAK-500 SA):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic nonsquamous NSCLC.
- Patients may not have a known targetable driver mutation, rearrangement or amplification (eg, EGFR, ALK, MET, ROS1, BRAF, KRASG12C).
- Must have had disease progression while on or following 2 prior lines of therapy:
  1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting.

     OR

     Disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

     Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or chemotherapy (eg, carboplatin and pemetrexed).
  2. Patients must have had disease progression while on or after ≥1, but not > 2, lines of chemotherapy in the recurrent locally advanced or metastatic setting. If the anti-PD-(L)1 therapy is given in combination with chemotherapy, patient must have progressed on an additional line of chemotherapy.
- Patients are eligible regardless of PD-L1 status.

d. For dose expansion in 2L pancreatic adenocarcinoma (TAK-500 SA and TAK-500 plus pembrolizumab):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic pancreatic adenocarcinoma.
- Must have had disease progression while on or following 1 prior line of therapy:
  1. One prior line of fluorouracil- or gemcitabine-based chemotherapy (eg, FOLFIRINOX, FOLFOX, FOLFIRI, gemcitabine/nab-paclitaxel) in the metastatic/recurrent locally advanced setting.

     Prior chemotherapy in the neoadjuvant/adjuvant setting does not qualify unless the patient had progression of disease within 6 months of completion of neoadjuvant/adjuvant chemotherapy.
- Must not have had prior exposure to anti-PD-(L)1 therapy.
- Patients with MSI-H/dMMR disease are not eligible.
- Patients are eligible regardless of PD-L1 status.

e. For dose expansion in 3L RCC (TAK-500 plus pembrolizumab):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic RCC.
- Must have had disease progression while on or following 2 prior lines of therapy:

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1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting.

   OR

   Disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

   Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or an anti-VEGFR TKI.

2. Patients must have had prior therapy with 1 or 2 lines of VEGFR TKIs in the metastatic/recurrent locally advanced setting. If anti-PD-(L)1 therapy was given in combination with a VEGFR TKI, the patient must have had progressive disease on an additional line of therapy (eg, VEGFR TKI or VEGFR TKI-containing combination).

- Patients are eligible regardless of PD-L1 status.

4. Patients must have at least 1 RECIST v1.1 measurable lesion. Lesions in previously irradiated areas (or other local therapy) should not be selected as measurable/target lesions unless there has been demonstrated radiographic progression in that lesion. RECIST v1.1 target lesions must include at least 1 lesion that was not previously irradiated.
5. Once a DL is reached where evidence of TAK-500 stimulation of the [redacted] has been observed in the blood and/or a clinical response (PR or CR) measured in at least 1 patient, subsequent patients treated at the equivalent or higher DL will be required to have 2 biopsies (at screening and on treatment), assuming the potential morbidity of the procedures is deemed acceptable by the treating physician.
6. Adequate bone marrow, renal, and hepatic functions, as determined by the following laboratory parameters:
   - Absolute neutrophil count (ANC) ≥1000/μL, platelet count ≥75,000/μL, and hemoglobin ≥8.0 g/dL without growth factor support for ANC or transfusion support for platelets within 14 days before the first study treatment dose.
   - Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN). For patients with Gilbert's disease or HCC, ≤3 mg/dL.
   - Serum alanine aminotransferase and aspartate aminotransferase ≤3.0 × ULN or ≤5.0 × ULN with liver metastases or HCC.
   - Albumin ≥3.0 g/dL.
   - Calculated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/minute.
7. For patients with HCC only: Child-Pugh score less than or equal to 7 (Child-Pugh A or B7).
8. Left ventricular ejection fraction >50%, as measured by echocardiogram or multiple-gated acquisition scan within 4 weeks before receiving the first dose of study drug.
9. Clinically significant toxic effects of previous therapy have recovered to Grade 1 (per NCI CTCAE v5.0) or baseline, except for alopecia, Grade 2 peripheral neuropathy, and/or autoimmune endocrinopathies with stable endocrine replacement therapy.
10. Patients previously treated with fully human/humanized antineoplastic monoclonal antibodies must not have received treatment with such antibodies for at least 4 weeks or the time period equal to the dosing interval, whichever is shorter. No washout period is required for prior treatment with pembrolizumab or other anti–

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programmed cell death protein 1 (PD-1) antibodies, although the first study dose of these drugs must not occur at an interval less than standard of care (ie, 3 weeks for 200 mg of IV pembrolizumab).

11. Suitable venous access for the collection of study-required blood sampling, including PK and pharmacodynamic blood samples.
12. Female patients must be:
    - Postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit, or
    - Surgically sterile, or
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug(s), or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient.
      – Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
13. Male patients, even if surgically sterilized (ie, status postvasectomy), must:
    - 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.
      – Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
14. 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.
15. Patients must be eligible for treatment with pembrolizumab at the dose(s) and schedule(s) recommended in the label/prescribing information, where applicable.

Exclusion Criteria:

1. History of any of the following ≤6 months before first dose of study drug(s): congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, persistent hypertension ≥160/100 mm Hg despite optimal medical therapy, ongoing cardiac arrhythmias of Grade >2 (including atrial flutter/fibrillation or intermittent ventricular tachycardia), other ongoing serious cardiac conditions (eg, Grade 3 pericardial effusion or Grade 3 restrictive cardiomyopathy), or symptomatic cerebrovascular events. Chronic, stable atrial fibrillation on stable anticoagulation therapy, including low molecular-weight heparin, is allowed.
2. QT interval with Fridericia correction method >450 milliseconds (men) or >475 milliseconds (women) on a 12-lead ECG during the screening period.
3. Grade ≥2 hypotension (ie, hypotension for which nonurgent intervention is required) at screening or during C1D1 predose assessment.

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4. Oxygen saturation <92% on room air at screening or during C1D1 predose assessment.
5. Patients treated with other STING agonists/antagonists, Toll-like receptor agonists, or CCR2 agonist/antagonist within the past 6 months.
6. Exclusion criterion removed
7. Exclusion criterion removed
8. Active diagnosis of pneumonitis, interstitial lung disease, severe chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, other restrictive lung diseases, acute pulmonary embolism, or Grade ≥2 pleural effusion not controlled by tap or requiring indwelling catheters.
9. History of brain metastasis or leptomeningeal disease unless:
   - Brain metastases are stable on cranial imaging (ie, ≥4 weeks) following prior surgery, whole-brain radiation, or stereotactic radiosurgery, and
   - Off corticosteroids for brain metastases.
10. Grade ≥2 fever of malignant origin.
11. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug. Patients are specifically excluded if they have active, severe infections such as tuberculosis (screening per local practice and epidemiology), sepsis, cytomegalovirus (including cytomegalovirus colitis), listeriosis, and opportunistic infections (including *Clostridium difficile*) until the infections are controlled.
12. Patients with either/both of:
    - Uncontrolled, known or suspected, autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
    - A diagnosis of an identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, uncontrolled HIV infection, organ transplantation).
13. Chronic, active hepatitis (eg, patients with known hepatitis B surface antigen seropositive and/or detectable hepatitis C virus [HCV] RNA).
    - Note: Patients who have positive hepatitis B core antibody can be enrolled but must have an undetectable serum hepatitis B virus-DNA. Patients who have positive HCV antibody must have an undetectable HCV-RNA serum level.
14. History of hepatic encephalopathy.
15. Prior or current clinically significant ascites, as measured by physical examination, that requires active paracentesis for control.
16. Any pre-existing condition or illness, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug or that would limit compliance with study requirements or compromise ability to provide written informed consent.
17. Treatment with any investigational products or other anticancer therapy (including chemotherapy, targeted agents, and immunotherapy), within 14 days or 5 half-lives, whichever is shorter, before C1D1 of study drug(s).

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18. Concurrent chemotherapy, immunotherapy (except for pembrolizumab in the combination arm), biologic, or hormonal therapy (except for adjuvant endocrine therapy for a history of breast cancer). Concurrent use of hormones for noncancer-related conditions is acceptable (except for corticosteroid hormones).
19. Radiation therapy within 14 days (42 days for radiation to the lungs) and/or systemic treatment with radionuclides within 42 days before C1D1 of study drug(s). Patients with clinically relevant ongoing pulmonary complications from prior radiation therapy are not eligible.
20. Use of systemic corticosteroids or other immunosuppressive therapy, concurrently or within 7 days of C1D1 of study drug(s), with the following exceptions:
    - Topical, intranasal, inhaled, ocular, intra-articular, and/or other nonsystemic corticosteroids.
    - Physiological doses of replacement steroid therapy (eg, for adrenal insufficiency), not to exceed the equivalent of 10 mg prednisone daily.
21. Use of medications that are known clinical organic anion transporting polypeptide (OATP)1B1 and/or OATP1B3 inhibitors, concurrently or within 14 days of C1D1 of study drug(s).
22. Receipt of live attenuated vaccine (eg, tuberculosis Bacillus Calmette-Guerin vaccine, oral polio vaccine, measles, rotavirus, yellow fever) within 28 days of C1D1 of study drug(s). Nonlive, approved vaccines are allowed (eg, coronavirus disease 2019 [COVID-19] vaccine).

    Note: COVID-19 vaccination should not be given ±3 days of systemic study treatments.
23. Recipients of allogeneic or autologous stem cell transplantation or organ transplantation.
24. Female patients who are lactating or have a positive serum/urine pregnancy test during the screening period or a positive serum/urine pregnancy test on Day 1 before first dose of study drug.

    Note: Female patients who are lactating will be eligible if they choose to discontinue breastfeeding before the first dose of study drug.

Additional criteria specific for patients in TAK-500 and pembrolizumab combination arm only:

25. Contraindication to the administration of pembrolizumab or prior intolerance to pembrolizumab or other anti–PD-1 or anti–programmed cell death protein ligand 1 antibody.
26. History of intolerance to any component of the study treatment agents or known serious or severe hypersensitivity reaction to any of the study drugs or their excipients. (Pembrolizumab is formulated with L-histidine, polysorbate 80, and sucrose.)

Main Criteria for Evaluation and Analyses:

The primary endpoints for the phase 1 dose escalation are:

- Frequency and severity of TEAEs.
- Number of patients with DLTs.
- Number/percentage of patients with 1 or more treatment-emergent serious adverse event (SAE).
- Number/percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations.

The primary endpoints for the phase 2 dose expansion are:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: cCR + cPR.

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The secondary endpoints are:

- PK parameters of TAK-500:
- C_{max}.
- t_{max}.
- Area under the serum concentration-time curve from time 0 to time t.
- Area under the serum concentration-time curve from time 0 to infinity.
- Terminal disposition phase half-life.
- Total clearance after intravenous administration.
- Volume of distribution at steady state after intravenous administration.

- Intratumoral T-cell infiltration upon TAK-500 treatment.
- Incidence of patients who are antidrug antibody–positive and acquired immunogenicity.

Additional secondary endpoints for the phase 1 dose escalation only:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: cCR + cPR.
  - Disease control rate (DCR): cCR + cPR + stable disease >6 weeks.
  - Duration of response (DOR): the time from the date of first documentation of a cPR or better to the date of first documentation of PD for responders (cPR or better).
  - Time to response (TTR): the time from the date of first dose administration to the date of first documented cPR or better by the investigator.

Additional secondary endpoints for the phase 2 dose expansion only:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - DCR: cCR + cPR + stable disease (SD) >6 weeks.
  - DOR: the time from the date of first documentation of a cPR or better to the date of first documentation of PD for responders (cPR or better).
  - TTR: the time from the date of first dose administration to the date of first documented cPR or better by the investigator.
  - Progression-free survival (PFS).
  - Overall survival (OS).
- Frequency and severity of TEAEs.
- Number of patients with DLTs.
- Number and percentage of patients with 1 or more treatment-emergent SAE.
- Number and percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations.

Statistical Considerations:

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.

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 the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG Performance Status will be summarized using a shift table. Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value. Graphical displays of key

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safety parameters, such as scatter plots of baseline vs worst postbaseline values, may be used to understand the TAK-500 safety profile.

For the dose escalation phase, antitumor activity is not the primary endpoint; secondary antitumor activity endpoints include ORR, DCR, DOR, and TTR. In the dose expansion phase, ORR is the primary endpoint; secondary antitumor activity endpoints include DCR, DOR, TTR, PFS, and OS. No formal statistical tests will be performed for these efficacy endpoints in the study. ORR and DCR will be summarized using descriptive statistics with 95% CI. DOR and TTR will be analyzed using Kaplan-Meier method for response-evaluable analysis set. PFS and OS will be analyzed using Kaplan-Meier method for the safety analysis set in dose expansion cohorts only.

Patients in the SA arm who cross over to the combination arm will be analyzed separately using all the post-crossover data, repeating the main analyses as appropriate, to show long-term safety and antitumor activity. These crossover patients will still be included in the main analyses, in which their post-crossover data will be excluded. Patients treated with a specific premedication regimen will be analyzed separately from cohorts treated without premedication or with other premedication regimens.

PK parameters will be summarized using descriptive statistics. Individual TAK-500 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort.

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Sample Size Justification:

Approximately 313 patients will be enrolled in the study, including approximately 82 in the dose escalation phase and approximately 231 in the dose expansion phase (assuming only 1 DL and dose schedule will be expanded).

In the phase 1 dose escalation phase, approximately 52 patients will be enrolled to achieve about 46 DLT-evaluable patients in the SA arm, and approximately 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients in the combination arm (assuming a drop-out rate of 10%). In the SA arm, a maximum of 42 DLT-evaluable patients is planned for BOIN escalation to cover 8 DLs and an additional 4 DLT-evaluable patients for the two 1 + 2 + 3 escalation DLs. In the combination arm, the number of patients will depend on the starting DL. Assuming the escalation starts at 80 μg/kg, a maximum of 27 DLT-evaluable patients will be enrolled. Additional patients may be enrolled for the evaluation of Q2W administration of TAK-500 if this schedule is explored in the dose escalation phase (in either the SA or combination arm).

In the phase 2 dose expansion phase, each cohort's sample size is based on Simon's 2-stage design or an exact binomial one-stage design with ORR as the endpoint, a one-sided alpha equal to 0.1, and an assumed dropout rate of 10%. In the following cohort-specific design specifications, H_0 represents the "null hypothesis," H_A represents the "alternative hypothesis," RE represents "response-evaluable," and power represents "statistical power." Note that some design scenarios are dependent on the results from preceding scenarios and may or may not be realized.

- *2L NSCLC TAK-500 + pembrolizumab RDE 1 versus RDE 2 [2:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 39 patients will be enrolled in the RDE 1 cohort, allowing for 35 RE patients. H_0: ORR ≤ 23%, H_A: ORR ≥40%, and power = 80%. The futility analysis will occur at 21 RE patients, where ≥5 responders are required for successfully passing futility.
  - Approximately 20 patients will be enrolled in the RDE 2 cohort allowing for 18 RE patients. If the futility analysis in RDE 1 fails, additional enrollment will be initiated to increase the RDE 2 RE sample size to 21 patients and Simon's 2-stage design will be applied in the same manner as planned for RDE 1. Given this, the total number of RE patients for RDE 2 may be 18, 21, or 35.
- *3L NSCLC TAK-500 SA RDE 1 versus RDE 2 [1:1 randomization]:*
  - Based on a single-stage exact binomial design, approximately 24 patients will be enrolled each in the RDE 1 cohort and the RDE 2 cohort, allowing for 21 RE patients per cohort. For each cohort, H_0: ORR

≤ 5%, H_A: ORR ≥20%, and power = 82%. The total RE sample size across the 2 cohorts will be 42 patients.

- *2L pancreatic adenocarcinoma TAK-500 + pembrolizumab RDE 1 versus 2L pancreatic adenocarcinoma TAK-500 SA RDE 1 [1:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 45 patients will be enrolled each in the combination cohort and the SA cohort, allowing for 40 RE patients per cohort. For each cohort, H_0: ORR ≤ 16%, H_A: ORR ≥30%, and power = 80%. For each cohort, a futility analysis will occur at 25 RE patients, where ≥4 responders are required for successfully passing futility.
- *3L RCC TAK-500 + Pembrolizumab RDE 1:*
  - Based on a single-stage exact binomial design, approximately 34 patients will be enrolled, allowing for 30 RE patients. H_0: ORR ≤ 8%, H_A: ORR ≥25%, and power = 90%.

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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 supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

The sponsor 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, and 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.

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3.3 List of Abbreviations

5-HT3	serotonin type 3 receptor
2L	second-line
3L	third-line
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{336}	area under the serum concentration-time curve from time 0 to 336 hours
AUC_{∞}	area under the serum concentration-time curve from time 0 to infinity
AUC_t	area under the serum concentration-time curve from time 0 to time t
AxMP	auxiliary medicinal product
BOIN	Bayesian Optimal Interval
BQL	below the quantifiable limit
cCR	confirmed complete response
CCR2	cysteine-cysteine chemokine receptor type 2
CDN	cyclic dinucleotide
CFR	Code of Federal Regulations
cGAS	cyclic GMP-AMP (guanosine monophosphate–adenosine monophosphate) synthase
CL	total clearance after intravenous administration
C_{max}	maximum observed serum concentration

CNS	central nervous system
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
cPR	confirmed partial response
CRS	cytokine release syndrome
CT	computed tomographic, computed tomography
CV	cardiovascular
CxDx	Cycle x Day x
DC	dendritic cell
DCR	disease control rate
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DOR	duration of response
DPV	during planned visit
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram, electrocardiographic, electrocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor-2
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN	interferon
Ig	immunoglobulin

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IL	interleukin
IO	immuno-oncology
IP-10	induced protein 10
IRB	institutional review board
IV	intravenous(ly)
LiMT	liver microtissue
LVEF	left ventricular ejection fraction
MABEL	minimum anticipated biological effect level
mCCR2-TAK-676	mouse surrogate for TAK-500
MCP-1	monocyte chemotactic protein-1
MDSC	myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIP	macrophage inflammatory protein
M-MDSC	monocytic-myeloid derived suppressor cell
MOA	mechanism of action
mOS	median overall survival
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NPC	nasopharyngeal carcinoma
NSCLC	non–small cell lung cancer
OATP	organic anion transporting polypeptide
ORR	overall response rate
OS	overall survival
PAD	pharmacologically active dose
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-(L)1	programmed cell death protein 1 or ligand 1
PDAC	pancreatic ductal adenocarcinoma
PFS	progression-free survival
PK	pharmacokinetic(s)

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PMDA	Pharmaceuticals and Medical Devices Agency
POC	proof-of-concept
[redacted]	[redacted]
[redacted]	[redacted]
Q2W	once every 2 weeks
Q3W	once every 3 weeks
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
RCC	renal clear cell carcinoma
RDE	recommended dose for expansion
RE	response-evaluable (patient)
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
SA	single agent
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SITC	Society for Immunotherapy of Cancer
SOE	schedule of events
SSR	special situation report
STING	Stimulator of Interferon Genes
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TAM	tumor-associated macrophage
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time of first occurrence of the maximum observed serum concentration
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor-alpha
TTR	time to response
UK	United Kingdom
ULN	upper limit of normal
US	United States
v	Version
VEGFR	vascular endothelial growth factor receptor

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V_{ss}	volume of distribution at steady state after intravenous administration
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

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4.0 INTRODUCTION

4.1 Background

Immuno-oncology has emerged as a major driver of anticancer therapeutics in both solid tumors and hematologic malignancies. Clinical data from immune checkpoint inhibitors (CPIs) such as CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) and programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors have changed the therapeutic paradigm in a growing number of indications. Overcoming T-cell inhibition in the tumor microenvironment (TME) with CPIs has proven to be a successful strategy to produce long-term benefit in a significant number of patients with metastatic solid tumors. However, despite these advances, many patients with advanced cancer are either refractory to CPIs or relapse after a period of tumor control, eventually succumbing to their disease. Some predictive biomarkers of CPI response, such as PD-L1 expression, microsatellite instability, and tumor mutational burden, have been clinically validated, but why some tumors are resistant or become refractory to CPIs remains less well-understood. Evolving data suggest that reduced interferon (IFN) signaling, immune escape through human leukocyte antigen loss, as well as altered antigen presentation may contribute to CPI resistance (Jenkins et al. 2018; Minn and Wherry 2016; Sharma et al. 2017). Furthermore, an emerging consensus acknowledges that CPI resistance (relapse or refractory in nature) may also be driven by tumor immunophenotype, specifically an immunosuppressive or "immune desert" phenotype (Liu et al. 2019). Accordingly, a possible strategy to overcome these elements of resistance is to stimulate innate immune cells (eg, myeloid cells, including antigen-presenting dendritic cells [DCs], granulocytes, eosinophils, neutrophils, or monocytes/macrophages, as well as lymphoid cells, including gamma/delta T cells, natural killer [NK] cells, and NK T cells) to condition the TME, thus converting immunologically "cold" tumors into "hot" tumors in which adaptive immune responses can be effectively activated.

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Stimulator of Interferon Genes (STING) is a cytosolic protein critical for the induction of type I IFN-dependent innate immunity (Ishikawa et al. 2009) and is specifically activated in the presence of cyclic dinucleotides (CDNs) derived from bacteria or produced by cyclic GMP-AMP (guanosine monophosphate–adenosine monophosphate) synthase (cGAS) (Sun et al. 2013; Wu et al. 2018). Emerging evidence indicates that the cGAS-STING pathway plays an important role specifically in driving tumor surveillance (Corrales and Gajewski 2015). The presence of cytosolic DNA in tumor cells leads to cGAS-dependent production of the second messenger cGAMP (2′,3′-cyclic guanosine monophosphate–adenosine monophosphate), which can subsequently transfer to professional antigen-presenting cells in the TME. Ultimately, this leads to induction of type I IFNs in DCs (Marcus et al. 2018). Type I IFNs and downstream regulated cytokines/chemokines serve as a potent "alert" to immune cells, including T cells and NK cells that may prime antitumor responses. Down-regulation of cGAS via epigenetic silencing has been reported in some human tumors, underscoring the potential significance of STING signaling in immune evasion (Konno et al. 2018). Additionally, recent studies have shown that STING (TMEM173)-deficient mice are susceptible to immunogenic tumors that wild type mice can reject, consistent with earlier studies demonstrating that tumor rejection in mice is dependent on

IFN alpha receptor 1 expression in DCs (Diamond et al. 2011). In immune-competent mice, administration of STING agonists activates DCs, which in turn generate a cytotoxic CD8+ T-cell response. In mouse models, synthetic STING agonists have demonstrated both single-agent (SA) antitumor efficacy and synergistic activity in combination with CPIs, including in aggressive tumor models (Sivick et al. 2018).

Cysteine-cysteine chemokine receptor type 2 (CCR2) is expressed on monocytes and other immune subsets of cells and is known to play an important role in the recruitment of monocytes/macrophages and T cells (Bakos et al. 2017). CCR2 and its ligand, chemokine CCL2, are elevated in certain types of advanced solid tumors and may influence survival in cancer patients (Lim et al. 2016). In the TME, CCR2 is most expressed in tumor-infiltrating myeloid cells, including tumor-associated macrophages (TAMs) and myeloid derived stromal cells. The presence of CCR2+ monocytic-myeloid derived suppressor cells (M-MDSCs) and TAMs promotes immune escape by limiting activated CD8 T-cell infiltration (Lesokhin et al. 2012), thereby decreasing the efficacy of immunotherapy (Kim et al. 2019). Nonclinical data and early clinical trial data suggest blockade of CCR2 may decrease the infiltration of myeloid derived suppressor cells (MDSCs) and TAMs and regulatory T cells in the TME (Flores-Toro et al. 2020; Lim et al. 2016; Loyher et al. 2016).

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TAK-500 is an immunostimulatory antibody-drug conjugate (ADC) consisting of 3 parts: (1) a genetically engineered humanized monoclonal antibody of the immunoglobulin (Ig)G1 class that is a potent specific antagonist of CCR2, (2) a CDN STING agonist exhibiting highly selective binding and activation of STING proteins from various species including mouse, rat, monkey, and human, and (3) a self-immolating maleimide-containing protease-cleavable peptide linker. The CDN agonist payload of TAK-500, referred to in this document as “conjugated TAK-676” or “TAK-676 payload”, is structurally based on TAK-676, a potent early clinical stage CDN STING agonist currently in phase 1 clinical studies. The IgG1 anti-CCR2 antibody used, referred to in this document as “TAK-202”, is based on TAK-202, previously evaluated in phase 1 clinical studies.

In recent years, there is emerging evidence showing an important role of MDSCs in tumor metastasis, drug resistance, and cancer immunosuppression (Hinshaw and Shevde 2019). The presence of CCR2+ M-MDSCs promotes immune escape by limiting activated CD8 T-cell infiltration, thereby decreasing the efficacy of immunotherapy (Lesokhin et al. 2012). By targeting both the STING pathway and CCR2, TAK-500 offers enhanced potency via improved pharmacokinetics (PK) and selective delivery in the preclinical models. As such, there are 3 potential anticancer mechanisms of action associated with TAK-500: (1) activation of IFN response via the TAK-676 payload, (2) reprogramming of intratumoral CCR2+ myeloid cells to an inflammatory phenotype, and (3) blockade of TAM recruitment via blockade of CCR2.

4.1.1 Nonclinical Background

Detailed information regarding the nonclinical pharmacology and toxicology of TAK-500 may be found in the investigator’s brochure.

4.1.1.1 Nonclinical Pharmacology

TAK-500 was found to elevate the expression level of CD69 and activate CD4 and CD8 T cells and NK cells in a dose-dependent manner, with similar sensitivity and activation potential among the 3 cell populations tested. TAK-500–mediated activation of human monocyte-derived DCs induced the expression of all activation markers tested (CD40, CD80, CD86, and HLA-DR) in a concentration-dependent manner. TAK-500 and the mouse surrogate for TAK-500 ([redacted]-TAK-676) had a comparable level of potency enhancement of [redacted] that was much improved when compared with TAK-676 alone. Additionally, TAK-202 and mouse [redacted]. In vitro receptor occupancy (RO) of [redacted]-TAK-676 in murine whole blood and TAK-500 in monkey and human whole blood was demonstrated on [redacted]. Half-maximal effective concentrations (EC_{50}s) of RO for TAK-500 in monkey and human blood were consistent with results of the on-cell binding assay of TAK-202.

In an in vitro cytokine release assay at 24 hours, TAK-500 induced the production of proinflammatory cytokines in the plasma of human peripheral whole blood. In vitro incubation of human peripheral blood mononuclear cells with TAK-500 resulted in the dose-dependent induction of monocyte populations, shown by increased expression of CD80 in monocytes, as well as a corresponding dose-dependent increase in the percentage of CD80 positive monocytes. This effect was most pronounced in both the total and classical monocyte populations, with additional moderate activation of CD80 in the intermediate monocytes. In intermediate monocytes, there was modest increased expression of the activation marker CD86, as well as modestly increased frequencies of CD86+ cells, after treatment with TAK-500.

In a PK study, mCCR2-TAK-676 exposure increased in a greater than dose-proportional manner in plasma and tumors after a single intravenous (IV) administration at 2, 10, and 50 µg/kg (based on TAK-676 payload) to C57BL/6 mice bearing MC38 syngeneic tumors. Deconjugated TAK-676 was below the quantifiable limit (BQL) in plasma, except for 1 animal at 50 µg/kg at 6 hours postdose, but was detectable in tumor samples at 10 and 50 µg/kg, starting at 6 hours postdose, and increased in a less than dose-proportional manner.

Significant activation and proliferation of immune cells within the TME, whole blood, and local tumor-associated lymphoid tissue were observed after administration of mCCR2-TAK-676 to female C57BL/6 mice bearing MC38 tumors. Significant antitumor activity was demonstrated after a single IV administration of mCCR2-TAK-676 to female C57BL6 mice bearing MC38 xenografts at 5, 10, and 25 µg/kg based on TAK-676 payload. Reduced antitumor activity was observed when mCCR2-TAK-676 was administered 24 hours after administration of anti–mouse IFNAR1 antibody at 1.0 mg/mouse, suggesting that type I IFN signaling plays a key role in the observed antitumor activity.

In vitro secondary pharmacology and cardiovascular (CV) liability assessments were not completed for TAK-500; however, these were completed for TAK-676. TAK-676 demonstrated no significant activity on a panel of various pharmacological targets (78 receptors, transporters,

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ion channels, and enzymes) and no CV liabilities were identified at concentrations up to 30 µM on the basis of in vitro results from a human ether-à-go-go–related gene assay and a human stem cell cardiomyocyte calcium transient proarrhythmia assay; TAK-676 was considered to be low risk for CV liabilities. It is important to note that circulating levels of deconjugated TAK-676 were low or undetectable in the TAK-500 Good Laboratory Practice (GLP)–compliant repeat-dose toxicity study in monkeys.

Safety pharmacology assessments were not performed on the non-GLP repeat-dose toxicity study in monkeys; however, in animals that underwent unscheduled removal from study, minimal microscopic findings in the heart and moribund clinical observations related to the CV system, central nervous system (CNS), and/or respiratory system were attributed to systemic immune stimulation. CV, CNS, and respiratory safety pharmacology assessments were completed as part of the GLP-compliant repeat-dose toxicity study in monkeys. There were no TAK-500–related changes in qualitative electrocardiology parameters, and, in animals surviving to scheduled necropsy, there were no CNS or respiratory clinical observations (including evaluation of respiration rates) and no microscopic findings in related tissues/organs. Microscopic findings of minimal neutrophilic infiltrates in the heart at scheduled necropsy were considered associated with a systemic pro-inflammatory response. In quantitative electrocardiology parameters, a moderate statistically significant TAK-500 RR-derived heart rate compared with pretreatment and vehicle control was observed on Day 1 at 0.9 mg/kg and was associated with an expected inverse correlation of shortened RR and QT intervals. These findings were still present but of a lesser magnitude on Day 8, indicative of partial recovery, and were considered likely to be associated with increases in serum cytokines. In the 2 female animals at 0.9 mg/kg euthanized in moribund condition (see Section 4.1.1.3), clinical observations included decreased activity, prolonged capillary refill time, pale skin, hunched posture, hypothermia and/or bradycardia at the time of euthanasia, and, microscopically, pulmonary edema with low numbers of inflammatory cells within alveoli, a finding not noted in animals surviving to scheduled necropsy. Cytokine concentrations in these animals ranged from higher than or similar to those in animals receiving TAK-500 that survived to scheduled necropsy. These findings support immune-mediated effects as the primary cause of moribundity, with pulmonary edema contributing to the clinical decline.

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4.1.1.2 Nonclinical PK

In vitro catabolite identification with acidified monkey liver S9, acidified human liver S9, recombinant human cathepsin B, papain, and human liver lysosomes identified 2 catabolites. The major catabolite was identified as deconjugated TAK-676, generated through hydrolysis of the amide bond. C1 was a minor metabolite that was determined to be TAK-676–linker fragment (2-[(methylamino)methyl]benzaldehyde) and addition of C_7H_9N. The location of the addition of C_7H_9N and the mechanism of formation of C1 is currently unknown.

After single IV administration of TAK-500 to monkeys, plasma exposure of total antibody and conjugated TAK-676 increased with increasing doses in a greater than dose-proportional manner between 0.1 and 0.5 mg/kg, and in a dose-proportional manner between 0.5 and 3 mg/kg. Plasma

exposure of deconjugated TAK-676 was not quantifiable or low across all doses, and PK parameters were not estimated.

Completed as part of the GLP-compliant repeat-dose toxicity study in monkeys, toxicokinetic analysis after each dose on Days 1, 15, and 29 showed that the time of first occurrence of the maximum observed serum concentration (t_{max}) for both TAK-500 and conjugated TAK-676 occurred at 0.083 hours postdose in all animals tested. The maximum observed serum concentration (C_{max}) and the area under the serum concentration-time curve (AUC) values increased with increasing IV DLs of TAK-500 in a dose-proportional and greater than dose-proportional manner, respectively. There were no apparent sex-related differences. Repeat administration of TAK-500 was associated with the development of antidrug antibodies (ADAs) in 35 of 36 animals at 1 or more time points after Day 15, resulting in lower exposure on Day 29 of TAK-500 and conjugated TAK-676. Deconjugated TAK-676 plasma concentrations were low or BQL for all dose groups and toxicokinetic parameters were not estimated.

Nonclinical PK studies with TAK-676 demonstrated that TAK-676 is mainly eliminated as a parent compound through biliary and urinary excretion in rats and monkeys. The contribution of metabolism to TAK-676 clearance pathways is anticipated to be minimal. TAK-676 is a substrate for organic anion transporting polypeptide (OATP)1B1, OATP1B3, and multidrug resistance associated protein 2 but is not likely a substrate for P-glycoprotein and breast cancer resistance protein. While the OATP inhibitors may affect plasma drug levels of the TAK-676, the impact of OATP1B1 polymorphism on TAK-676 exposure is anticipated to be low. Nevertheless, as a precautionary measure, concomitant use of clinical inhibitors of OATP1B1 and OATP1B3 should be avoided before the first dose of study drug(s) and during the study as detailed in Section 7.2, Section 8.6, and Appendix D.

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4.1.1.3 Nonclinical Toxicology

No single-dose toxicity studies have been conducted with TAK-500.

In a non-GLP cynomolgus monkey repeat-dose toxicity study (0.3, 1, or 3 mg/kg; slow IV bolus Q2W for 3 doses), TAK-500 was well tolerated at 0.3 mg/kg. Although the first administration was well tolerated up to 3 mg/kg, repeat dosing at ≥1 mg/kg was not tolerated, resulting in early euthanasia (2) or death (1) out of a total of 12 animals receiving TAK-500. In the early euthanasia animals and in animals surviving to scheduled euthanasia, findings were primarily attributed to immune-mediated effects of uncertain pathophysiology, either directly related to TAK-500 administration and/or secondary to immunogenicity/hypersensitivity, as well as hepatocellular effects that included minimal, focal to multifocal hepatocellular necrosis. Repeat dosing was associated with a high incidence of ADA and a partial reduction in exposure at all doses in most animals by the third dose. Levels of deconjugated TAK-676 were low or undetectable after administration of TAK-500 in monkeys.

In a GLP-compliant monkey repeat-dose toxicity study (0.1, 0.3, or 0.9 mg/kg; slow IV bolus Q2W for 3 doses), TAK-500 was well tolerated up to 0.3 mg/kg but resulted in early euthanasia

of 2 female animals due to moribundity (adverse clinical observations) at 0.9 mg/kg approximately 6 to 7 hours after receiving a dose (1 animal each on Days 1 and 15).

The majority of TAK-500–related findings were present in both early euthanasia and scheduled euthanasia animals at ≥0.1 mg/kg and were considered attributable to direct immune-mediated effects of TAK-500, although secondary effects of immunogenicity and/or nonspecific infusion-related reactions may have contributed to the underlying pathophysiology. Additionally, minimal to mild pulmonary edema was uniquely observed in early euthanasia animals and was also considered to have contributed to the clinical decline in these animals.

Immune-mediated findings observed at ≥0.1 mg/kg TAK-500 included a number of dose-related, transient clinical signs generally noted 4 to 8 hours after dosing, which consisted of vomiting and, at ≥0.3 mg/kg, decreased activity, hunched posture, and/or red face. Increased RR-derived heart rate was found after a single dose of 0.9 mg/kg in jacketed telemetry-designated animals, and was considered likely to be associated with increases in serum cytokines. In addition, clinical pathology changes consistent with an acute phase response were noted on Day 3 only. Microscopic findings at ≥0.1 mg/kg consisted of generally minimal neutrophilic infiltrates in the spleen, liver, adrenal cortex, and/or atrioventricular valves of the heart; scattered inflammatory foci with degeneration/necrosis in the liver, decreased cellularity or lymphoid necrosis in spleen and thymus; and at ≥0.3 mg/kg, minimal adrenocortical hemorrhage. Transient cytokine elevations consisted of increases in interleukin (IL)-1 receptor antagonist, IL-6, and tumor necrosis factor-alpha (TNF-α) concentrations at 6 hours postdose on Days 1, 15, and/or 29. Other TAK-500–related findings observed at ≥0.1 mg/kg were consistent with expected pharmacology and included decreases in circulating monocytes on Day 3 and increases in serum monocyte chemotactic protein-1 (MCP-1) and induced protein 10 (IP-10) concentrations peaking at 6 hours postdose on Days 1, 15, and 29. Additional hepatocellular effects consisted of increases in serum chemistry liver parameters (on Day 3 only), and there were minor organ weight changes that lacked histologic correlates in the spleen, liver, adrenal gland, and thymus at scheduled necropsy.

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All findings were completely reversible after a 2-week recovery period (Day 43), with the exception of histologic findings in the adrenal gland and spleen, which partially recovered. In addition to effects on exposure, the ADA that developed in all animals administered TAK-500 likely correlated with attenuation of clinical pathology findings and findings attributable to pharmacology by Day 29 (effects on monocytes and MCP-1 and IP-10 concentrations).

Nonclinical toxicity studies with TAK-676 included in vitro studies for genotoxicity, cytokine release in human whole blood, and in vivo studies in Sprague Dawley rats and cynomolgus monkeys. TAK-676 was nongenotoxic in in vitro genotoxicity tests and stimulated cytokine release in human whole blood. In the rat GLP toxicity study, the predominant finding was single-cell necrosis across multiple tissues and organs that was consistent with death of lymphocytes and leukocytes, while in the monkey GLP study pulmonary edema was considered the dose-limiting toxicity (DLT). The amount of circulating deconjugated TAK-676 was found to be low to BQL after administering repeat doses of TAK-500; the toxicities noted in rats and monkeys after IV administration of TAK-676 are unlikely to translate to that after TAK-500 administration. Tissue cross reactivity studies with a surrogate for the TAK-202 antibody portion

of TAK-500 in monkey and human tissues showed similar [redacted] immunoreactivity patterns between species that were consistent with published data. TAK-202 was safe and well tolerated in cynomolgus monkeys for up to 6 months of dosing after single and once weekly IV or subcutaneous administration and the no-observed-adverse-effect level (NOAEL) was the high dose (100 mg/kg) in each study (Katschke et al. 2001; Millennium Pharmaceuticals Inc 2003; Ruth et al. 2001).

4.1.2 Clinical Background

This study (Study TAK-500-1001) is the first-in-human (FIH) dose escalation and expansion study with TAK-500, administered both as an SA and in combination with pembrolizumab in patients with select locally advanced or metastatic solid tumors. Potential safety concerns and/or biological activity may be extrapolated from preclinical efficacy and GLP toxicology studies with TAK-500, as detailed in Sections 4.1.1.1 and 4.1.1.3. There are no prior reports of clinical trials involving STING ADCs and only limited reports from clinical trials involving nontargeted STING agonists for comparison.

The dose escalation of TAK-500 in combination with pembrolizumab is included as part of the FIH study based on the mechanism of action (MOA) of TAK-500 and evidence of synergistic antitumor activity when STING agonists are administered in combination with anti–PD-1 antibodies in nonclinical models. This synergy is currently being explored in phase 1 studies with TAK-676. Pertinent clinical experience with the components of TAK-500 (TAK-202 and TAK-676) are summarized in Sections 4.1.2.1 and 4.1.2.2.

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4.1.2.1 TAK-202

TAK-202 doses administered in prior clinical studies of TAK-202 are 20 to 300 times higher than the maximum planned dose in the dose escalation phase of TAK-500-1001. Consequently, it is unlikely that the adverse events (AEs) previously reported for TAK-202 will be reproduced in the current study. Regardless, for informational purposes, the pertinent clinical findings from prior TAK-202 studies are summarized below.

Final data from 5 completed clinical studies are the primary basis for characterizing the safety, PK, and pharmacodynamic profile of TAK-202 (also known as MLN1202) in humans. These 5 clinical studies included 2 phase 1 studies (Studies MLN120202-046 and C06002) and 3 phase 2 studies (Studies C06004, MLN120203-055, and MLN120204-063), in which 187 subjects were treated with TAK-202, including 60 healthy subjects, 23 patients with rheumatic arthritis, 54 patients with risk factors for atherosclerotic CV disease, and 50 patients with relapsing-remitting multiple sclerosis. Subjects in these trials received single IV doses ranging from 0.1 to 10.0 mg/kg, or subcutaneous doses of 75 or 150 mg.

In addition, 9 patients with advanced melanoma received TAK-202 in combination with nivolumab. Two patients discontinued the study due to AEs, 1 patient withdrew consent, and 6 patients discontinued treatment due to progressive disease (PD). There were no on-study deaths reported and only 1 patient reported treatment-related AE of Grade 3 (alanine aminotransferase

[ALT] increase). Fatigue and nausea were the most commonly reported treatment-related AEs. No convincing antitumor effect was seen in this study.

The nonclinical and clinical experience to date suggests that TAK-202 is well tolerated and suitable for further investigation in human clinical studies.

4.1.2.2 TAK-676

As of 27 February 2022, 50 patients are enrolled and TAK-676 has been evaluated in a total of 49 patients across 2 ongoing studies:

1. Study TAK-676-1002, a phase 1 FIH study evaluating TAK-676 as an SA and in combination with pembrolizumab in adult patients with advanced or metastatic solid tumors.
2. Study TAK-676-1003, a phase 1 dose escalation study to evaluate the safety, tolerability, and preliminary antitumor activity of TAK-676 and pembrolizumab following radiation therapy in the treatment of non–small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), or squamous-cell carcinoma of the head and neck (SCCHN) patients who have progressed on CPIs.

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Study TAK-676-1002

As of 27 February 2022, a total of 44 patients had received at least 1 dose of TAK-676: 25 patients had received at least 1 dose of TAK-676 administered as an SA and 19 patients had received at least 1 dose of TAK-676 in combination with pembrolizumab. As an SA, TAK-676 has been administered to patients at the following doses: 0.1 mg (1 patient), 0.2 mg (3 patients), 0.4 mg (3 patients), 0.8 mg (4 patients), 1.2 mg (4 patients), 1.6 mg (3 patients), 2.0 mg (3 patients), and 2.5 mg (4 patients). TAK-676 has been administered in combination with pembrolizumab to patients at the following doses: 0.2 mg (3 patients), 0.4 mg (4 patients), 0.8 mg (5 patients), 1.2 mg (4 patients), and 1.6 mg (3 patients). As of 27 February 2022, 23 (92.0%) patients receiving TAK-676 SA experienced treatment-emergent adverse events (TEAEs). The most common TEAEs were fatigue (8 [32.0%] patients), nausea (6 [24.0%] patients), and vomiting (5 [20.0%] patients). Thirteen (52.0%) patients experienced TEAEs considered related to study drug by the investigators. Six (24.0%) patients receiving TAK-676 SA experienced Grade 3 or higher TEAEs. TEAEs that led to study drug discontinuation in 3 (12.0%) patients in the TAK-676 SA arm were the following: Grade 4 small intestinal obstruction (considered not related to TAK-676), Grade 2 infusion-related reaction (considered related to TAK-676), and Grade 3 alanine aminotransferase increased (considered related to TAK-676). Seven (28.0%) patients experienced treatment-emergent SAEs; SAEs included dyspnea, pulmonary embolism, pneumonia, small intestinal obstruction (resulting in death in 1 patient), abdominal pain, pancreatitis, hypercalcemia, cancer pain, and confusional state. None of these SAEs were considered to be related to study drug. There was 1 death, considered unrelated to study drug, due to a Grade 5 small bowel obstruction. There were no DLTs among patients receiving TAK-676 SA.

As of 27 February 2022, 19 (100%) patients receiving TAK-676 in combination with pembrolizumab experienced TEAEs. The most common TEAEs were cough (7 [36.8%]

patients), fatigue (6 [31.6%] patients), diarrhea (6 [31.6%] patients), and nausea (5 [26.3%] patients). Sixteen (84.2%) patients experienced TEAEs considered related to study drug by the investigators. Nine (47.4%) patients receiving TAK-676 in combination with pembrolizumab experienced Grade 3 or higher TEAEs. TEAEs that led to study drug discontinuation in 2 patients (10.5%) in TAK-676 in combination with pembrolizumab arm were Grade 3 clostridium difficile colitis and Grade 4 sepsis; both were considered as not related to TAK-676. Eight (42.1%) patients experienced treatment-emergent SAEs; SAEs included acute respiratory failure (resulting in death), pleural effusion, sepsis (resulting in death), coronavirus disease 2019 (COVID-19), *Clostridium difficile* colitis, conduction disorder, electrocardiogram T wave abnormality, and bone pain. One patient experienced electrocardiogram T wave abnormality of Grade 2 severity that was considered related to TAK-676 administration though the patient remained asymptomatic throughout the course of treatment. There were no DLTs among patients receiving TAK-676 in combination with pembrolizumab.

To date, the preliminary PK of TAK-676 has been evaluated in Study TAK-676-1002 (n = 37). Across the dose range of 0.1 to 1.6 mg, the PK of TAK-676 was linear with an approximately dose-proportional increase in area under the concentration-time curve from time 0 to infinity (AUC_∞) and biphasic decline in plasma concentrations. Following repeated administration, the PK of TAK-676 remained similar suggesting little to no accumulation after repeated administration. Similar C_{max}, AUC_∞ and terminal elimination half-life for TAK-676 were observed when TAK-676 was administered as an SA or in combination with pembrolizumab.

Evaluation of the TAK-676–mediated [redacted] is observed in peripheral blood collected from 1.2 mg SA and 0.8 mg combination treated patients. This data is consistent with TAK-676 target engagement [redacted] regulated by [redacted].

There has been 1 confirmed partial response (cPR) as of the data cutoff date in a [redacted]-year-old [redacted] patient with metastatic sebaceous carcinoma dosed at 0.8 mg TAK-676 + pembrolizumab. The patient was αPD-(L)1–naïve and received 4 prior lines of therapy. [redacted] has tolerated the study treatment well and remains on study in Cycle 9 as of the data cutoff.

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Study TAK-676-1003

As of 27 February 2022, 6 patients are enrolled in the study and received radiation therapy and 5 patients have received at least 1 dose of TAK-676 in combination with pembrolizumab following radiation therapy. TAK-676 has been administered to patients at 0.2 mg (4 patients) and 0.4 mg (2 patients).

Four (66.7%) patients receiving TAK-676 experienced TEAEs. The most common TEAEs were cough and esophagitis (2 [33.3%] patients each). None of the patients experienced TEAEs related to TAK-676. None of TEAEs were of Grade 3 or higher severity. There were no DLTs or treatment-emergent SAEs reported.

4.1.2.3 TAK-500

Currently, TAK-500 is being investigated only in this ongoing FIH study (TAK-500-1001) as an SA and in combination with pembrolizumab for the treatment of adult patients with select advanced solid tumors.

As of data cutoff date of 14 September 2022, 7 patients have received TAK-500 administered as an SA at doses of 8 µg/kg (3 patients) and 16 µg/kg (4 patients).

[redacted].

Table 4.a [redacted]

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Table 4.a [redacted]

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Table 4.a [redacted]

[redacted]

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4.2 Rationale for the Proposed Study

TAK-500-1001 is an FIH, dose escalation and dose expansion study with TAK-500 administered as an SA and in combination with pembrolizumab.

In the TAK-500 SA dose escalation arm, the study will enroll adult patients with select histologically or cytologically confirmed select locally advanced or metastatic solid tumors (gastroesophageal [esophageal, gastroesophageal junction, and gastric] adenocarcinoma, pancreatic adenocarcinoma, hepatocellular carcinoma [HCC], nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC) with no available standard therapeutic options, either due to disease progression or intolerance to therapy. Patients who are intolerant to therapy are those who have developed clinical or laboratory abnormalities that prevent continued drug

administration as evaluated by the principal investigator at the time of screening. This patient population represents a traditional cohort for an FIH phase 1 study, where the investigational agent lacks a well-defined, biomarker-driven, or clearly defined tumor-specific target. As such, a broad locally advanced or metastatic solid tumor patient population presents the most favorable balance between patient risk and benefit.

The TAK-500 and pembrolizumab combination dose escalation arm will enroll the same population as the TAK-500 SA dose escalation arm. Pembrolizumab is a humanized monoclonal IgG4 kappa PD-1–blocking antibody approved for use by the United States (US) Food and Drug Administration (FDA) in numerous tumor types.

In dose expansion, both TAK-500 SA and TAK-500 in combination with pembrolizumab will be explored in nonsquamous NSCLC, RCC, and pancreatic adenocarcinoma. These tumor types were selected for expansion due to the immune contexture of their tumor microenvironment and unmet clinical need. For detailed rationale behind indication selection for TAK-500 dose expansion cohorts, see Sections 4.2.1.2, 4.2.1.4, and 4.2.1.8.

There is nonclinical evidence that TAK-500 has antitumor synergy when combined with an anti–PD-1 antibody. However, it is also established that CPIs have SA antitumor activity across a wide range of tumor types, even when these antitumor effects were not sufficiently robust to support a label indication. As such, the patient selection for this combination approach will include the following 2 broad groups:

- Patients who are refractory to or have developed resistance to prior anti–PD-1/anti–PD-L1 therapy. This set includes patients with malignancies that have relapsed on or are refractory to anti–PD-1/anti–PD-L1 therapy and will include, but is not limited to, patients with the following tumor types: locally advanced or metastatic gastroesophageal adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC.
- Patients who are CPI-naïve. This set includes patients with malignancies that have not yet been exposed to anti–PD-1/anti–PD-L1 and will include, but is not limited to, patients with pancreatic adenocarcinoma.

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4.2.1 Rationale for the Patient Population Selection

This study will enroll adult patients with histologically confirmed select locally advanced or metastatic solid tumors. This patient population represents a traditional cohort for phase 1 studies containing a new regimen without a well-defined, biomarker-driven or tumor-specific target. This patient population often has the most favorable balance between patient risk and benefit for a phase 1 study. During dose escalation, this study will collect tumor tissue and blood samples to identify potential pharmacodynamic biomarkers to support future patient selection or enrichment.

Eligible patients for this study include both patients who are CPI-naïve and those who are refractory to or have developed resistance to anti–PD-1/anti–PD-L1 therapies. There is

preclinical evidence that the addition of a STING agonist may reverse the mechanisms of resistance in tumors with prior exposure to anti–PD-1/anti–PD-L1 therapies (see Section 4.1.1.1). While it is unknown whether the combination of anti–PD-1 antibody and TAK-500 will provide meaningful clinical benefit, this regimen represents a promising approach to addressing CPI recalcitrance. Tumor responses in this group of patients may provide early insight into the clinical benefit produced by the combination of TAK-500 and pembrolizumab for patients in which CPI alone is not sufficient to drive or maintain a sustained clinical response.

The tumor types identified in Sections 4.2.1.1 to 4.2.1.7 were selected on the basis of clinical unmet need and the presence of the following biomarkers: [redacted].

4.2.1.1 Gastroesophageal Adenocarcinoma

Gastroesophageal adenocarcinomas are malignant tumors arising in the upper gastrointestinal tract (GIT; esophagus, gastroesophageal junction, stomach). Both in gastric and esophageal cancers, patients with advanced stage disease have poor survival rates. The American Cancer Society estimates that about 26,560 cases of stomach cancer and 19,260 cases of esophageal cancer will be diagnosed in 2021 (Siegel et al. 2021). In 2020, studies showed that the combination of nivolumab plus chemotherapy improved overall survival in some patients with advanced gastric or gastroesophageal junction cancer (Moehler et al. 2020). Conversely, pembrolizumab plus chemotherapy failed to show an overall survival benefit over chemotherapy alone (Shitara et al. 2020). Further clinical trials to investigate immunotherapy-based combinations are needed for patients with tumors refractory or resistant to CPI.

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4.2.1.2 Pancreatic Adenocarcinoma

Pancreatic cancer is one of the deadliest of all types of cancer. In 2021, 60,430 Americans are estimated to be diagnosed with pancreatic cancer, and about 48,220 are expected to die of the disease (Siegel et al. 2021). The mainstay of curative treatment for pancreatic cancer is surgery. The prognosis of locally advanced or metastatic pancreatic cancer remains poor (Siegel et al. 2022). Overall response rates (ORRs) to second-line (2L) combination chemotherapy ranges from 13% to 17%, with median progression-free survival (mPFS) of 3.1 to 5.8 months and median OS (mOS) of 6.1 to 9.9 months (Huh et al. 2021; Mita et al. 2019; Wang-Gillam et al. 2019; Zaibet et al. 2022). In the third-line (3L) or later setting, ORRs range from 0% to 3.9%, with mPFS of 1.6 to 2.4 months and mOS of 3.9 to 4.6 months (Chun et al. 2022; Mie et al. 2021; Yu et al. 2021).

4.2.1.2.1 Role of Immunotherapy in the Treatment of Pancreatic Adenocarcinoma

Despite advances in immunotherapy in many tumor types, the role of immunotherapy in pancreatic cancer remains limited. Pembrolizumab is currently only approved for the patients with the microsatellite-high/DNA mismatch repair–deficient tumors (Marabelle et al. 2020), which accounts for only 1% to 2% of all pancreatic adenocarcinoma (Cancer Genome Atlas

Research et al. 2017; Luchini et al. 2021). Multiple studies conducted to investigate CPIs in pancreatic cancer have reported disappointing results (Henriksen et al. 2019; O'Reilly et al. 2019; Renouf et al. 2022; Ullman et al. 2022).

4.2.1.2.2 STING Signaling, CCR2 Expression, and Myeloid Infiltration in Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma is characterized by an immunosuppressive TME with a fibrous stroma and prominent myeloid cell infiltration. The high density of myeloid subpopulations, such as MDSCs and TAMs, have been associated with worse prognosis (Morrison et al. 2018; Murray 2017; Vayrynen et al. 2021). Moderate CCR2 expression is found in pancreatic adenocarcinoma by bulk RNA-seq (Cancer Genome Atlas Research et al. 2017) and by scRNA-seq in myeloid populations in the pancreatic adenocarcinoma TME (Cheng et al. 2021). Despite their lack of CPI-responsiveness, pancreatic adenocarcinoma tumors span the range of immunological "cold" to "hot," likely due to tumor heterogeneity (Rubin et al. 2022; Ullman et al. 2022). Tumor RNA-seq analysis showed moderate to high STING and interferon-related gene expression (Cancer Genome Atlas Research et al. 2017). Furthermore, STING agonists have been shown to activate antitumor immunity in preclinical pancreatic cancer models (Kabashima et al. 2022; Mohseni et al. 2021). Given the high myeloid content and potential of STING pathway–mediated immune activation, systemic administration of TAK-500 may hypothetically provide clinical antitumor activity in pancreatic adenocarcinoma.

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4.2.1.3 HCC

In 2021, an estimated 42,230 new cancers of the liver and intrahepatic bile duct are expected to be diagnosed in the US, and 30,230 people will die of the disease (Siegel et al. 2021). The most common form of primary liver cancer is HCC. In 2020, FDA approved atezolizumab plus bevacizumab as first-line therapy with advanced HCC (Finn et al. 2020). Pembrolizumab and ipilimumab with nivolumab are also approved for 2L or later use in HCC, but therapeutic options after progression while on a CPI are limited.

4.2.1.4 Nonsquamous NSCLC

NSCLC is the leading cause of cancer mortality in the US with an estimated 140,000 patients dying of the disease this year, which is greater than the number of cancer mortalities from colon, breast, and prostate cancer combined (Siegel et al. 2021). The majority of NSCLC patients present with metastatic disease. NSCLC can be subcategorized as nonsquamous (up to 80%) and squamous (up to 30%) histological types. Lung adenocarcinoma makes up the majority of nonsquamous NSCLC and is viewed as a distinct entity compared with squamous NSCLC (Oliver et al. 2015).

4.2.1.4.1 Role of Immunotherapy in the Treatment of Nonsquamous NSCLC

Recently, immunotherapy with or without chemotherapy (depending on PD-L1 expression) has become the proven preferred first-line or 2L systemic therapy in patients without actionable

tumor driver mutations (Borghaei et al. 2019; Gandhi et al. 2018; Reck et al. 2019). Even though a number of CPIs are approved for the treatment in the later-line settings, as CPIs become the standard of care in first-line nonsquamous NSCLC, most 2L and later patients will likely have developed resistance to CPI therapy and have to undergo a chemotherapy-based regimen. In the REVEL study, in 2L after disease progression on a platinum-based regiment ramucirumab (an anti-vascular endothelial growth factor [VEGFR] tyrosine kinase inhibitor [TKI]) + docetaxel showed an ORR of 23%, mPFS of 4.5 months, and mOS of 10.5 months (Garon et al. 2014). For 3L and later patients, treatment options are limited to chemotherapy, such as docetaxel SA, for which ORRs have been reported to range from 5% to 7% with mPFS of approximately 3.5 months and mOS of 8 to 9 months. Despite the overall success of CPIs in patients with NSCLC, the majority of patients eventually develop resistance to immunotherapy and have disease progression (Schoenfeld and Hellmann 2020). Novel treatment options, both as initial approach and upon development of resistance to CPI therapy, are needed.

4.2.1.4.2 STING Signaling, CCR2 Expression, and Myeloid Infiltration in Nonsquamous NSCLC

The NSCLC TME is complex and harbors both tumor-promoting and tumor-suppressive activities (Altorki et al. 2019). Various studies have identified enriched myeloid-derived cells, such as MDSCs, TAMs, and neutrophils, in the NSCLC TME (Lavin et al. 2017; Singhal et al. 2019; Zilionis et al. 2019), and their presence or associated transcriptional signatures have been associated with clinical outcomes (Gentles et al. 2015; Jackute et al. 2018; Messmer et al. 2015). High CCR2 expression is found in the NSCLC TME by bulk RNA-seq (Cancer Genome Atlas Research et al. 2017) and by scRNA-seq in myeloid populations (Cheng et al. 2021). Tumor RNA-seq analysis shows high STING and interferon-related gene expression (Cancer Genome Atlas Research et al. 2017). The immune TME with high CCR2+ myeloid cells and STING activity, combined with the CPI responsiveness, leads to the hypothesis that TAK-500 can induce antitumor activity in nonsquamous NSCLC.

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4.2.1.5 SCCHN

In 2021, an estimated 54,010 new cancers of the oral cavity and pharynx are expected to be diagnosed, and 10,850 people will die of the disease (Siegel et al. 2021). Key risk factors for SCCHN are smoking, alcohol consumption, and history of human papillomavirus and Epstein-Barr virus infection. Only 29% of patients are diagnosed with localized disease that is curable by surgery alone. SCCHN has a predominantly locoregional pattern of recurrence, with only 25% of patients presenting with distant metastases at recurrence, and this mostly to the lungs. Recently, pembrolizumab was FDA approved in the first-line setting for the treatment of metastatic or unresectable SCCHN as monotherapy for patients with positive PD-L1 expression and in combination with platinum and fluorouracil in patients whose tumors are PD-L1 negative. Nivolumab is also approved for use in the 2L setting after progression on a platinum-containing agent. There is an unmet clinical need for those patients who have PD while on CPI and chemotherapy.

4.2.1.6 Mesothelioma

Mesothelioma is a rare and aggressive cancer, accounting for less than 0.3% of all cancer diagnoses in the US. About 3000 new cases are diagnosed each year (Carbone et al. 2019). The average life expectancy of patients with advanced stage mesothelioma is usually less than 1 to 2 years (Shavelle et al. 2017). In 2020, FDA approved nivolumab in combination with ipilimumab for the first-line treatment of adults with unresectable malignant pleural mesothelioma (Wright 2020). Pembrolizumab was also approved for patients with a high tumor mutational burden. Given the modest overall effectiveness under immunotherapy, there is an unmet medical need for patients with refractory and resistant disease under CPI treatment.

4.2.1.7 TNBC

In 2021, an estimated 284,200 new breast cancers are expected to be diagnosed, and 44,130 people will die of the disease (Siegel et al. 2021). TNBC, defined by the lack of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor-2 (HER2)/neu, represents 10% to 20% of all breast cancers. Patients with TNBC do not benefit from hormone therapy or HER2 monoclonal antibody. Therefore, TNBC is more aggressive and has poorer prognosis than other types of breast cancers. In recent years, the introduction of immunotherapy brings some promising results in metastatic TNBC (Cortes et al. 2020). On the basis of the IMPASSION 130 phase 3 trial, atezolizumab in combination with nab-paclitaxel is now approved for first-line use in patients with metastatic TNBC and positive PD-L1 expression levels (Schmid et al. 2018). In 2020, FDA also granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent resectable or metastatic TNBC whose tumors express PD-L1 (Slater 2020). Unmet medical need remains in metastatic TNBC, given the short progression-free survival (PFS; <10 month) in first-line therapy, and primary and acquired resistance to CPIs.

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4.2.1.8 RCC

RCC comprises approximately 5% of all new diagnoses of malignancy with an estimated 80,000 new cases and almost 14,000 deaths in 2021 in the US (seer.cancer.gov/statfacts/html/kidrp.html, Cancer Stat Facts: Kidney and Renal Pelvis Cancer). Clear cell RCC accounts for 70% to 80% of RCC cases with about 20% of new diagnoses being locally advanced or metastatic while 30% of nonmetastatic disease will develop metastases (Lalani et al. 2019).

4.2.1.8.1 Role of Immunotherapy in the Treatment of RCC

The systemic treatment paradigm for metastatic RCC has been dynamically changing (Gkolfinopoulos et al. 2021). Antiangiogenic drugs, such as sorafenib, axitinib, cabozantinib, lenvatinib, and pazopanib, all small molecule TKIs of VEGFR, have shown significant antitumor activity in the first-line and 2L settings (Choueiri et al. 2016; Escudier et al. 2007; Kudo et al. 2018; Motzer et al. 2013). Recently, drug combinations that include CPIs and TKIs have shown improved benefit and emerged as the standard of care in the first-line setting (Choueiri et al.

2021; Lombardi et al. 2022; Motzer et al. 2021; Motzer et al. 2019; Rini et al. 2019). However, for RCC patients whose disease progresses following initial CPI/TKI combination therapy, treatment options in later lines remain limited. In the 3L setting, TKIs, such as tivozanib and sorafenib, remain the standard of care with ORRs ranging from 8% to 18%, mPFS of 3.9 to 5.6 months, and mOS of 16.4 to 19.2 months (Rini et al. 2020).

4.2.1.8.2 STING Signaling, CCR2 Expression, and Myeloid Infiltration in RCC

Large-scale transcriptome analyses showed that RCC tumors are among the most highly immune-rich tumor types, with abundant myeloid cell infiltration and high levels of CCR2 expression (Becht et al. 2016; Chevrier et al. 2017; Ricketts et al. 2018). Various immune signatures have shown correlation with disease progression and treatment response (Au et al. 2021; Helmink et al. 2020; Rappold et al. 2022; Ricketts et al. 2018). Notably, high T cell/low myeloid infiltration are reported to be enriched in responders to anti-PD-1/PD-L1 (Helmink et al. 2020; McDermott et al. 2018). RCC also shows high expression levels of STING and genes involved in the cGAS-STING and interferon pathways, likely partially related to the abundant immune infiltration (Ricketts et al. 2018). Given RCC's responsiveness to immunotherapy, high level of CCR2 expression and myeloid-rich TME, we hypothesize that TAK-500's CCR2-mediated STING activation represents a promising agent for patients in RCC.

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4.2.1.9 NPC

NPC is an epithelial carcinoma arising from the nasopharyngeal mucosal lining. In 2018, there were about 129,000 worldwide new cases of NPC, with 70% of cases in East and Southeast Asia. Infection with EBV is a major etiologic factor in the development of NPC (Chen et al. 2019). Most NPC patients present with advanced disease and chemotherapy (plus radiation therapy for locoregional disease) was previously the standard of care. Recently, CPIs (eg, toripalimab, camrelizumab, and tislelizumab) in combination with chemotherapy have been approved as first-line treatment for metastatic NPC in China. The CPI/chemotherapy combination will likely become the new first-line standard of care with significant improvement in efficacy.

NPC shows high levels of infiltration of exhausted CD8 T-cells, myeloid cells, and expression of STING and CCR2. Furthermore, high levels of CCR2 expression and myeloid-derived suppressor cells are associated with poor prognosis (Chen et al. 2021; Yang et al. 2016) making NPC an opportunity to test TAK-500's ability to induce immune-mediated tumor elimination.

4.2.2 Rationale for the Starting Dose, Dose Range, and Schedule

To appropriately balance the potential risk of developing acute AEs from immune stimulation in the cancer patient population and the potential for pharmacologic activity at the starting dose, the NOAEL from the GLP-compliant 28-day repeat-dose monkey toxicity study and the minimum anticipated biological effect level (MABEL) were considered in selecting the starting dose of TAK-500 as an SA.

4.2.2.1 Maximum Recommended Starting Dose Based on Nonclinical Toxicology Findings in Monkeys

In the GLP repeat-dose toxicity study in monkeys (described in Section 4.1.1.3), TAK-500 was administered Q2W for 3 doses at 0.1, 0.3, or 0.9 mg/kg via IV slow bolus injection. TAK-500 was well tolerated up to 0.3 mg/kg, but resulted in early euthanasia of 2 females with adverse clinical observations at 0.9 mg/kg. Major findings at early euthanasia and in animals that survived to scheduled necropsy were attributable to immune-mediated processes consisting of increased serum cytokines, a systemic pro-inflammatory response, and a possible contribution of effects secondary to immunogenicity. These findings were noted at all doses and included dose-responsive, transient clinical signs considered likely related to increases in serum cytokine concentrations, clinical pathology endpoints consistent with a transient acute phase response, and microscopic findings including generally minimal to mild inflammatory cell infiltrates in several organs/tissues. Pulmonary edema was present in early euthanasia animals only, which contributed to clinical decline. Increases in heart rate in jacketed telemetry animals (0.9 mg/kg) were considered likely related to increases in serum cytokines. Based on these findings, the NOAEL and highest nonseverely toxic dose in this repeat-dose study was 0.3 mg/kg. Using this dose, the estimated maximum recommended starting dose (MRSD) in humans was 16 µg/kg. This estimation was based on body surface area calculations, and includes a one-sixth safety factor calculation per ICH S9.

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4.2.2.2 Recommended Starting Dose Based on MABEL

As an alternate approach to estimate the starting dose in humans, the MABEL dose of TAK-500 was estimated using 3 different approaches that included:

- The application of in vitro–to–in vivo extrapolation from in vitro [redacted] in human whole blood using predicted human Cmax (Approach 1).
- An in vitro–to–in vivo extrapolation from in vitro human [redacted] using predicted Cmax (Approach 2).
- An in vitro–to–in vivo extrapolation from an in vitro human whole blood cytokine release study, using predicted human C_{max} (Approach 3).

The MABEL was defined as the 20% maximal effective concentration for RO and EC_{50} for other pharmacological responses, since potent agonists produce pharmacodynamic responses with a smaller fraction of RO (Kenakin 2004). These thresholds correspond to the recommended threshold of 20% to 80% by Saber et al (Saber et al. 2016) for MABEL dose estimation based on a summary of the starting dose and clinical maximum tolerated dose (MTD) of 32 immune agonistic therapeutics for cancer therapy in the clinic. The dose in humans predicted to result in the MABEL at C_{max} was projected as the MABEL dose.

Among the tested pharmacological readouts for MABEL, the lowest projected relevant MABEL dose was derived from in vitro monocyte activation, which is estimated to reach EC_{50} at C_{max}

with 2.63 µg/kg of TAK-500 through 1 hour IV infusion (Approach 2). The dose is similar to the lowest end of the MABEL dose derived from TAK-500 RO (4.11 µg/kg) (Approach 1) and lower than MABEL dose obtained from detection of relevant in vitro cytokine release in human whole blood (IFN-β release, 231 µg/kg) (Approach 3). Although TAK-500–related induction of MCP-1, IP-10, macrophage inflammatory protein (MIP)-1β, and IL-29/IFN-λ1 in the in vitro human whole blood assay was observed at a lower concentration than other cytokines, these responses were not considered relevant for the MABEL dose associated with acute immune toxicity. While these cytokines are useful as pharmacodynamic markers for [redacted] activation, in the preclinical models there is a lack of an obvious association between release of these cytokines and CRS or other adverse effects.

4.2.2.3 Selection of Final Recommended Starting Dose for the Study

To further promote safety in the study patient population while avoiding treating a large number of patients with locally advanced or metastatic solid tumors with potentially non-PADs, an FIH starting dose of 8 µg/kg was selected on the basis of consideration of the TAK-500 MABEL and MRSD, as well as prior nonclinical and clinical experience with TAK-676 and other STING agonists (Harrington et al. 2018; Meric-Bernstam et al. 2019; Zandberg et al. 2020). The proposed starting dose is approximately 3-fold higher than the starting dose (2.6 µg/kg) based on a MABEL approach, one-half of the MRSD from the GLP monkey toxicology study (16 µg/kg), and represents a safety factor of one-twelfth of the NOAEL human equivalent dose scaled by body surface area. The starting dose of 8 µg/kg is projected to result in less than 35% RO on monocytes and below the 80% maximal effective concentration for monocyte activation at C_{max}. Exposure multiples at the NOAEL (0.3 mg/kg) from the GLP repeat-dose toxicity study in monkeys (Day 1 conjugated TAK-676 area under the serum concentration-time curve from time 0 to 336 hours [AUC_{336}] of 1680 h*ng/mL and concentration of drug at time 0 of 142 ng/mL after a slow IV bolus administration) compared with the projected human AUC_{336} and C_{max} values for conjugated TAK-676 at a starting dose of 8 µg/kg TAK-500 (69.3 h*ng/mL and 3.62 ng/mL, respectively, with 1-hour infusion) are approximately 24- and 39-fold, respectively.

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As described in Section 4.1.2.2, the clinical IV dose of TAK-676 has been escalated to 2.5 mg from the MRSD/MABEL-based TAK-676 starting dose of 0.2 mg without any observed DLTs. The proposed starting dose of 8 µg/kg for TAK-500 is equivalent to 9.4 µg of TAK-676 contained in the ADC payload, after adjusting for the molecular weight of TAK-500, a drug-antibody ratio of 4, and a body weight of 60 kg. Following this, the TAK-676 payload dose associated with the administration of 8 µg/kg of TAK-500 is approximately 21-fold lower than the TAK-676 MRSD of 0.2 mg. The lower payload dose reflects the higher potency/improved PK of TAK-500 noted in Sections 4.1.1.1 and 4.1.1.2. The clinical tolerability profile of TAK-676, coupled with the projected safety multiples of the TAK-500 MRSD, the low to nondetectable circulating free payload (deconjugated TAK-676) in monkeys, and the dose and exposure of both TAK-500 and associated conjugated TAK-676 at the NOAEL, provide confidence in selecting a starting dose that is above the MABEL, while also below the MRSD. As such, the TAK-500 starting dose of 8 µg/kg balances the risk of acute toxicity while avoiding

treating a larger number of patients at doses that are not projected to be pharmacologically active.

4.2.2.4 Dose Range

The proposed dose range for TAK-500 SA in the initial dose escalation phase is 4 to 480 µg/kg administered on Day 1 of every 21-day cycle (once every 3 weeks [Q3W]). The default starting dose for SA dose escalation will be 8 µg/kg. A 4 µg/kg DL may be explored if unacceptable toxicity is observed at the 8 µg/kg DL as either an SA or in combination with pembrolizumab. The rationale for the highest dose of TAK-500 (480 µg/kg) was based on consideration of the projected human exposures and observed exposures in monkey GLP toxicology studies after administration of 0.9 mg/kg, which were associated with early mortalities. The predicted human serum exposure of TAK-500 at the proposed highest dose of 480 µg/kg (AUC_{336} of 5570 ng*h/mL) is expected to be approximately 83% of the exposures at which toxicity was seen in monkeys at a dose of 0.9 mg/kg (AUC_{336} of 6700 ng*h/mL).

The TAK-500 therapeutic hypothesis is premised on the ability to augment the adaptive immune system–mediated anticancer potential when combined with an anti–PD-1 antibody. Nonclinical experiments in mouse models indicate that lower doses of TAK-500 are sufficient to induce antitumor activity when combined with an anti–PD-1 antibody as compared with TAK-500 SA. The intent in this study is to inform the selection of an optimal dose and schedule of TAK-500 that produces the desirable immune-activated state for combination with pembrolizumab.

While the potential explorable dose range for TAK-500 in the pembrolizumab combination arm is the same as for the SA dose escalation (4 to 480 µg/kg), the proposed initial DL for the pembrolizumab combination arm is 80 µg/kg, to be initiated after safety clearance of the TAK-500 SA 80 µg/kg DL. If it is determined during the conduct of the SA dose escalation that the TAK-500 SA minimum PAD is ≤40 µg/kg, the combination TAK-500 plus pembrolizumab dose escalation will begin enrollment at a dose no higher than the TAK-500 SA minimum PAD DL. The combination dose escalation may begin at a dose level of TAK-500 that is below the TAK-500 SA PAD if this is determined to be necessary from the evaluation of safety and toxicity data. It is anticipated that this approach, combined with evaluating all available data for each dosing cohort (such as PK, pharmacodynamics, determination of the PAD range, clinical safety, and antitumor activity), will provide an optimal balance between potential antitumor activity and safety. The decision regarding which DL of TAK-500 will be used as starting dose for the combination is explained in detail in Section 6.1.

4.2.2.5 Dosing Schedule of TAK-500

In the dose escalation phase, TAK-500 will be administered in a Q3W schedule (Day 1 of every 21-day cycle) for the SA and combination arms. As described in Section 6.1.1, TAK-500 SA will be administered at a starting dose of 8 µg/kg on a Q3W 21-day cycle. The maximum DL for TAK-500 escalation is 480 µg/kg. The proposed explorable TAK-500 dose escalation levels are as follows: 4, 8, 16, 24, 40, 80, 160, 240, 360, and 480 µg/kg. As described in Section 6.1.2.2, TAK-500 in combination with pembrolizumab may also explore the dose range from 4 to

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480 µg/kg, on an initial dosing schedule of TAK-500 administered Q3W in 21-day cycles; however, the default starting dose of TAK-500 in the combination arm will be 80 µg/kg, and the combination arm will not begin enrollment until after safety clearance of the TAK-500 SA 80 µg/kg DL or determination of an TAK-500 SA minimum PAD that is ≤40 µg/kg. In the latter instance, the starting TAK-500 DL for the combination arm will be the TAK-500 SA minimum PAD. While Q3W dosing of TAK-500 will be explored initially, Q2W administration of TAK-500 in a 42-day cycle may also be explored once the Q3W PAD range has been established.

In the dose expansion phase of TAK-500 plus pembrolizumab (Section 6.1.3), TAK-500 will be administered in a Q3W schedule with the additional option of pursuing a Q2W dosing schedule of TAK-500 if inadequate immune activation or clinical activity is observed with Q3W dosing. All expansion cohorts will be administered in a 42-day cycle. The Q3W and any Q2W expansion cohorts will be administered TAK-500 at DLs that have previously been proven to be pharmacologically active in combination with pembrolizumab.

During the conduct of the study, should a determination be made that the totality of the data derived from PK, pharmacodynamics, and safety are supportive of an alternative dosing schedule, the TAK-500 schedule of administration or cycle length may be adjusted accordingly.

For all cohorts in dose escalation and expansion, pembrolizumab will be administered at 200 mg Q3W as an IV infusion according to the most current prescribing information.

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4.2.3 Rationale for European Union Auxiliary Medicinal Products for CRS Mitigation

[redacted] may be utilized as auxiliary medicinal products (AxMPs) to mitigate the risk of CRS before and after infusion of TAK-500, as described in Section 6.1.1, Section 8.9.1, and Table 8.d. For details on CRS and CRS management, please refer to Section 4.3.1.1 and Section 8.9.1, respectively.

For an overview on the AxMPs, please refer to Section 8.1.4 and Table 8.a.

4.2.4 Rationale for Tumor and Blood Tissues Collection

Tumor and blood tissues will be collected to assess pharmacodynamic and potential predictive biomarkers supportive of TAK-500's MOA and PAD determination.

4.2.4.1 Tumor Biopsies

Tumor biopsies at baseline and on-treatment will be collected to determine [redacted] within the tumor, as well as the functional modulation of the [redacted] within the TME. To minimize the risk of performing invasive procedures on patients at TAK-500 DLs with no measurable pharmacodynamic activity, biopsies will be required once TAK-500 is shown to demonstrate peripheral evidence of pharmacodynamic activity in the blood or clinical antitumor response in at least 1 patient. However, if the lesions are safely accessible, paired biopsies are highly desired in all patients. The pharmacodynamic and mechanistic information gained from patient biopsies will be required to demonstrate clinical

proof-of-concept (POC) for TAK-500 and to evaluate changes in immune cell infiltration within the tumor (secondary endpoint). On-study biopsies are needed to identify possible signals of [redacted] at DLs below MTD and to help in the identification of the PAD range. Additionally, this strategy enables the determination of the dynamic range of the pharmacodynamic activity. These data will be essential to establish the dose for further development of TAK-500. [redacted].

4.2.4.2 Blood

Blood samples will be collected to evaluate [redacted]. The TAK-500–mediated impact on the immune system will be assessed by measuring concentrations of select [redacted]. These samples will also be used to help in the identification of the PAD range, recommended dose for expansion (RDE), the dose for further development, and POC.

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4.2.5 Rationale for PK Assessments

Serial serum sample collections will enable the characterization of TAK-500, total antibody, consisting of conjugated and deconjugated monoclonal antibody, and deconjugated TAK-676 PK, released from TAK-500 on cleavage of the linker-payload bond. The PK data collected on these occasions will generally coincide with pharmacodynamic assessments. PK data in conjunction with pharmacodynamic data can help in the understanding of the PK-pharmacodynamic relationship of TAK-500. Such data will be used to build mathematical models to describe the PK-pharmacodynamic and/or PK-safety/antitumor activity relationship of TAK-500 to help predict the time course of PK and pharmacodynamic effects of TAK-500. This information will provide context for safety findings from the study and will be helpful in identifying the PAD range, the dose for further development, and schedule for TAK-500.

4.3 Potential Risks and Benefits

TAK-500 is currently being evaluated in an ongoing FIH phase 1/2 study in patients with solid tumors (Study TAK-500-1001) and the clinical benefits and risks have not been fully determined.

4.3.1 Potential Risks and Effects of TAK-500

The potential effects listed below are primarily based on the findings from nonclinical studies with TAK-500 and publicly available data on CDN STING agonists that are currently in clinical

development. These events may or may not develop in human patients treated with TAK-500. It is also possible that the administration of TAK-500 during a clinical study will result in AEs that were not observed or predicted from the completed nonclinical studies conducted in animals.

Clinical study protocols for TAK-500 will include monitoring for the potential AEs specified for this compound using physical and laboratory examinations, vital signs, electrocardiograms (ECGs), and imaging as clinically indicated. The timing of these tests and evaluations is detailed in the schedules of events (SOEs) (Appendix A). Additional tests and evaluations will be considered on the basis of symptoms and findings observed in the study. Details on the mitigation for and monitoring of these potential toxicities are included in Section 8.9.

4.3.1.1 CRS

Findings in the in vitro cytokine release assay in human whole blood and the repeat-dose toxicity studies in monkeys suggest a potential for CRS in patients treated with TAK-500.

Systemic increases of pro-inflammatory cytokines including TNF-α, IL-1ra, and IL-6, as well as secretion of the IFN pathway biomarker cytokines IP-10 and MCP-1, were observed in the non-GLP and GLP toxicity studies in cynomolgus monkeys after administration of TAK-500. In the non-GLP study, similar magnitudes of cytokine elevations were observed in early euthanasia and scheduled euthanasia animals to those found in the GLP study (described below). In the GLP toxicity study, these increases peaked at 6 hours after each administered dose on Days 1, 15, and/or 29 at all DLs (0.1, 0.3, or 0.9 mg/kg) and returned or partially returned to baseline at 24 hours postdose. These changes were of the highest magnitude observed on study in the 1 animal administered 0.9 mg/kg TAK-500 that was euthanized on Day 1 at 7 hours postdose. In the other early euthanasia animal that was removed from study 8 hours postdose on Day 15, the alterations were more comparable to animals surviving to scheduled euthanasia. In animals surviving to scheduled euthanasia on the GLP toxicity study, these increases in cytokines were considered likely correlated with increased heart rate, as noted in jacketed external telemetry animals; clinical signs of vomiting, hunched posture, decreased activity, and/or red face that were observed from 4 to 8 hours after each administered dose; and changes in clinical pathology consistent with an acute phase response. In the cytokine release assay in human whole blood, TAK-500 induced the production of pro-inflammatory cytokines and chemokines including IFN-β, IFN-α2a, IFN-γ, TNF-α, IL-1β, IL-4, IL-6, IL-12p70, MCP-1, IP-10, MIP-1α, MIP-1β and IL-29/IFN-λ1.

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CRS has been observed in patients receiving TAK-500 in SA dose escalation (refer to Section 4.1.2.3 for details). Management of CRS is described in Sections 6.1.1 and 8.9.1.

4.3.1.2 Pulmonary Edema

Findings in the toxicity studies in monkeys suggest a potential for pulmonary edema in patients treated with TAK-500.

In the non-GLP study, there was no evidence of pulmonary edema in the early euthanasia animals that were removed from study on Days 15 (2 animals at 3 mg/kg) or 29 (1 animal at

1 mg/kg) and no evidence of pulmonary edema or other respiratory findings in animals surviving to scheduled euthanasia. However, in the GLP monkey toxicology study, minimal to mild pulmonary edema was observed in the 2 early euthanasia animals at 0.9 mg/kg in which 1 was removed from the study on Day 1 and the other on Day 15. The primary cause of early euthanasia in these animals was attributed to immune-mediated processes, but the pulmonary edema was considered to have contributed to these animals' early decline. This microscopic finding was not associated with in-life evidence (clinical observations) of respiratory distress, elevations in respiratory rate, or macroscopic findings, and there was no evidence of pulmonary edema or other findings in the lungs of animals that survived to early euthanasia.

Management of this potential risk is described in Section 8.9.2.

4.3.1.3 Immune/Lymphoid System Toxicity

Findings in the toxicity studies in monkeys suggest a potential for immune/lymphoid toxicity in patients treated with TAK-500.

In the non-GLP toxicity study, minimally decreased cellularity of bone marrow (all cellular lineages) was observed in 2 animals at ≥0.1 mg/kg, which correlated with mild reductions in red cell mass and in 1 animal, markedly decreased lymphocytes. In addition, in the GLP cynomolgus monkey toxicity study, minimal to mild, multifocal lymphoid necrosis was observed in the germinal centers of splenic lymphoid follicles and minimal lymphoid necrosis within the thymic cortex was observed at ≥0.1 mg/kg TAK-500. These findings lacked clinical pathology correlates on hematology, and nonspecific stress may have contributed to the underlying pathophysiology.

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4.3.1.4 Liver Toxicity

Findings in the toxicity studies in monkeys suggest a potential for liver toxicity in patients treated with TAK-500.

In the non-GLP study, on Day 3, at ≥0.3 mg/kg, transient minimal to moderate elevations in ALT, aspartate aminotransferase (AST), glutamate dehydrogenase, and creatine kinase were observed, consistent with muscle and/or hepatocellular origin. Similar elevations in ALT, AST, and glutamate dehydrogenase were observed in the GLP study on Day 3 at 0.9 mg/kg as well as in a single female at 0.1 mg/kg. Minimal to mild foci of inflammation and/or hepatocellular degeneration/necrosis were observed at low incidence of ≥0.3 mg/kg in the non-GLP study and at ≥0.1 mg/kg in the GLP study at scheduled necropsy; however, there were no correlative increases in liver serum chemistry parameters at that time. Additionally, minimal neutrophilic infiltrates were noted within hepatic sinusoids in males and females at ≥0.1 mg/kg in the GLP study that were considered related to the systemic pro-inflammatory response.

4.3.1.5 CV Toxicity

Findings in the toxicity studies in monkeys suggest a potential for CV effects in patients treated with TAK-500.

In the non-GLP toxicity study, microscopic findings in the heart consisted of mild epicardial/myocardial hemorrhage in 1 animal at 1 mg/kg. In early mortality animals at 3 mg/kg, there was additionally minimal myocardial degeneration in the left ventricle and auricle associated with minimal to mild mononuclear cell infiltrates. These CV findings were considered immune-mediated in nature.

In the GLP toxicity study, an increase in RR-derived heart rate was observed from approximately 3.75 hours postdose through the 21-hour recording period in animals administered 0.9 mg/kg TAK-500 (the only DL tested) and were considered likely to be associated with increases in serum cytokines (as observed in main study animals; cytokines were not specifically measured in CV safety satellite animals). There were no TAK-500–related changes in the PR interval, QRS interval, or the individual rate-corrected QT interval. Microscopic findings of minimal mixed cell infiltrates in the heart valves or chordae tendineae were present at ≥0.1 mg/kg TAK-500 and were considered related to a systemic proinflammatory response.

4.3.2 Risks and Effects of TAK-500 in Combination With Pembrolizumab

The pembrolizumab prescribing information (USPI dated November 2020), includes warnings for severe and fatal immune-mediated adverse reactions, infusion-related reactions, complications of allogeneic hematopoietic stem cell transplantation (both before and after treatment), and embryo-fetal toxicities. In addition, the most common AEs after pembrolizumab administered as an SA, as reported in ≥20% of patients, were: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. The most current prescribing information for pembrolizumab should be consulted.

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Nonclinical toxicology studies evaluating the combination of TAK-500 and pembrolizumab were not conducted and are considered not warranted per ICH S9. Pembrolizumab is a monoclonal antibody that binds to the human PD-1 receptor and blocks the interaction of PD-1 with PD-L1/PD-L2 (programmed cell death ligand 2). TAK-500 and pembrolizumab both activate the immune system, so known PD-1 immunotherapy-related toxicities (such as pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, and solid organ transplant rejection) associated with the administration of pembrolizumab may be enhanced when combined with TAK-500.

Details on the mitigation for and monitoring of these potential toxicities are included in Section 8.9.8.

4.3.3 Risks Associated With Same Class of Compound

Potential risks related to exposure to the payload and antibody portions of TAK-500 (TAK-676 and TAK-202, respectively) are considered to be negligible as circulating levels of deconjugated TAK-676 were low to undetectable in monkeys administered TAK-500, and TAK-202 was extremely well tolerated. For informational purposes, the potential risks identified after administration of TAK-676 are listed in Appendix E. Clinical background information is provided in Section 4.1.2.

There were no relevant findings from TAK-676 nonclinical toxicology studies indicating a potential for skin-related toxicities. Grade 2 erythema multiforme, assessed as lichenoid/bullous drug eruption, was reported with the use of another STING agonist. Patients with congenital STING activating mutations (STING-associated vasculopathy with onset in infancy-like disorder) have skin lesions, including telangiectatic lesions on nose and cheeks and violaceous, scaling atrophic plaques on hands, and vascular inflammation in skin biopsy (Jeremiah et al. 2014; Liu et al. 2014).

Vascular toxicity at the injection site, including injection site pain (Grade 3) and skin necrosis (Grade 3), have been reported with other STING agonists.

Details on the mitigation for and monitoring of potential toxicities associated with same class of compound are included in Section 8.9.

4.3.4 Risks Associated With the AxMPs

[redacted]

4.3.5 Additional Safety Concerns

4.3.5.1 Infusion-Related Reactions

An infusion-related reaction is a disorder characterized by an adverse local or general response from exposure to an allergen. Such reactions are common in patients treated with IV anticancer medications and typically occur during the infusion or shortly thereafter.

TAK-500's immune-activating properties may produce AEs in the category of infusion-related reactions. If an infusion-related reaction were to occur, it could present as fever, chills, rigors, headache, rash, flushing, pruritus, arthralgias, hypotension or hypertension, bronchospasm, or other symptoms.

Details on the mitigation for and monitoring of infusion-related reactions are included in Section 8.9.7.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective for the phase 1 dose escalation phase is:

- To determine the safety and tolerability of TAK-500 administered as SA and in combination with pembrolizumab in patients with select locally advanced or metastatic solid tumors, including gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC.

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The primary objectives for the phase 2 dose expansion phase are:

- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic nonsquamous NSCLC.
- To assess the preliminary antitumor activity of TAK-500 SA in 3L recurrent locally advanced or metastatic nonsquamous NSCLC.
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To assess the preliminary antitumor activity of TAK-500 SA in 2L recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To assess the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in 3L recurrent locally advanced or metastatic RCC.
- To determine the dose for further development of TAK-500 administered as SA and in combination with pembrolizumab.

5.1.2 Secondary Objectives

The secondary objectives for the phase 1 dose escalation are:

- To determine the RDE of TAK-500 administered as SA and in combination with pembrolizumab.
- To characterize the single and multiple dose PK of TAK-500 administered as SA and in combination with pembrolizumab.
- To evaluate the preliminary antitumor activity of TAK-500 administered as SA and in combination with pembrolizumab.
- To evaluate the dose-responsive impact on T-cell infiltration into the tumor following TAK-500 administered as SA and in combination with pembrolizumab.
- To determine the immunogenicity of TAK-500.

The secondary objectives for the phase 2 dose expansion are:

- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic nonsquamous NSCLC.
- To determine the safety and tolerability of TAK-500 as SA and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic pancreatic adenocarcinoma.
- To determine the safety and tolerability of TAK-500 combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic RCC.

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5.1.3 Exploratory Objectives

The exploratory objectives are:

- To assess [redacted] induced by TAK-500 as an SA and in combination with pembrolizumab in blood as evidence of pharmacodynamic modulation.
- To determine whether TAK-500 as an SA and in combination with pembrolizumab results in changes in peripheral blood and/or tumor consistent with [redacted].
- To examine whether the combination of TAK-500 as an SA and in combination with pembrolizumab results in blockade of [redacted] and activation of [redacted].
- To explore relationships between serum concentrations of TAK-500, total antibody, and deconjugated TAK-676 in combination with pembrolizumab with pharmacodynamics, antitumor activity, and safety endpoints.

- To assess the relationship between [redacted].
- To characterize [redacted] of TAK-500 as an SA and in combination with pembrolizumab and relationship to dose.
- To characterize [redacted], including [redacted], for correlations with clinical outcome, pharmacodynamics, and PK, including future pharmacogenomic exploration of [redacted].

[redacted]

[redacted]

[redacted]

[redacted]

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5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints for the phase 1 dose escalation are:

- Frequency and severity of TEAEs.
- Number of patients with DLTs.
- Number and percentage of patients with 1 or more treatment-emergent SAE.
- Number and percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations.

The primary endpoints for the phase 2 dose expansion are:

- Response assessments made by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: confirmed complete response (cCR) + cPR.

5.2.2 Secondary Endpoints

The secondary endpoints for dose escalation and dose expansion are:

- PK parameters of TAK-500:
  - C_{max}.
  - t_{max}.
  - Area under the serum concentration-time curve from time 0 to time t (AUC_t).
  - AUC_∞.
  - Terminal disposition phase half-life ($t_{1/2z}$).
  - Total clearance after intravenous administration (CL).
  - Volume of distribution at steady state after intravenous administration (V_{ss}).
- Intratumoral T-cell infiltration upon TAK-500 treatment.
- Incidence of patients who are ADA-positive and have acquired immunogenicity.
- Additional secondary endpoints for the phase 1 dose escalation only:
- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - ORR: cCR + cPR.
  - Disease control rate (DCR): cCR + cPR + stable disease (SD) >6 weeks.
  - Duration of response (DOR): the time from the date of first documentation of a cPR or better to the date of first documentation of PD for responders (cPR or better).
  - Time to response (TTR): the time from the date of first dose administration to the date of first documented cPR or better by the investigator.

Additional secondary endpoints for the phase 2 dose expansion only:

- Response assessments made by the investigator per RECIST v1.1 for both the SA and combination treatment. Preliminary antitumor activity will be described as follows:
  - DCR: cCR + cPR + stable disease (SD) >6 weeks.
  - DOR: the time from the date of first documentation of a cPR or better to the date of first documentation of PD for responders (cPR or better).
  - TTR: the time from the date of first dose administration to the date of first documented cPR or better by the investigator.
  - PFS.
  - OS.

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- Frequency and severity of TEAEs.
- Number of patients with DLTs.
- Number and percentage of patients with 1 or more treatment-emergent SAE.
- Number and percentage of patients with 1 or more TEAE leading to dose modifications and treatment discontinuations.

5.2.3 Exploratory Endpoints

The exploratory endpoints include:

- Changes in [redacted] between pretreatment and on-treatment peripheral blood samples.
- The following endpoints will be assessed to evaluate changes in peripheral blood and/or tumor:
  - Changes in concentrations of plasma biomarkers, including [redacted].
  - Changes between pretreatment and on-treatment peripheral blood samples in [redacted].

[redacted].

- Relationship between [redacted].
- Relationship between serum concentrations of TAK-500, total antibody, and deconjugated TAK-676 in combination with pembrolizumab with pharmacodynamics, antitumor activity, and safety endpoints.

[redacted].

- [redacted] assessed by sequencing of tumor and normal tissue.

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

6.0 STUDY DESIGN

6.1 Overview of Study Design

TAK-500-1001 is a phase 1/2, open-label, dose escalation and expansion study designed to determine the safety, tolerability, antitumor activity, PK pharmacodynamics, and preliminary antitumor activity of TAK-500 as SA and in combination with pembrolizumab. This information will be used to determine the PAD range, RDE, and the dose for further development of TAK-500 as an SA and in combination with pembrolizumab. The study will proceed in 2 main phases: (1) a phased dose escalation of each treatment arm (TAK-500 as SA and in combination with pembrolizumab), and (2) the evaluation of TAK-500 as SA and in combination with pembrolizumab in select single tumor type expansion cohorts.

Approximately 313 patients with the following 9 types of locally advanced or metastatic solid tumors will be enrolled: gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN, mesothelioma, TNBC, RCC, and NPC.

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6.1.1 Premedication

[redacted]

[redacted]

6.1.2 TAK-500 Dose Escalation

The proposed explorable dose range of TAK-500 is from 4 to 480 µg/kg (4, 8, 16, 24, 40, 80, 160, 240, 360, and 480 µg/kg) administered Q3W in a 21-day cycle. Q2W administration of TAK-500 in a 42-day cycle may also be explored once the PAD range has been established (Figure 6.a). All patients will be hospitalized for 24 (±4) hours after the first 2 doses of TAK-500 (Cycle [C]1 Day [D]1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500). Regardless of the treatment cycle, if a Grade ≥2 CRS or infusion-related reaction occurs during or after the administration of study drug, hospitalization is required for 24 (±4) hours after the end of the next 2 TAK-500 infusions. For patients without evidence of Grade ≥2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in the clinic for at least 6 hours after the end of infusion (EOI). Patients who do not experience an infusion-related reaction or Grade ≥2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour. Patient evaluation including a complete set of vital signs is required before their discharge home from either the hospital or clinic.

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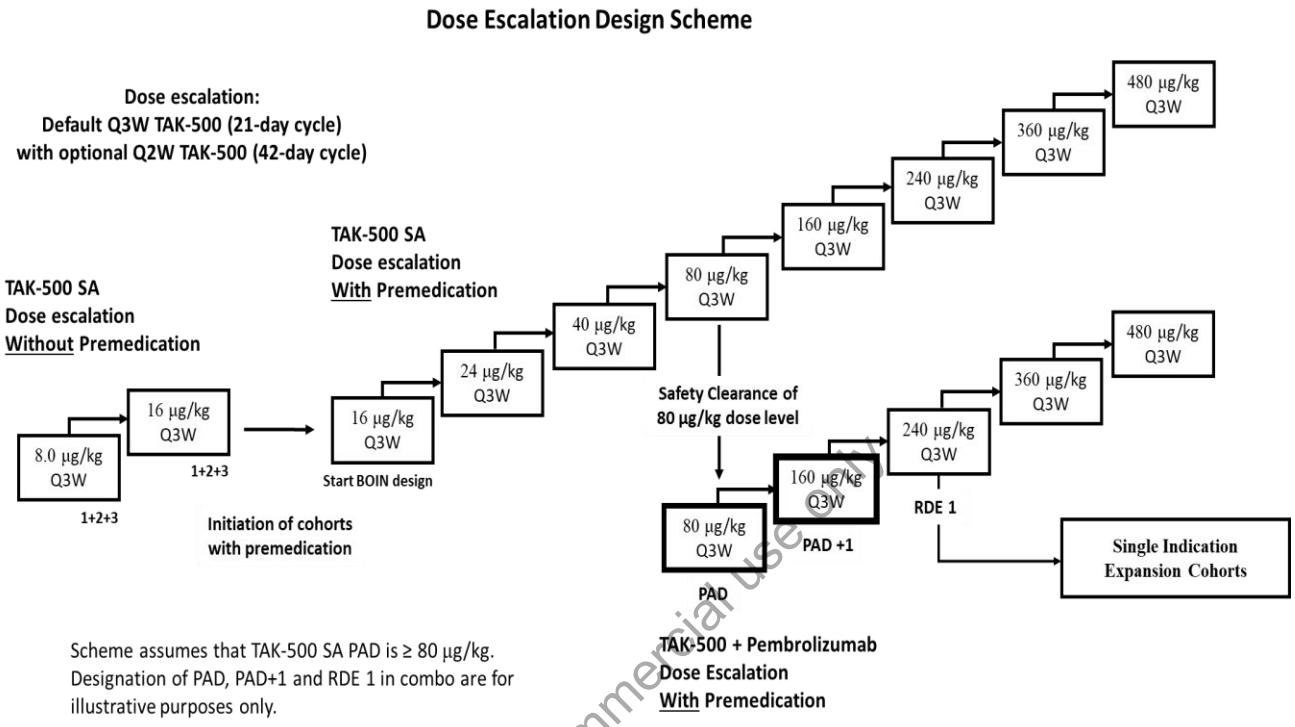
Figure 6.a Overview of Study Design – Dose Escalation (Phase 1)



BOIN: Bayesian Optimal Interval; DL: dose level; Q2W: once every 2 weeks; Q3W: once every 3 weeks; PAD: pharmacologically active dose; RDE: recommended dose for expansion; SA: single agent.

PAD in figure refers to the minimum PAD.

Detailed dose escalation rules are found in Section 8.3.

Scheme assumes that TAK-500 SA PAD is ≥80 µg/kg. Designation of PAD, PAD +1, and RDE in combination are for illustrative purposes only.

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6.1.2.1 TAK-500 SA Dose Escalation

SA dose escalation will begin at 8 µg/kg. The first 2 DLs (8 and 16 µg/kg) will be evaluated using a 1 + 2 + 3 accelerated titration design without intrapatient dose escalation as described by Simon et al (Simon et al. 1997).

Rules for this rapid titration are as follows:

- The cohort will expand to 3 patients if the single patient dosed at 8 or 16 µg/kg Q3W experiences a DLT or any of the following Grade ≥2 AEs considered by the investigator to be at least possibly related to TAK-500: fever, hypotension, arrhythmia, tachycardia, delirium, dyspnea, hypoxia, pulmonary edema, or symptoms or signs consistent with capillary leak syndrome. If a DLT is observed in any of those 3 patients, a 3 + 3 design will be used to further evaluate the safety of this DL. Note that any AEs in which the relationship to study drug cannot be ruled out will be considered possibly related to the study drug.

- If the single patient dosed at either 8 or 16 µg/kg Q3W completes Cycle 1 of treatment without a DLT or any Grade ≥2 event listed above, the TAK-500 SA dose escalation will proceed to the next highest DL.
- Once a DLT or any Grade ≥2 AE is observed at a given DL, all higher DLs will enroll with a minimum of 3 patients, following the Bayesian Optimal Interval (BOIN) design as detailed in Section 8.3.1 (Liu and Yuan 2015).
- Intrapatient dose escalation will not be permitted as part of the DLT-evaluable dose escalation set, but patients treated at TAK-500 SA DLs below minimum PAD (as discussed in Section 6.1.2.2 and in Section 8.4) will be allowed to escalate to minimum PAD once the minimum PAD DL has been confirmed and cleared from a safety perspective by the sponsor and investigators.

Once the DL of 16 µg/kg is cleared, further dose escalation/de-escalation decisions will follow the BOIN design (Liu and Yuan 2015) (see Section 8.3.1 and Appendix F for more detail of the BOIN design). Each DL will enroll at least 3 patients initially. A cohort size different from 3 is permissible thereafter. There will be a 24-hour dosing delay between the first patient of any new DL and subsequent patients enrolled at the same DL.

SA dose escalation/de-escalation will continue until full determination of the PAD range. As defined in Section 8.4, PAD determination is based on observation of peripheral pharmacodynamic activity, including peripheral biomarkers evaluating both [redacted]. Although clinical activity is not necessary to confirm SA PAD, observation of a PR or CR is sufficient to declare PAD regardless of other translational data. To confirm the minimum PAD, 2 DLs must each meet PAD criteria, and consequently the minimum PAD and PAD +1 DLs may be confirmed simultaneously. In the circumstance where a radiographic response (PR or CR) is observed at a given dose level, that dose level may be declared as meeting PAD requirements without waiting for confirmation of PAD in a subsequent dose level. Once PAD is confirmed, additional patients (approximately 3 to 6 additional patients per DL) may be enrolled at the minimum PAD and PAD +1 DLs to establish a more robust statistical basis for comparison of pharmacodynamic biomarkers across the TAK-500 SA DLs. Additional patients may be added to other DLs above the minimum PAD, as required, to identify the DL with optimal pharmacodynamic activity and inform determination of the RDE. Backfill cohorts may or may not be enriched for specific tumor type(s) selected from those included in dose escalation.

TAK-500 SA dose escalation may continue past the minimum PAD and PAD +1 DLs as dictated by the BOIN design until either (1) the SA MTD is determined, (2) peripheral pharmacodynamic biomarkers demonstrate a marked decrease in [redacted] in comparison to prior DLs, or (3) the maximum planned DL of 480 µg/kg is completed.

Safety clearance of the 80 µg/kg TAK-500 SA DL will trigger initiation of the TAK-500 plus pembrolizumab dose escalation at a TAK-500 DL of 80 µg/kg as described in Section 6.1.2.2.

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6.1.2.2 TAK-500 in Combination With Pembrolizumab Dose Escalation

While the potential explorable dose range of TAK-500 in combination with pembrolizumab is also from 4 to 480 µg/kg, by default the combination arm will begin at a TAK-500 dose level of 80 µg/kg, triggered upon safety clearance of the 80 µg/kg TAK-500 SA DL. If it is determined during the conduct of the SA dose escalation that the TAK-500 SA minimum PAD is ≤40 µg/kg, the combination TAK-500 plus pembrolizumab dose escalation will begin at a dose no higher than the TAK-500 SA minimum PAD DL. The determination to initiate the combination dose escalation arm will be based on the accumulated safety and pharmacodynamic data from all TAK-500 SA cohorts available at that time. The combination dose escalation may begin at a dose level of TAK-500 that is below the TAK-500 SA PAD if this is determined to be necessary from the evaluation of safety and toxicity data.

Each combination DL will enroll at least 3 patients initially. A cohort size different from 3 is permissible thereafter. There will be a 24-hour dosing delay between the first patient of any new combination DL and subsequent patients enrolled at the same DL. The dose escalation/de-escalation decisions will follow the same BOIN design as the TAK-500 SA arm. If a DL of TAK-500 SA is considered to be too toxic in the SA arm, it and any higher DLs will be excluded from the explorable dose range of the combination arm.

Pembrolizumab will be administered at the fixed dose of 200 mg Q3W, to be administered on the same day as TAK-500 on a Q3W schedule in a 21-day cycle, or if Q2W dosing of TAK-500 is explored, pembrolizumab will be administered on Days 1 and 22 in a 42-day cycle.

As with the TAK-500 SA arm, dose escalation/de-escalation for the combination arm will continue until determination of its minimum PAD. Once the minimum PAD is confirmed in the combination arm, additional patients (approximately 3 to 6 additional patients per DL) may be enrolled to both the minimum PAD and PAD +1 DLs to establish a more robust statistical basis for comparison across DLs. Additional patients may be added to other DLs above the minimum PAD, as required, to identify the DL with optimal pharmacodynamic activity and inform determination of the RDE. Backfill cohorts may or may not be enriched for specific tumor type(s) selected from those included in dose escalation. The criteria for the determination of minimum PAD and PAD +1 DLs are the same for both the SA and combination arms (see Sections 6.1.1 and 8.4).

Combination TAK-500 plus pembrolizumab dose escalation may continue in parallel to the expansion cohort(s) described in Section 6.1.3. As with the TAK-500 SA arm, dose escalation of the combination will occur as dictated by the BOIN statistical design until either (1) the combination MTD is determined, (2) peripheral pharmacodynamic biomarkers demonstrate a marked decrease in [redacted] in comparison to prior DLs, or (3) the maximum planned DL of 480 µg/kg is completed.

6.1.2.3 General Rules for Dose Escalation

In the dose escalation of both arms (except for the initial 2 accelerated titration SA DLs), escalation/de-escalation rules from BOIN with consideration of non-DLT safety and other

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available clinical, PK, or pharmacodynamic data will be used to inform subsequent DL recommendations, dose escalation decisions, and potential MTD estimation for TAK-500. Patients not receiving all required doses of TAK-500 or pembrolizumab or not remaining on study for reasons other than a DLT for 21 days from first dosing of TAK-500 (C1D21) will not be considered DLT-evaluable. While in principle a patient who is not DLT-evaluable may be replaced within the same cohort, due to the flexible nature of the BOIN design, this replacement may not be mandatory except for the initial BOIN cohort of each arm. Consequently, the need for replacement will be determined on the basis of the total number of DLT-evaluable patients in the cohort and as agreed on by the sponsor and investigators. Regardless of the need for replacement, a patient who is not considered DLT-evaluable may still be allowed to continue on study if deemed appropriate by the sponsor and site investigator.

In the dose escalation of both arms, enrolling additional patients for more conservative dose escalation, evaluation of intermediate doses (eg, 60 µg/kg), and alternative dose schedules are permissible following discussions between the sponsor and the investigators. In addition, any DL not exceeding MTD can be backfilled with additional patients for further evaluation of safety, PK, pharmacodynamics, and antitumor activity.

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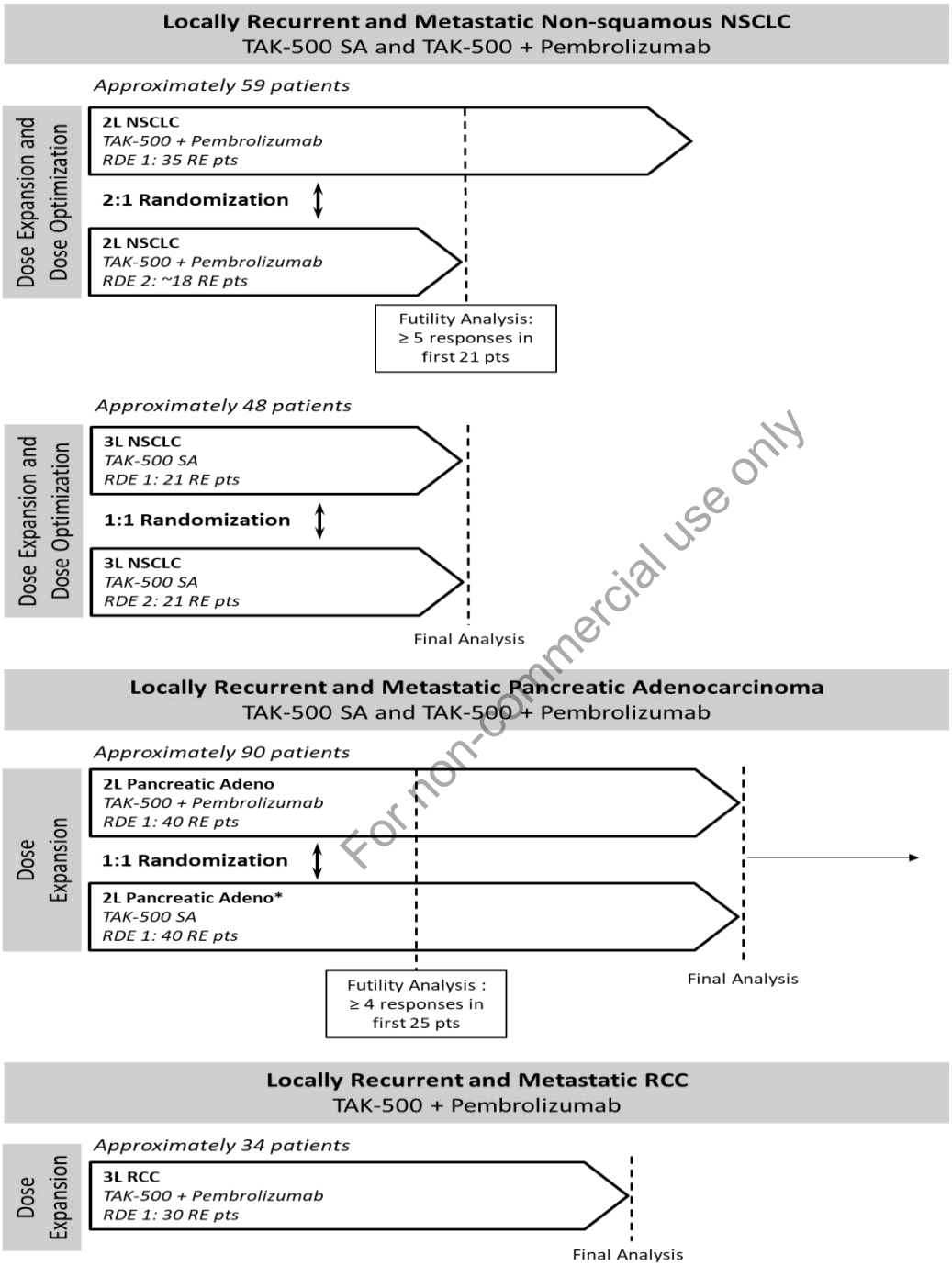
6.1.3 TAK-500 Dose Expansion and Randomized Dose Comparison

In addition to TAK-500 SA and TAK-500 plus pembrolizumab combination dose escalation, the preliminary antitumor activity along with the safety, tolerability, PK, and PD of TAK-500 will be further evaluated in single-indication expansion cohorts. Dose expansion may proceed with both TAK-500 SA and TAK-500 with pembrolizumab and include the opportunity to simultaneously explore 2 dose levels of TAK-500 (RDE 1 and RDE 2) to provide additional data for identification of the dose for further development. See Figure 6.b for overview of dose expansion design.

As noted in Sections 6.1.2.1 and 6.1.2.2, dose escalation in both the SA and pembrolizumab combination arms may proceed beyond identification of PAD until (1) the respective MTD is determined, or (2) peripheral pharmacodynamic biomarkers demonstrate a marked decrease in [redacted] in comparison to prior DLs, or (3) the maximum planned DL of 480 µg/kg is completed. Once complete, the totality of data from dose escalation will be utilized to identify the RDE(s) and dosing schedule of TAK-500 (Q2W and/or Q3W, both in a 42-day cycle) for single-indication dose expansion cohorts. The RDE(s) of TAK-500 may be the same as the MTD or may be below the MTD if the totality of data (safety and tolerability, PK and PD, and clinical antitumor activity) suggest a lower dose is favorable. Additionally, the RDE(s) for dose expansion may or may not be different for the TAK-500 SA versus the TAK-500 plus pembrolizumab combination expansion cohorts. For all combination TAK-500 plus pembrolizumab cohorts, pembrolizumab administration will remain constant at 200 mg IV Q3W in a 42-day cycle.

To accommodate the possible comparison between the Q3W and Q2W schedules, all expansion cohorts will be administered in a 42-day cycle. Any Q2W DL evaluated in dose expansion must be at or below a Q2W DL previously shown to be tolerated in dose escalation.

Figure 6.b Schematic of Study Design – Dose Expansion (Phase 2)



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2L: second-line; 3L: third-line; length of bar meant to represent relative patient numbers and not time required for a given cohort; NSCLC: non–small cell lung cancer; Pancreatic Adeno: pancreatic ductal adenocarcinoma; pts: patients; RCC: renal clear cell carcinoma; RDE: recommended dose for expansion; RE: response-evaluable; SA: single agent.

6.1.3.1 Expansion Cohort Tumor Type Selection

Selection of tumor types and line of therapy for single-indication dose expansion cohorts was based primarily on scientific rationale for targeting with TAK-500, including [redacted] (see Section 4.2.1). High unmet clinical need and clinical tractability were also considered. Based on this analysis, 3 tumor types were prioritized for initial dose expansion cohorts: **nonsquamous NSCLC, pancreatic adenocarcinoma, and RCC**. These cohorts may begin simultaneously, or one or two indications may be prioritized over the other(s). Other single indication expansion cohorts may be explored instead of, or in addition to, these indications, if anti-tumor activity is seen during dose escalation in a given tumor.

6.1.3.2 Dose Expansion in Nonsquamous NSCLC

The preliminary antitumor activity, safety, tolerability, PK, and PD of TAK-500 SA and/or in combination with pembrolizumab will be evaluated in treatment-refractory nonsquamous NSCLC patients without driver mutations in both the 2L and 3L setting.

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6.1.3.2.1 Combination TAK-500 With Pembrolizumab Dose Expansion With Randomized Dose Comparison in 2L NSCLC

Enrollment in 2L NSCLC cohorts will include patients with treatment-refractory nonsquamous NSCLC (without targetable driver mutations) with recurrent locally advanced or metastatic disease that has previously progressed while on or following 1 prior line of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given in combination with an anti-CTLA4 antibody or chemotherapy (eg, carboplatin and pemetrexed). Patients are eligible to enroll regardless of PD-L1 status.

The combination TAK-500 plus pembrolizumab dose expansion in 2L NSCLC will proceed as outlined below with concurrent start of early randomized dose comparison.

- Expansion in 2L NSCLC will proceed simultaneously at 2 separate dose levels of TAK-500 following a 2:1 randomized approach, to RDE 1 and RDE 2, respectively. The 2 dose levels will be chosen such that adequate dose/response and exposure/response analyses can be performed to support the selection of the dose for further development. RDE 1 and RDE 2 selection will be made on the totality of data, including safety, antitumor activity, PK and pharmacodynamic analysis, with both doses having a positive benefit-risk ratio for further study at the time of selection. Neither RDE 1 nor RDE 2 will be higher than the highest dose level assessed in the dose escalation phase or the MTD, whichever is lower.

- Approximately 59 patients will enroll in this cohort, with up to 39 patients randomized to RDE 1 (to achieve an approximate total of 35 response-evaluable patients assuming a 10% drop-out rate) and up to 20 patients randomized to RDE 2 (to achieve an approximate total of 18 response-evaluable patients assuming a 10% drop-out rate). A futility analysis will be performed based on ORR at the time when there are 21 response-evaluable patients in RDE 1 (for definition refer to Section 13.1.1) and each of these 21 patients has experienced at least 1 of the following: (1) shown a clinical response (cPR or cCR), (2) had at least 2 posttreatment response assessments, or (3) documented PD or death. If a partial response or complete response is initially observed at the second posttreatment response assessment, a third posttreatment response assessment will be performed to confirm the response before the patient may be included in the futility analysis. If there are ≥5 responders among the first 21 response-evaluable patients treated at RDE 1, then the futility analysis is successful, and the enrollment will continue to 35 response-evaluable patients. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.
- If RDE 1 enrollment is terminated due to failing futility at the stage 1 analysis or fails to meet the number of responses needed for proof of concept at final analysis, additional patients may be enrolled to RDE 2 in a nonrandomized manner to include 21 response-evaluable patients (for definition, refer to Section 13.1.1). A futility analysis will then be performed based on ORR as described for RDE 1. If there are ≥5 responders among the first 21 response-evaluable patients treated at RDE 2, then the futility analysis is successful, and the enrollment will continue to 35 response-evaluable patients. Otherwise, the cohort will be terminated for futility. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.

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6.1.3.2.2 TAK-500 SA Dose Expansion With Randomized Dose Comparison in 3L NSCLC

Enrollment in 3L NSCLC cohorts will include patients with treatment-refractory nonsquamous NSCLC (without targetable driver mutations) with recurrent locally advanced or metastatic disease that has previously progressed while on or following 2 prior lines of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given in combination with an anti-CTLA4 antibody or chemotherapy (eg, carboplatin and pemetrexed). Patients must have had disease progression while on or after 1 or 2 lines of chemotherapy in the recurrent locally advanced or metastatic setting. If the anti-PD-(L)1 therapy is given in combination with chemotherapy, the patient must have progressed on an additional line of chemotherapy. Patients are eligible to enroll regardless of PD-L1 status.

- Expansion in 3L NSCLC will proceed simultaneously at 2 separate dose levels of TAK-500 following a 1:1 randomized approach, to RDE 1 and RDE 2, respectively. The 2 dose levels will be chosen such that adequate dose/response and exposure/response

analyses can be performed to support the selection of the dose for further development. RDE 1 and RDE 2 selection will be made on the totality of data, including safety, antitumor activity, PK and pharmacodynamic analysis, with both doses having a positive benefit-risk ratio for further study at the time of selection. Neither RDE 1 nor RDE 2 will be higher than the highest dose level assessed in the dose escalation phase or the MTD, whichever is lower.

- The 3L nonsquamous NSCLC expansion cohorts will be based on a single-stage design.
- Approximately 48 patients will be enrolled in this cohort, with 24 patients randomized to RDE 1 and RDE 2 each (to achieve an approximate total of 21 response-evaluable patients, assuming a 10% drop-out rate in each dose level).

6.1.3.3 TAK-500 SA and in Combination With Pembrolizumab Dose Expansion in 2L Pancreatic Adenocarcinoma

The preliminary antitumor activity, safety, tolerability, PK, and PD of TAK-500 SA and in combination with pembrolizumab will be evaluated in treatment-refractory pancreatic adenocarcinoma with 1 prior line of therapy.

Enrollment in the 2L pancreatic adenocarcinoma expansion will include patients with treatment-refractory pancreatic adenocarcinoma with recurrent locally advanced or metastatic disease that has previously progressed while on or following 1 prior line of therapy. Patient must have had disease progression while on or following 1 prior line of fluorouracil- or gemcitabine-based chemotherapy (eg, FOLFIRINOX, FOLFOX, FOLFIRI, gemcitabine/nab-paclitaxel) in the metastatic/recurrent locally advanced setting. Prior chemotherapy in the neoadjuvant/adjuvant setting does not qualify unless the patient had progression of disease within 6 months of completion of neoadjuvant/adjuvant chemotherapy. Patients cannot have had prior exposure to anti-PD-(L)1 therapy. Patients are eligible to enroll regardless of PD-(L)1 status. Patients with MSI-H/dMMR disease are not eligible.

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- Expansion in 2L pancreatic adenocarcinoma will randomize TAK-500 SA and TAK-500 in combination with pembrolizumab. Both arms will include TAK-500 at the TAK-500 RDE 1 identified during combination TAK-500 plus pembrolizumab dose escalation, unless the RDE 1 for the combination is below the PAD established during the TAK-500 SA dose escalation. In this instance, the RDE 1 for TAK-500 SA would be utilized for the corresponding arm (see Section 6.1.2.2 and Section 6.1.3).
- The 2L pancreatic adenocarcinoma expansion cohorts will be based on Simon's 2-stage design with ORR as an endpoint and separate futility analyses for the TAK-500 SA and TAK-500 combination cohorts.
- Approximately 45 patients will be enrolled in each arm to achieve an approximate total of 40 response-evaluable patients, assuming a 10% drop-out rate per cohort. A futility analysis will be performed at the time when there are 25 response-evaluable patients. The same futility criteria will be applied for each arm. If there are ≥4 responders among the first 25 response-evaluable patients, then the futility analysis is successful, and the

enrollment will continue to 40 response-evaluable patients in the respective cohort. Otherwise, the cohort will be terminated for futility. Enrollment may or may not pause while the response assessments needed for the futility analysis are pending.

6.1.3.4 Combination TAK-500 With Pembrolizumab Dose Expansion in 3L RCC

The preliminary antitumor activity, safety, tolerability, PK, and PD of TAK-500 in combination with pembrolizumab will be evaluated in treatment-refractory RCC with 2 prior lines of therapy.

Enrollment in the 3L RCC cohort will include patients with treatment-refractory RCC with recurrent locally advanced or metastatic disease that has previously progressed while on or following at least 2 prior lines of therapy. Patients must have had disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting or must have had disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting. Anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or an anti-VEGFR tyrosine kinase inhibitor (TKI) (eg, cabozantinib). Patients must have had prior therapy with 1 or 2 lines of VEGFR TKIs in the metastatic/recurrent locally advanced setting. If anti-PD-(L)1 therapy was given in combination with a VEGFR TKI, the patient must have had progressive disease on an additional line of therapy (eg, VEGFR TKI or VEGFR TKI-containing combination). Patients are eligible to enroll regardless of PD-L1 status.

- Expansion in 3L RCC will occur at the RDE 1 of TAK-500 identified during combination TAK-500 plus pembrolizumab dose escalation (see section 6.1.2.2 and section 6.1.3).
- The 3L RCC expansion cohorts will be based on a single-stage design, with enrollment of up to approximately 34 patients to achieve a total of 30 response-evaluable patients (assuming a 10% drop-out rate).

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6.1.4 Study Assessments

During dose escalation, all patients will be hospitalized for approximately 24 (±4) hours after the first 2 doses of TAK-500 (C1D1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500). Regardless of the treatment cycle, if a Grade ≥2 CRS or infusion-related reaction occurs during or after administration of study drug, hospitalization is required for 24 (±4) hours after the end of the next 2 TAK-500 infusions. For patients without evidence of grade ≥2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in clinic for at least 6 hours after infusion. Patients who do not experience an infusion-related reaction or Grade ≥2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour. During hospitalization, vital signs will be taken no less frequently than every 6 hours until discharge (See Appendix A). Before discharge from the hospital and/or clinic, a symptom-directed physical examination including assessment of the respiratory and neurologic systems and complete set of vital signs will be required.

AEs will be assessed, and laboratory values, vital signs, ECGs, and other clinically indicated examinations will be obtained to evaluate the safety and tolerability of the study treatment. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v5.0. DLTs are defined in Section 8.2. A DLT will be defined as any of the TEAEs described in the Section 8.2 that occurs during the first 21 days on study (C1D21) and are considered by the investigator to be at least possibly related to TAK-500 alone or in combination with pembrolizumab. TEAEs meeting DLT definitions occurring in later cycles will be considered in the determination of the dose for further development of TAK-500.

Radiological evaluations (contrast-enhanced computed tomographic [CT] scan and/or magnetic resonance imaging [MRI] as clinically indicated) will be used to assess the status of the patient's underlying disease. [redacted] tumor tissue or a minimum number of unstained slides of the tumor tissue will be collected, if available, from all enrolled patients to assess baseline features such as [redacted] that may emerge from future nonclinical or clinical studies. All patients with a safely accessible lesion enrolling at or above DLs where TAK-500 has previously shown pharmacodynamic activity will have mandatory tumor biopsies performed per the SOEs (Appendix A).

Serial blood samples will be collected for circulating biomarkers ([redacted]). An evaluation of disease response will be performed using the RECIST v1.1 (as determined by the investigator) and per the SOEs (Appendix A). Clinically validated peripheral tumor markers will also be collected for patients with appropriate tumor types (AFP, CA 27.29, and CA 19-9). Serial blood samples for determination of the serum concentration of TAK-500 and related metabolites to understand TAK-500 metabolism and excretion mechanisms will be obtained at prespecified time points as described in the SOEs (Appendix A).

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See Appendix A for SOEs for TAK-500 Q3W treatment (21-day cycle), TAK-500 Q3W treatment (42-day cycle), and TAK-500 Q2W treatment (42-day cycle).

6.2 Number of Patients

Approximately 313 patients in total will be enrolled in this study at approximately 70 sites globally. For the phase 1 dose escalation phase, in the SA arm, about 52 patients will be enrolled to achieve about 46 DLT-evaluable patients (includes cohorts treated with and without premedication); in the combination arm, the number of patients will depend on the starting DL. Assuming the starting DL is 80 µg/kg, about 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients. Additional patients may be enrolled for the evaluation of the Q2W administration of TAK-500 if this schedule is explored in the dose escalation phase.

For the phase 2 dose expansion phase, assuming only 1 TAK-500 administration schedule is expanded, approximately 231 patients will be enrolled to achieve a total of approximately

205 response-evaluable patients. This number may increase if more than 1 TAK-500 administration schedule is explored.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients may receive TAK-500 for up to 1 year. Patients with demonstrated clinical benefit may continue treatment beyond this point if recommended by the investigator and approved by the sponsor (see also Section 9.4.13). These patients can continue receiving treatment in this study or in any of the poststudy access modalities described in Section 6.3.5. Patients will discontinue treatment when they meet any of the discontinuation criteria in Sections 8.5.5 or 9.7.

Patients in the combination arm who discontinue study treatment (TAK-500) due to PD will be discontinued from both TAK-500 and pembrolizumab administration. Patients without evidence of PD or clinical progression for whom the investigator decides to discontinue TAK-500 (ie, due to safety issues that cannot be managed with dose reductions) will be considered to have ended study treatment. These patients will not continue with SA pembrolizumab as part of this study. Patients will proceed to the end of treatment (EOT) visit and then continue to be followed until disease progression or the initiation of a subsequent systemic anticancer therapy, whichever occurs first (See Appendix A).

Patients receiving TAK-500 SA may be eligible for optional crossover to combination treatment with pembrolizumab, after documented disease progression on TAK-500 SA. Eligibility for crossover is described in Section 8.5.2.

Patients without evidence of PD for whom the investigator decides to discontinue pembrolizumab due to intolerance, may continue on TAK-500 as an SA at the discretion of the investigator and sponsor. This should only occur in instances where the AE is clearly due to pembrolizumab and not TAK-500.

All patients will attend an EOT visit 30 days (+7 days) after receiving their last dose of study drug or before the start of subsequent systemic anticancer therapy to permit detection of any delayed TEAEs and to resolve any ongoing events. If a patient is not able to return for the EOT visit, the EOT assessments may be performed at the time of treatment discontinuation after discussion with the sponsor.

To assess the resolution of any ongoing immune-mediated AEs or to document the occurrence of any new treatment-related immune-mediated AEs, patients will be contacted or have the option to return for a safety follow-up at 90-days (±3 days) after receiving their last dose of study drug or before the start of a subsequent systemic anticancer therapy, whichever occurs first.

Patients who have discontinued treatment before documented disease progression will continue to have imaging assessments after EOT until disease progression or start of a subsequent systemic anticancer therapy, whichever occurs first. Subsequent systemic anticancer therapy will be documented. An end of study (EOS) case report form will be completed for all patients at last study contact.

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6.3.2 EOS and Study Completion Definition and Planned Reporting

It is anticipated that this study will last for approximately 50 months. The final data cutoff for the clinical study report will be conducted after all patients have been discontinued from treatment or are transferred to a long-term safety study, single-patient and site-initiated Investigational New Drug, or a similar program (see Section 6.3.5).

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

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Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Primary		
Frequency and severity of TEAEs	Standard safety assessments	Up to ~50 months
Number of patients with DLTs	Standard safety assessments	Up to ~50 months
Number and percentage of patients with 1 or more treatment-emergent SAE	Standard safety assessments	Up to ~50 months
Number and percentage of patients with 1 or more TEAEs leading to dose modifications and/or treatment discontinuations	Standard safety assessments	Up to ~50 months
Secondary		
PAD range	Evaluation of pharmacodynamic activity	Up to ~50 months
Dose for further development	Evaluation of pharmacodynamic activity	Up to ~50 months
PK parameters after administration of TAK-500: C_{max}, t_{max}, AUC_t, AUC_∞, $t_{1/2z}$, CL, V_{ss}	Standard PK parameters to allow determination of PK profile	Up to ~50 months
ORR (cCR + cPR) per RECIST v1.1	ORR per RECIST v1.1	Up to ~50 months
DCR (cCR + cPR + SD)	DCR	Up to ~50 months
DOR	DOR	Up to ~50 months
TTR	TTR	Up to ~50 months
PFS [b]	PFS	Up to ~50 months
OS [b]	OS	Up to ~50 months
Intratumoral T-cell infiltration upon TAK-500 treatment	Evaluation of pharmacodynamic activity	Up to ~50 months
Incidence of patients who are ADA-positive and acquired immunogenicity	Immunogenicity	Up to ~50 months

ADA: antidrug antibody; AUC_t: area under the serum concentration-time curve from time 0 to time t; AUC_∞: area under the serum concentration-time curve from time 0 to infinity; cCR: confirmed complete response; CL: total clearance after intravenous administration; C_{max}: maximum observed serum concentration; cPR: confirmed partial response; DCR: disease control rate; DLT: dose-limiting toxicity; DOR: duration of response; IFN: interferon; ORR: overall response rate; OS: overall survival; PAD: pharmacologically active dose; PFS: progression-free survival; PK: pharmacokinetic(s); RECIST: Response Evaluation Criteria in Solid Tumor; SAE: serious adverse event; SD: stable disease; STING: Stimulator of Interferon Genes; $t_{1/2z}$: terminal disposition phase half-life; TEAE: treatment-emergent adverse event; t_{max}: time of first occurrence of C_{max}; TTR: time to response; v: version; V_{ss}: volume of distribution at steady state after intravenous administration.
[a] Maximum time frame to last assessment for that endpoint for the study.
[b] For phase 2 expansion cohort only.

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6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 50 months.

Study start is defined as the first patient signing the informed consent form (ICF), and study end is defined as the last patient last contact.

6.3.5 Poststudy Access

Patients who are still on study treatment after the estimated study completion time of approximately 50 months will be allowed to continue to receive TAK-500 in poststudy access for this study, in a separate open-label rollover study, other poststudy access, such as through a single-patient Investigational New Drug application or equivalent. The mechanism of access will depend on the number of patients who require it. This access will be permitted only when the investigator and sponsor confirm that a patient has experienced a clinically important response to TAK-500 that outweighs the potential risks of continued treatment. Additionally, these patients should have no comparable or satisfactory alternative therapeutic option and would be negatively affected without continued access.

6.3.5.1 Duration of Poststudy Access

Continued access to TAK-500 in poststudy access will be terminated for those individuals who no longer benefit (eg, they have completed the recommended course of therapy, or their disease has progressed), the benefit-risk no longer favors the individual, or when an alternative appropriate therapy becomes available. Poststudy access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of TAK-500 has been suspended or stopped by the sponsor, or TAK-500 is no longer manufactured.

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7.0 STUDY POPULATION

7.1 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 of 0 to 1.
3. Patients with the following pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic solid tumors, whose disease has progressed on or are intolerant to standard therapy:
   a) For dose escalation with TAK-500 SA and combination TAK-500 with pembrolizumab:
      - Patients with the following pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic solid tumors, whose disease has progressed on or are intolerant to all standard therapy: gastroesophageal (esophageal, gastroesophageal junction, and gastric) adenocarcinoma, pancreatic adenocarcinoma, HCC, nonsquamous NSCLC, SCCHN,

mesothelioma, TNBC, RCC, and NPC. Patients who are intolerant to all standard therapies are those who have developed clinical or laboratory abnormalities that prevent continued drug administration as evaluated by the principal investigator at the time of screening.

b) For dose expansion in 2L nonsquamous NSCLC (TAK-500 plus pembrolizumab):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic nonsquamous NSCLC.
- Patients may not have a known targetable driver mutation, rearrangement or amplification (eg, EGFR, ALK, MET, ROS1, BRAF, KRASG12C, etc.).
- Must have had disease progression while on or following 1 prior line of therapy:
    1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting.

       OR

       Disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

       Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or chemotherapy (eg, carboplatin and pemetrexed).
- Patients are eligible regardless of PD-L1 status.

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c) For dose expansion in 3L nonsquamous NSCLC (TAK-500 SA):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic nonsquamous NSCLC.
- Patients may not have a known targetable driver mutation, rearrangement or amplification (eg, EGFR, ALK, MET, ROS1, BRAF, KRASG12C, etc.).
- Must have had disease progression while on or following 2 prior lines of therapy:
    1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting

       OR

Disease progression/recurrence within 6 months of the completion of 1 prior anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or chemotherapy (eg, carboplatin and pemetrexed).

2. Patients must have had disease progression while on or after 1 or 2 lines of chemotherapy in the recurrent locally advanced or metastatic setting. If the anti-PD-(L)1 therapy is given in combination with chemotherapy, patient must have progressed on an additional line of chemotherapy.

- Patients are eligible regardless of PD-L1 status.

d) For dose expansion in 2L pancreatic adenocarcinoma (TAK-500 SA and TAK-500 plus pembrolizumab):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic pancreatic adenocarcinoma.
- Must have had disease progression while on or following 1 prior line of therapy:

1. One prior line of fluorouracil- or gemcitabine-based chemotherapy (eg, FOLFIRINOX, FOLFOX, FOLFIRI, gemcitabine/nab-paclitaxel) in the metastatic/recurrent locally advanced setting.

   Prior chemotherapy in the neoadjuvant/adjuvant setting does not qualify unless the patient had progression of disease within 6 months of completion of neoadjuvant/adjuvant chemotherapy.

- Must not have had prior exposure to anti-PD-(L)1 therapy.
- Patients with MSI-H/dMMR disease are not eligible.
- Patients are eligible regardless of PD-L1 status.

e) For dose expansion in 3L RCC (TAK-500 plus pembrolizumab):

- Patients with pathologically confirmed (cytological diagnosis is adequate) locally advanced or metastatic RCC.
- Must have had disease progression while on or following 2 prior lines of therapy:

1. Disease progression while on or following at least 6 weeks of 1 prior anti-PD-(L)1 therapy in the recurrent locally advanced or metastatic setting.

   OR

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Disease progression/recurrence within 6 months of the completion of anti-PD-(L)1 therapy if administered in the adjuvant/neoadjuvant setting.

Prior anti-PD-(L)1 therapy may have been given with or without an anti-CTLA4 antibody and/or an anti-VEGFR TKI.

2. Patients must have had prior therapy with 1 or 2 lines of VEGFR TKIs in the metastatic/recurrent locally advanced setting. If anti-PD-(L)1 therapy was given in combination with a VEGFR TKI, the patient must have had progressive disease on an additional line of therapy (eg, VEGFR TKI or VEGFR TKI-containing combination).

- Patients are eligible regardless of PD-L1 status.

4. Patients must have at least 1 RECIST v1.1 measurable lesion. Lesions in previously irradiated areas (or other local therapy) should not be selected as measurable/target lesions unless there has been demonstrated radiographic progression in that lesion. RECIST v1.1 target lesions must include at least 1 lesion that was not previously irradiated.
5. Once a DL is reached where evidence of TAK-500 stimulation of the [redacted] has been observed in the blood and/or a clinical response (PR or CR) measured in at least 1 patient, subsequent patients treated at the equivalent or higher DL will be required to have 2 biopsies (at screening and on treatment), assuming the potential morbidity of the procedures is deemed acceptable by the treating physician.
6. Adequate bone marrow, renal, and hepatic functions, as determined by the following laboratory parameters:
   - Absolute neutrophil count (ANC) ≥1000/µL, platelet count ≥75,000/µL, and hemoglobin ≥8.0 g/dL without growth factor support for ANC or transfusion support for platelets within 14 days before the first study treatment dose.
   - Total bilirubin ≤1.5 times the institutional upper limit of normal (ULN). For patients with Gilbert's disease or HCC, ≤3 mg/dL.
   - Serum ALT and AST ≤3.0 × ULN or ≤5.0 × ULN with liver metastases or HCC.
   - Albumin ≥3.0 g/dL.
   - Calculated creatinine clearance using the Cockcroft-Gault formula (Cockcroft and Gault 1976) ≥30 mL/minute.
7. For patients with HCC only: Child-Pugh score less than or equal to 7 (Child-Pugh A or B7).
8. Left ventricular ejection fraction (LVEF) >50%, as measured by echocardiogram or multiple-gated acquisition scan (MUGA) within 4 weeks before receiving the first dose of study drug.

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9. Clinically significant toxic effects of previous therapy have recovered to Grade 1 (per NCI CTCAE v5.0) or baseline, except for alopecia, Grade 2 peripheral neuropathy, and/or autoimmune endocrinopathies with stable endocrine replacement therapy.
10. Patients previously treated with fully human/humanized antineoplastic monoclonal antibodies must not have received treatment with such antibodies for at least 4 weeks or the time period equal to the dosing interval, whichever is shorter. No washout period is required for prior treatment with pembrolizumab or other anti–PD-1 antibodies, although the first study dose of these drugs must not occur at an interval less than standard of care (ie, 3 weeks for 200 mg of IV pembrolizumab).
11. Suitable venous access for the collection of study-required blood sampling, including PK and pharmacodynamic blood samples.
12. Female patients must be:
    - Postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit, or
    - Surgically sterile, or
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception at the same time, from the time of signing the informed consent through 180 days after the last dose of study drug(s), or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient.
      – Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
13. Male patients, even if surgically sterilized (ie, status postvasectomy), must:
    - 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.
      – Note: Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.
14. 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.
15. Patients must be eligible for treatment with pembrolizumab at the dose(s) and schedule(s) recommended in the label/prescribing information, where applicable.

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7.2 Exclusion Criteria

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

1. History of any of the following ≤6 months before first dose of study drug(s): congestive heart failure New York Heart Association Grade III or IV, unstable angina, myocardial infarction, persistent hypertension ≥160/100 mm Hg despite optimal medical therapy, ongoing cardiac arrhythmias of Grade >2 (including atrial flutter/fibrillation or intermittent ventricular tachycardia), other ongoing serious cardiac conditions (eg, Grade 3 pericardial effusion or Grade 3 restrictive cardiomyopathy), or symptomatic cerebrovascular events. Chronic, stable atrial fibrillation on stable anticoagulation therapy, including low molecular-weight heparin, is allowed.
2. QT interval with Fridericia correction method (QTcF) >450 milliseconds (men) or >475 milliseconds (women) on a 12-lead ECG during the screening period.
3. Grade ≥2 hypotension (ie, hypotension for which nonurgent intervention is required) at screening or during C1D1 predose assessment.
4. Oxygen saturation <92% on room air at screening or during C1D1 predose assessment.
5. Patients treated with other STING agonists/antagonists, Toll-like receptor agonists, or CCR2 agonist/antagonist within the past 6 months.
6. Exclusion criterion removed
7. Exclusion criterion removed
8. Active diagnosis of pneumonitis, interstitial lung disease, severe chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, other restrictive lung diseases, acute pulmonary embolism, or Grade ≥2 pleural effusion not controlled by tap or requiring indwelling catheters.
9. History of brain metastasis or leptomeningeal disease unless:
    - Brain metastases are stable on cranial imaging (ie, ≥4 weeks) following prior surgery, whole-brain radiation, or stereotactic radiosurgery, and
    - Off corticosteroids for brain metastases.
10. Grade ≥2 fever of malignant origin.
11. Systemic infection requiring IV antibiotic therapy or other serious infection within 14 days before the first dose of study drug. Patients are specifically excluded if they have active, severe infections such as tuberculosis (screening per local practice and epidemiology), sepsis, cytomegalovirus (including cytomegalovirus colitis), listeriosis, and opportunistic infections (including *Clostridium difficile*) until the infections are controlled.

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12. Patients with either/both of:
    - Uncontrolled, known or suspected, autoimmune disease. Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
    - A diagnosis of an identified congenital or acquired immunodeficiency (eg, common variable immunodeficiency, uncontrolled HIV infection, organ transplantation).
13. Chronic, active hepatitis (eg, patients with known hepatitis B surface antigen seropositive and/or detectable hepatitis C virus [HCV] RNA).
    - Note: Patients who have positive hepatitis B core antibody can be enrolled but must have an undetectable serum hepatitis B virus-DNA. Patients who have positive HCV antibody must have an undetectable HCV-RNA serum level.
14. History of hepatic encephalopathy.
15. Prior or current clinically significant ascites, as measured by physical examination, that requires active paracentesis for control.
16. Any pre-existing condition or illness, metabolic dysfunction, physical examination finding, or clinical laboratory finding that give reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug or that would limit compliance with study requirements or compromise ability to provide written informed consent.
17. Treatment with any investigational products or other anticancer therapy (including chemotherapy, targeted agents, and immunotherapy), within 14 days or 5 half-lives, whichever is shorter, before C1D1 of study drug(s).
18. Concurrent chemotherapy, immunotherapy (except for pembrolizumab in the combination arm), biologic, or hormonal therapy (except for adjuvant endocrine therapy for a history of breast cancer). Concurrent use of hormones for noncancer-related conditions is acceptable (except for corticosteroid hormones).
19. Radiation therapy within 14 days (42 days for radiation to the lungs) and/or systemic treatment with radionuclides within 42 days before C1D1 of study drug(s). Patients with clinically relevant ongoing pulmonary complications from prior radiation therapy are not eligible.
20. Use of systemic corticosteroids or other immunosuppressive therapy, concurrently or within 7 days of C1D1 of study drug(s), with the following exceptions:
    - Topical, intranasal, inhaled, ocular, intra-articular, and/or other nonsystemic corticosteroids.
    - Physiological doses of replacement steroid therapy (eg, for adrenal insufficiency), not to exceed the equivalent of 10 mg prednisone daily.

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21. Use of medications that are known clinical OATP1B1 and/or OATP1B3 inhibitors, concurrently or within 14 days of C1D1 of study drug(s) (see Appendix D).
22. Receipt of live attenuated vaccine (eg, tuberculosis Bacillus Calmette-Guerin vaccine, oral polio vaccine, measles, rotavirus, yellow fever) within 28 days of C1D1 of study drug(s). Nonlive, approved vaccines are allowed (eg, coronavirus disease 2019 [COVID-19] vaccine).

    Note: COVID-19 vaccination should not be given ±3 days of systemic study treatments.
23. Recipients of allogeneic or autologous stem cell transplantation or organ transplantation.
24. Female patients who are lactating or have a positive serum/urine pregnancy test during the screening period or a positive serum/urine pregnancy test on Day 1 before first dose of study drug.

    Note: Female patients who are lactating will be eligible if they choose to discontinue breastfeeding before the first dose of study drug.

Additional criteria specific for patients in TAK-500 and pembrolizumab combination arm only:

25. Contraindication to the administration of pembrolizumab or prior intolerance to pembrolizumab or other anti–PD-1 or anti–PD-L1 antibody.
26. History of intolerance to any component of the study treatment agents or known serious or severe hypersensitivity reaction to any of the study drugs or their excipients. (Pembrolizumab is formulated with L-histidine, polysorbate 80, and sucrose.)

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8.0 STUDY DRUG

Investigational medicinal product(s): TAK-500 drug product.

Combination product: pembrolizumab.

8.1 Study Drug Administration

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

Additional details regarding investigational medicinal product(s) can be found in the pharmacy manual. In instances of a discrepancy between the protocol text and the pharmacy manual regarding the investigational medicinal product, the pharmacy manual shall supersede the text within the protocol.

8.1.1 TAK-500

Route of administration: IV infusion administered as directed in the pharmacy manual.

DL: To be assigned at time of enrollment.

Dose Escalation: TAK-500 will be administered as an IV infusion on a dosing schedule of Q3W or Q2W, as assigned at time of enrollment, in a 21-day (Q3W) or 42-day (Q2W) cycle.

Dose Expansion: TAK-500 will be administered as an IV infusion on a dosing schedule of either Q2W or Q3W, as assigned at time of enrollment, in a 42-day cycle.

Alternate dosing schedules of administration in combination with pembrolizumab may also be considered during dose escalation if the collective data including safety, PK, and pharmacodynamics support it, without requiring a protocol amendment. TAK-500, pembrolizumab and other drugs must not be administered through the same infusion line.

TAK-500 will be administered by IV infusion at a defined infusion rate. Detailed dosage preparation and dose administration instructions are provided in the Directions for Use located in the pharmacy manual. Administration should always be performed on schedule; however, if extenuating circumstances prevent a patient from beginning treatment on a particular dosing day, a ±3-day window may be allowable. On the basis of emerging data (eg, severity of infusion-related reactions), the infusion time may be adjusted to less than the defined time on agreement with the sponsor and investigators. The infusion may be slowed or stopped and restarted for any infusion-related reactions. All infusion times must be recorded.

Due to the risk of developing CRS after administration of TAK-500, [redacted].

Enrollment of SA TAK-500 or TAK-500 + pembrolizumab combination dose escalation cohorts with premedication may proceed in parallel with cohorts enrolling without premedication or with different premedication regimens, with each premedication regimen separately following the BOIN design for dose escalation/de-escalation decisions.

[redacted].

For administrations of TAK-500, vital signs will be measured immediately before the start of the infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured

immediately before the start of the infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vital signs will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Vital signs should be measured and recorded at any time if the patient develops symptoms associated with potential risks of TAK-500 and/or pembrolizumab. The frequency and timing of vital sign monitoring may be modified on the basis of emerging data and agreement between sponsor and investigators.

TAK-500 administration will occur in facilities with readily available resuscitation equipment, diagnostic equipment and supportive care/medications such as oxygen, antihistamines, acetaminophen, corticosteroids, epinephrine, anti–IL-6 agents, and bronchodilators.

As with other potentially toxic compounds, caution should be exercised in handling this drug. The use of gloves is recommended. Given the possibility of extravasation, it is advisable to closely monitor the infusion site per nursing institutional guidelines for possible infiltration during drug administration. Administration through a central port is always preferred versus a peripheral line.

For TAK-500 SA dose escalation, TAK-500 will be administered as described in Section 6.1.1.

For detailed information on the preparation and administration of TAK-500, refer to the pharmacy manual.

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8.1.2 Pembrolizumab

Route of administration: IV infusion administered as directed in the most current product information available for pembrolizumab (eg, package insert).

DL: 200 mg.

Pembrolizumab will be administered on C1D1 at 200 mg IV following the label and on a Q3W basis thereafter. Administration will continue until disease progression, intolerance to pembrolizumab (defined as the development of a TEAE that is at least possibly related to pembrolizumab and for which dose discontinuation is recommended), or withdrawal of consent, whichever occurs first.

For administrations of pembrolizumab, vital signs will be measured immediately before the start of the infusion (within 30 minutes) and any time when clinically indicated.

For preparation, handling, and administration instructions related to pembrolizumab, please consult the pharmacy manual and the most current product information available for pembrolizumab (eg, package insert).

8.1.3 TAK-500 in Combination With Pembrolizumab

This combination arm will be initiated at a TAK-500 DL of 80 µg/kg, triggered upon safety clearance of the 80 µg/kg TAK-500 SA DL. If it is determined during the SA dose escalation that the TAK-500 SA minimum PAD is ≤40 µg/kg, the combination TAK-500 plus

pembrolizumab dose escalation will begin at a dose no higher than the TAK-500 SA minimum PAD DL. The combination dose escalation may begin at a DL of TAK-500 that is below the TAK-500 SA PAD if this is determined to be necessary from the evaluation of safety and toxicity data.

For both the dose escalation and dose expansion cohort(s), TAK-500 may be administered in either a Q2W or Q3W dosing schedule, as described in Sections 6.1.1 and 6.1.3. TAK-500 will be administered on Day 1 of each cycle in combination with 200 mg pembrolizumab administered IV Q3W following the label instructions. On days when both drugs are administered (ie, Day 1 of each cycle), pembrolizumab should be administered first, followed by TAK-500, with a 1-hour interval between completion of pembrolizumab infusion and the administration of TAK-500. Alternative schedules of administration of TAK-500 in combination with pembrolizumab may be considered if clinical safety, PK, and pharmacodynamics data support it. If TAK-500 dosing is delayed for any reason, pembrolizumab dosing should also be delayed to coincide with TAK-500 administration.

The same inpatient and outpatient vital sign monitoring described in Sections 8.1.1 and 8.1.2 will be performed for administration of TAK-500 with the pembrolizumab combination.

For detailed information on the preparation and administration of TAK-500, refer to the pharmacy manual.

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8.1.4 List of European Union Auxiliary Medicinal Products

[redacted]

Table 8.a [redacted]

[redacted]

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE v5.0, effective 27 November 2017. A DLT will be defined as any of the following phase 1 TEAEs, that occur during the first 21 days on study (through C1D21) and are considered by the investigator to be at least possibly related to TAK-500 as an SA or in combination with pembrolizumab. (Note that AEs in which the relationship to study drug cannot be ruled out should be considered possibly related to study drug.)

1. Any Grade 5 AE.
2. Grade 4 anemia.
3. Grade 4 neutropenia lasting ≥5 days or requiring use of granulocyte colony-stimulating factor (G-CSF).
4. Any febrile neutropenia.
5. Platelet count <10,000/μL at any time.
6. Grade 4 thrombocytopenia lasting ≥5 days; or Grade ≥3 thrombocytopenia with clinically significant bleeding.
7. Grade ≥3 CRS.
8. Grade ≥2 immune-mediated uveitis that does not respond to topical therapy and does not improve to Grade ≤1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment.
9. Delay in the initiation of Cycle 2 by more than 14 or 21 days (for Q2W and Q3W administration schedule of TAK-500, respectively) from the calculated start date due to a lack of adequate recovery of treatment-related hematological or nonhematologic toxicities.
10. Any Grade ≥3 nonhematologic toxicity with the following exceptions:
    - Grade 3 arthralgia/myalgia that responds to nonsteroidal anti-inflammatory drugs within 1 week.
    - Grade 3 fatigue lasting less than 7 days.
    - Any Grade 3 endocrinopathy that is adequately controlled by hormonal replacement.
    - Grade 3 or 4 inflammatory reaction attributed to a local antitumor response (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
    - Transient (≤48 hours) Grade 3 flu-like symptoms, which resolve spontaneously or are controlled with medical management.
    - Grade 3 asymptomatic laboratory changes (other than renal function) that can be successfully corrected (reversion of Grade ≤1 or baseline) within 3 days.

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- The following Grade 4 asymptomatic laboratory changes: creatine kinase increased, gamma glutamyl transferase increased, and alkaline phosphatase increased.
- Grade 3 nausea and/or emesis that can be controlled to Grade ≤1 in ≤3 days with the use of antiemetics (such as metoclopramide, prochlorperazine, serotonin type 3 receptor [5-HT3] antagonist and/or neurokinin-1 receptor antagonists).
- Grade 3 rash and pruritis that respond to a standard treatment and resolve or improve to Grade <3 within 7 days.
- Grade 3 diarrhea that can be controlled to Grade ≤2 in ≤3 days with supportive treatment.
- Alopecia.
- Transient (< 4-hour) Grade 3 hypertension occurring in association with CRS-related rigor, which resolves either spontaneously or with medical management.

TEAEs meeting DLT definitions occurring after 21 days on study will be considered in the determination of the dose for further development of TAK-500, both in the TAK-500 SA and the combination with pembrolizumab.

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8.3 Dose Escalation Rules

8.3.1 BOIN Dose Escalation

Except for the initial 2 TAK-500 SA 1 + 2 + 3 accelerated titration cohorts, dose escalation of TAK-500 in both the SA and combination arms will follow the BOIN design to inform dose escalation decisions and potential MTD estimation, as described in Appendix F. Each DL of TAK-500 following the BOIN dose escalation will enroll 3 patients initially. A cohort size different from 3 is permissible thereafter per the escalation/de-escalation guidelines outlined in Appendix F, Table F-1. There will be a 24-hour dosing delay between the first patient of any new DL and subsequent patients enrolled at the same DL. The target toxicity rate is $\phi = 0.3$. To guide dose escalation decisions, if the observed DLT rate at the current dose is ≤0.236, the next cohort of patients will be treated at the next higher DL; if it is ≥0.358, the next cohort of patients will be treated at the next lower DL; if it is within 0.236 and 0.358, additional patients will be enrolled in this DL. For the purpose of overdose control, dose j and higher levels will be eliminated from further examination if $Pr(p_j>0.3 \mid data) >0.95$, where p_j is the true DLT rate of DL j. When the lowest dose is eliminated, the dose escalation will be stopped for safety. Dose escalation will continue until either: (1) the maximum sample size is reached, or (2) the number of patients treated at the current DL reaches 9 and the recommendation is to retain at the current DL.

In the SA dose escalation, after the BOIN escalation starts, the maximum number of DLT evaluable patients to be enrolled is 42 (40 rounded up to the nearest multiple of 3). In the combination escalation, the maximum number of DLT-evaluable patients to be enrolled depends on the starting DL. In principle, we plan an average of about 5 patients per DL from the starting

DL to 480 µg/kg. For example, if the starting DL is 80 µg/kg, the maximum number of DLT-evaluable patients to be enrolled is 27 (25 rounded up to the nearest multiple of 3).

Isotonic regression will be used on the cumulative DLT rate for each DL to determine the MTD, defined as the highest TAK-500 dose as an SA or in combination with pembrolizumab that does not result in unacceptable toxicity. Note that dose escalation cohorts treated with a specific premedication regimen will be analyzed separately from cohorts treated without premedication or with other premedication regimens.

8.3.2 Stopping Rules

The sponsor may stop or halt enrollment or treatment of ongoing patients, depending on the nature and severity of a safety-related event. A final decision to terminate the study or a protocol amendment will be made only after a full review of the safety data by the sponsor's Safety Management Team and the investigators.

A threshold of fatal AEs related to TAK-500 SA or TAK-500 and pembrolizumab treatment will initially be set at 6% per arm. Any rate of fatal events related to TAK-500 SA or TAK-500 + pembrolizumab combination therapy that is over 6% with at least an 80% posterior probability will result in stopping the study. The study will also be stopped if the rate of TAK-500 SA-related or TAK-500 + pembrolizumab combination therapy–related Grade ≥4 events in any nonhematologic System Organ Class exceeds 25% per arm (with the exception of Grade ≥4 asymptomatic laboratory abnormalities) with at least an 80% posterior probability. A study stop for a safety issue will result in an immediate halt in enrollment and may also necessitate cessation of treatment of ongoing patients, depending on the nature and the severity of the safety risk. A final decision to terminate the study will be made only after a full review of the safety data by the sponsor and the safety management team.

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8.4 Definition of PAD

Determination of the PAD dose range for TAK-500 will be used to inform decision-making regarding selection of the starting dose for the combination with pembrolizumab dose escalation and for dose selection for both the SA and combination dose expansion cohorts. PAD for TAK-500 is defined as any dose at which there is evidence of TAK-500–mediated pharmacodynamic effects and may include, but is not limited to:

- Evidence of [redacted] in peripheral blood.
- Evidence of [redacted] in peripheral blood.

  OR

- Clinical evidence of antitumor activity (eg, PR or CR) as determined by RECIST v1.1 (Section 9.4.13).

To enhance and refine PAD and dose selection for expansion cohorts, additional peripheral and tumoral pharmacodynamic biomarkers will be assessed. Peripheral pharmacodynamic

biomarkers may include [redacted].

8.5 Dose Modification Guidelines

Treatment with TAK-500 as an SA or in combination with pembrolizumab will occur in 21- or 42-day cycles. Toxicities are to be assessed according to the NCI CTCAE v5.0. All toxicities that occur during the study will be actively managed following the System Organ Class unless otherwise specified in the protocol. The causal relationship of any reported events (AEs or SAEs) should be assessed by the investigator in relation to TAK-500, pembrolizumab, or both. Patients experiencing AEs attributed to TAK-500 as an SA or in combination with pembrolizumab may continue study treatment and maintain the same dose, have doses held, have doses of TAK-500 reduced, or permanently discontinue from the study. Patients who have the TAK-500 dose held due to a treatment-related or possibly related AE may resume study drug after resolution of the AE, and may either maintain the same DL or have doses of TAK-500 reduced after consultation with the sponsor. When a dose reduction occurs, the TAK-500 dose will be reduced to the next lower dose that has been established as a safe dose during dose escalation. If initial dose adjustment does not provide sufficient relief, the dose of TAK-500 can be further reduced if the treating physician considers that the patient is benefiting from study treatment. If TAK-500 dosing is delayed for more than 14 or 21 days (for Q2W and Q3W dosing, respectively) beyond scheduled dosing for TAK-500–related or possibly related toxicities, despite maximal supportive treatment per standard clinical practice or if more than 2 dose reductions are required in a patient, the patient will have study treatment discontinued.

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For AEs that occur during the study but are not related to TAK-500 or pembrolizumab, the dose modification of TAK-500 and/or pembrolizumab, in principle, is not required. However, on the basis of medical conditions and the possibility of potential worsening of toxicities by the continued administration of TAK-500 and/or pembrolizumab, investigators in consultation with the sponsor can decide to have the TAK-500 and/or pembrolizumab dose held or reduced (in the case of TAK-500) until the resolution of the AE in consultation with the sponsor, as needed.

Dose modification guidelines for TAK-500 are described in Table 8.b and Table 8.c on the basis of the nature and severity of AEs and causality determination by investigators. Further clarification can be obtained in consultation with the sponsor. The pembrolizumab dose cannot be reduced; it may only be skipped (ie, patient is not dosed), interrupted (ie, dosing is paused during infusion), or discontinued.

8.5.1 Intrapatient Dose Escalation

Intrapatient dose escalation will not be permitted as part of the DLT-evaluable dose escalation set, but patients treated at TAK-500 SA DLs below minimum PAD (as discussed in Section 8.4) will be allowed to escalate to minimum PAD once the minimum PAD DL has been confirmed and cleared from a safety perspective.

For patients to be eligible for intrapatient dose escalation, they must continue on study without interruption and without evidence of progressive disease by imaging or clinical deterioration.

8.5.2 Criteria for Crossover From SA to Combination Treatment

Crossover is optional and at the discretion of the site investigator and sponsor and in agreement with the patient. Patients with objective evidence of PD in the TAK-500 SA treatment arm may crossover to the TAK-500 + pembrolizumab combination arm into the last DL that is or was accruing patients. Crossover to combination treatment will not be possible until the completion of the first TAK-500 + pembrolizumab dosing cohort.

The sponsor will use the SA data from crossover patients in the primary analysis, but after crossover will then consider these patients a separate cohort so as to not confound their data with the patients originally enrolled into the combination arm.

Patients who meet the following criteria are eligible for crossover:

- Documentation of PD on TAK-500 SA regardless of prior exposure to PD-1/PD-L1; no evidence of uncontrolled brain metastases or any other uncontrolled CNS disease.
- Complete an EOT visit for TAK-500 SA (must occur before initiation of combination therapy).
- ECOG Performance Status 0 to 1.
- No DLT or DLT-like toxicity at the TAK-500 SA DL.
- Patient has no contraindication for treatment with pembrolizumab.

Crossover combination therapy must begin within 28 days of documentation (CT or MRI) of PD and the full EOT assessments must be completed. Patients will complete procedures as described in the SOE starting again at C1D1 with the combination therapy and the data would be entered on case report forms for crossover.

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If crossover is approved, TAK-500 SA should continue through the EOT visit and initiation of pembrolizumab.

8.5.3 Criteria for Administering a Subsequent Dose/Starting a New Treatment Cycle

Treatment with TAK-500 as an SA or in combination with pembrolizumab will use a cycle length of 21 days for Q3W dosing of TAK-500 and 42 days for Q2W dosing of TAK-500 in dose escalation. A cycle length of 42 days will be used in dose expansion. For a subsequent dose of TAK-500 to be administered, or a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC ≥1000/μL, platelet count ≥75,000/μL, and hemoglobin ≥8.0 g/dL.
- Total bilirubin ≤1.5 times the institutional ULN. For patients with Gilbert's disease or HCC, ≤3 mg/dL.
- Serum ALT and AST ≤3.0 × ULN or ≤5.0 × ULN with liver metastases or HCC.
- Estimated creatinine clearance using the Cockcroft-Gault formula ≥30 mL/minute.

- Oxygen saturation of ≥92% on room air.
- Before administering a subsequent dose or starting a new treatment cycle, TAK-500–related or pembrolizumab-related AEs and/or clinically significant laboratory abnormalities must have returned to Grade ≤1 or baseline, except for alopecia, Grade 2 peripheral neuropathy, and/or autoimmune endocrinopathies with stable endocrine replacement therapy.

If the patient does not meet the above cited criteria for re-treatment, treatment should be delayed by 1 week, at the end of which the patient will be re-evaluated to determine whether the criteria for re-treatment have been met. If a dose reduction is considered (eg, after 2 dose delays), TAK-500 will be reduced by 1 DL. For dose reduction criteria, please see Section 8.5.4. Should the start of the following cycle be delayed by more than 14 or 21 days (for Q2W and Q3W dosing, respectively), the patient should have study treatment discontinued unless the investigator in consultation with the sponsor considers that the patient will receive benefit by continuing in the study. For TAK-500 plus pembrolizumab combination cohorts, if dosing of TAK-500 is delayed, pembrolizumab dosing should also be delayed by the same period of time. This means that for Q3W dosing of TAK-500, TAK-500 and pembrolizumab will always dose on the same day.

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8.5.4 Criteria for Dose Modification

Dosing of pembrolizumab cannot be reduced, only delayed, skipped, interrupted, or discontinued. Refer to the pembrolizumab prescribing information for recommended dose modification and/or discontinuation guidelines.

Dosing of TAK-500 should be reduced according to the dose modification recommendations listed in Table 8.b for nonhematologic toxicity and Table 8.c for hematologic toxicities except for those AEs that are considered DLTs in Cycle 1 requiring discontinuation. If indicated, TAK-500 dose should be reduced by 1 DL (or by 50% if the patient is receiving the first DL). For Grade 1 and Grade 2 toxicities, the investigator may consider making a dose adjustment to TAK-500. For Grade ≥3 AEs, dose adjustments to TAK-500 must be made as indicated in the following tables. During this study, further adjustment to dose reduction guidelines may be made following discussion with the sponsor and study investigators.

If the initial dose adjustment does not provide sufficient relief, the dose of TAK-500 can be further reduced by 1 additional DL with agreement by the sponsor if the treating physician believes that the patient is receiving benefit. Generally, once a dose is reduced, it will not be re-escalated. However, if further evaluation reveals that the AE that led to the dose reduction was not study drug related, or there were other circumstances contributing to the AE that are unlikely to recur, the dose may be re-escalated to the original DL after discussion with the sponsor and the treating physician. Additionally, after discussion with the sponsor, patients previously dose-reduced for a Grade 2 CRS occurring after dosing of TAK-500 without corticosteroid pretreatment (per Protocol Amendment 1), may be re-escalated with the addition of corticosteroid pretreatment before TAK-500 administration. If pursued, dose re-escalation for these patients should proceed by no more than 1 DL each cycle and may not exceed the initially

assigned DL. A patient can have up to 2 DL reductions of TAK-500 as an SA or in combination due to AEs, but further reductions are not permitted (the patient should discontinue study drug in this case).

Table 8.b Guidelines for TAK-500 Dose Modification and/or Discontinuation for Nonhematologic Toxicity

Refer to the pembrolizumab prescribing information for recommended discontinuation guidelines.	
NCI CTCAE Grade	**TAK-500 Dose Modification**
CRS	
Grade 1: Fever with or without constitutional symptoms	• Continue TAK-500 at the same DL.
Grade 2: Hypotension responding to fluids; hypoxia responding to <40% FiO_2	• Hold TAK-500 until recovers to Grade ≤1. • Once recovered, restart TAK-500 at the same dose. If the patient was not previously premedicated with corticosteroids, add corticosteroid pretreatment for subsequent doses of TAK-500.
Grade 3: Hypotension managed with 1 pressor; hypoxia requiring ≥40% O_2	• Permanently discontinue TAK-500.
Grade 4: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue TAK-500.
Infusion-related reactions	
Grade 2	• Hold TAK-500 infusion until symptoms resolve to Grade ≤1. • Resume at a slower rate. • Consider premedication before the subsequent dose. • Permanently discontinue if recurrent on re-challenging despite premedication use.
Grade 3 or 4	• Permanently discontinue TAK-500.
Colitis	
Grade 2 or 3	• Hold TAK-500 until improvement to a Grade ≤1 or baseline. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Grade 4	• Permanently discontinue TAK-500.

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Table 8.b Guidelines for TAK-500 Dose Modification and/or Discontinuation for Nonhematologic Toxicity

Refer to the pembrolizumab prescribing information for recommended discontinuation guidelines.	
NCI CTCAE Grade	**TAK-500 Dose Modification**
Hepatotoxicity	
AST/ALT <3 × ULN, or ≤5 × ULN in the case of known liver metastases	• Continue TAK-500 at the same DL. • Hepatic laboratory tests, including ALT, AST, ALP, T-Bil, D-Bil, PT-INR, more than once a week is recommended until improved to AST/ALT ≤1.5 × baseline or ≤5.0 × ULN with liver metastases or HCC.
AST/ALT >3-5 × ULN	• Hold TAK-500 until resolution to AST/ALT ≤3.0 × ULN or ≤5.0 × ULN with liver metastases or HCC. • Resume at same DL. • Permanently discontinue if recurrent on re-challenging. • Monitoring of hepatic laboratory tests, including ALT, AST, ALP, T-Bil, D-Bil, PT-INR is recommended until improved AST/ALT ≤1.5 × baseline.
AST/ALT >5-10 × ULN	• Hold TAK-500 until improvement to AST/ALT ≤3.0 × ULN or ≤5.0 × ULN with liver metastases or HCC. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging. • Monitoring of hepatic laboratory tests, including ALT, AST, ALP, T-Bil, D-Bil, and PT-INR is recommended until improved AST/ALT ≤1.5 × baseline.
AST/ALT >10 × ULN or Child-Pugh score ≥9	• Permanently discontinue TAK-500.
Elevated bilirubin (Grade 2)	• Hold TAK-500 until resolution to T-Bil ≤1.5 × ULN or ≤3 mg/dL for patients with Gilbert's disease or HCC. • Resume at same DL. • Reduce by 1 lower DL if recurrent.
Elevated bilirubin (Grade 3 or 4)	• Permanently discontinue TAK-500.
Endocrinopathies	
Grade 2	• Continue TAK-500 at the same DL. • Replacement therapy as clinically indicated.
Grade 3 or 4	• Hold TAK-500 until clinically stable. • Resume at 1 lower DL. • Replacement therapy as clinically indicated.

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Table 8.b Guidelines for TAK-500 Dose Modification and/or Discontinuation for Nonhematologic Toxicity

Refer to the pembrolizumab prescribing information for recommended discontinuation guidelines.	
NCI CTCAE Grade	**TAK-500 Dose Modification**
Increased creatinine	
Grade 1	• Continue TAK-500 at the same dose and monitor creatinine weekly.
Grade 2	• Hold TAK-500 until resolution to Grade ≤1 or baseline. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Grade 3 and 4	• Permanently discontinue TAK-500.
Pneumonitis	
Grade 2	• Hold TAK-500 until resolution to Grade ≤1 or baseline. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Grade 3 or 4	• Permanently discontinue TAK-500.
Rash (skin and subcutaneous tissue disorders)	
Grade 2	• Hold TAK-500 until resolution to Grade ≤1 or baseline. • Resume TAK-500 at same DL. • Reduce TAK-500 by 1 DL if recurrent.
Grade 3	• Hold TAK-500 until resolution to Grade ≤1 or baseline. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Grade 4	• Permanently discontinue TAK-500.
Other immune-mediated AEs	
Grade 2	• Hold TAK-500 until resolution to Grade <1. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Grade 3 or 4	• Permanently discontinue TAK-500.
Hypertension	
Grade 1 and 2	• Continue TAK-500 at the same dose.

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Table 8.b Guidelines for TAK-500 Dose Modification and/or Discontinuation for Nonhematologic Toxicity

Refer to the pembrolizumab prescribing information for recommended discontinuation guidelines.	
NCI CTCAE Grade	**TAK-500 Dose Modification**
Grade 3	• Hold TAK-500 until resolution to Grade ≤2 or baseline. • If hypertension is associated with rigors and resolves to Grade ≤2 or baseline with resolution of the rigors (with or without medical intervention, eg, meperidine), continue TAK-500 at the same dose and closely monitor blood pressure during/post subsequent TAK-500 administration. • If the patient was not previously premedicated with corticosteroids, add corticosteroid pretreatment for subsequent doses of TAK-500. • If hypertension does not resolve with resolution of rigors and/or persists continuously >4 hours with or without rigors, permanently discontinue TAK-500.
Grade 4	• Permanently discontinue TAK-500.
Other nonhematologic toxicities	
All other Grade 3 nonhematologic toxicities (except for Grade ≥3 nonhematological exceptions outlined in Section 8.2)	• Hold TAK-500 until resolution to Grade ≤1 or baseline. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
All other Grade 4 nonhematologic toxicities (except for Grade ≥4 nonhematological exceptions outlined in Section 8.2)	• Permanently discontinue TAK-500.

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRS: cytokine release syndrome; D-Bil: direct bilirubin; DL: dose level; FiO_2: fraction of inspired oxygen; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; HCC: hepatocellular carcinoma; PT-INR: prothrombin international normalized ratio; T-Bil: total bilirubin; ULN: upper limit of normal.

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Table 8.c Guidelines for TAK-500 Dose Modification and/or Discontinuation for Hematologic Toxicity

Refer to the pembrolizumab prescribing information for recommended discontinuation guidelines.	
NCI CTCAE Grade	**TAK-500 Dose Modification**
Neutrophil count (ANC) decreased	
Grade 4 lasting >5 days [a]	• Hold TAK-500 until resolved to ≥1000/mm^3 or baseline, and fever/infection resolved. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Febrile neutropenia [a]	• Hold TAK-500 until resolved to ≥1500/mm^3 or baseline, and fever/infection have resolved. • Resume at 1 lower DL. • Permanently discontinue if recurrent on re-challenging.
Platelet count decreased	
Grade 3 without bleeding.	• Hold TAK-500 until resolved to ≥75,000/mm^3, then: – If spontaneously resolved in ≤7 days, resume at same DL. – If resolved in >7 days, reduce by 1 DL.
Grade 4	• Hold TAK-500 until resolved to ≥75,000/mm^3, then reduce by 1 DL. • Permanently discontinue if recurrent on re-challenging.
Platelets <10,000 cells/µL, or thrombocytopenia Grade ≥3 associated clinically significant bleeding.	• Permanently discontinue TAK-500.
Anemia	
Grade 3	• Transfuse PRBCs as clinically indicated. • Resume at 1 lower DL lower.
Grade 4	• Permanently discontinue TAK-500.

ANC: absolute neutrophil count; CxDx: Cycle x Day x; DL: dose level; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; PRBC: packed red blood cell.

[a] If observed in the DLT-evaluable period (through C1D21), the patient will be discontinued from the study. If observed after C1D21, management should proceed as in table.

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8.5.5 Criteria for Discontinuation of TAK-500

Patients who meet criteria for DLT during the first 21 days after enrollment (C1D21) will be discontinued from therapy.

In addition to the above, the following events should lead to discontinuation of TAK-500:

- Nonhematological toxicity:
  - Grade >3 nonhematological toxicities that do not meet the DLT exception criteria.
  - Grade ≥3 CRS

- Grade ≥3 infusion-related reactions or recurrent Grade 2 infusion-related reactions.
- Grade ≥3 pneumonitis or recurrent Grade 2 pneumonitis despite 1 TAK-500 dose reduction.
- Grade ≥3 creatinine increase.
- Grade ≥3 immune-mediated AEs.
- Grade ≥3 bilirubin increase.
- ALT and/or AST >10 × ULN or Child-Pugh score ≥9.
- Grade ≥2 drug-related uveitis.

- Hematological toxicity:
  - Grade 4 anemia.
  - Recurrent Grade 4 neutropenia lasting >5 days or febrile neutropenia despite 1 TAK-500 dose reduction.
  - Recurrent Grade 4 thrombocytopenia despite 1 TAK-500 dose reduction.
  - Platelets <10,000 cells/μL or thrombocytopenia Grade ≥3 associated clinically significant bleeding.

If more than 2 dose reductions for other AEs are required, or if the subsequent dose or cycle of TAK-500 is delayed for >14 or 21 days (for Q2W or Q3W administration of TAK-500, respectively) because of TAK-500–related toxicities, the patient should have study treatment discontinued. If treatment discontinuation is decided on, the EOT visit should be completed within 30 (+10) days of the last administration of TAK-500 or before the start of subsequent anticancer therapy, whichever occurs first.

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8.5.6 Criteria for Discontinuation of Pembrolizumab

Patients who discontinue TAK-500 for any reason will also discontinue pembrolizumab. Pembrolizumab will also be discontinued if any of the criteria described in the package insert have been met.

8.6 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Prophylactic use of myeloid growth factors (eg, G-CSF) is not allowed in Cycle 1 during dose escalation. Patients who experience severe (ie, Grade 4) neutropenia or febrile neutropenia in Cycle 1 of dose escalation can be managed with growth factor support, if needed, in accordance with American Society of Clinical Oncology (ASCO) guidelines and/or institutional practices. G-CSF 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.

- Any investigational agent other than TAK-500 (except for pembrolizumab in the combination arm).
- Any concurrent anticancer therapy, including but not limited to chemotherapy, immunotherapy (except for pembrolizumab in the combination arm), biologic or hormonal therapy (except for adjuvant endocrine therapy for a history of breast cancer).
- Systemic treatment with any known clinical OATP1B1 and/or OATP1B3 inhibitors including:
  - Atazanavir.
  - Clarithromycin.
  - Cyclosporine.
  - Erythromycin.
  - Gemfibrozil.
  - Lopinavir.
  - Rifampin (single dose).
  - Ritonavir.
  - Simeprevir.
  - Remdesivir.

  Note: As the above list is not exhaustive, the investigator should consult the prescribed information for any medication under consideration for use to assess if it is a potent OATP1B1 and/or OATP1B3 inhibitor. These drugs are also listed in Appendix D.
- Concomitant systemic use of corticosteroids or other immunosuppressive medication, [redacted], concurrent or within 7 days of administration of investigational drug with the following exceptions:
  - Topical, intranasal, inhaled, ocular, intra-articular, and/or other nonsystemic corticosteroids.
  - Physiological doses of replacement steroid (eg, for adrenal insufficiency), not to exceed the equivalent of 10 mg prednisone daily.
- Any live vaccines while on study.
- COVID-19 vaccinations given ±3 days of systemic study treatments. COVID-19 vaccinations outside of this time period are allowed. To the extent possible, administration of COVID-19 vaccinations should be avoided during the 21-day DLT window (up to C1D21); however, vaccination timing remains at the discretion of the investigator.

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8.7 Permitted Concomitant Medications and Procedures

All concomitant medications (defined as any medication given during the study) including prescription and over-the-counter medications, influenza vaccines, and significant nondrug therapies, such as physical therapy and blood transfusions, should be recorded in the designated electronic case report form (eCRF) from signing of the ICF through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first. This also includes recording of multivitamins or any folate/folic acid supplementation. Patients must be instructed not to take any medications, including over-the-counter medications and herbal supplements, without first consulting with the investigator.

The following medications and procedures are permitted while the patient is receiving the study drug:

- Topical, intranasal, inhaled, ocular, intra-articular, and/or other nonsystemic corticosteroids are permitted as outlined in Section 8.6.
- Physiological doses of replacement steroid (eg, for adrenal insufficiency), not to exceed the equivalent of 10 mg prednisone daily.
- Patients should be transfused with red blood cells and platelets as clinically indicated.
- Patients currently on chronic erythropoietin support for anemia may continue to receive erythropoietin.
- Concomitant treatment with bisphosphonates or denosumab will be allowed for patients with evidence of lytic destruction of bone or with osteopenia, according to the ASCO Clinical Practice guidelines or institutional practice in accordance with the product label, unless specifically contraindicated.
- Local radiation of isolated lesions for palliative intent (for example, pain control) is acceptable provided that the requirement for radiation does not represent a progression of the disease and that the radiated lesion is not a target lesion.
- For antiemetics see Section 8.9.5.
- The cautious use of medications that are known to prolong corrected QT interval (QTc) interval is permissible if the patient is taking such medications continuously at the time of enrolling in this study and as long as the patient's baseline QTcF is <450 milliseconds (men) or <475 milliseconds (women) on a 12-lead ECG. Patients may not initiate a new treatment of such medications on C1D1 until completion of the last triplicate ECG collection.
- Adjuvant endocrine therapy for a history of breast cancer.
- Supportive measures consistent with optimal patient care may be given throughout the study.

8.8 Precautions and Restrictions

Precautions and requirements for a safe TAK-500 administration are detailed in Section 8.1.

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TAK-500 was evaluated in toxicity studies in cynomolgus monkeys (Section 4.1.1.3); however, animal studies do not always predict what happens in humans. It is not known if side effects and risks observed in animals will occur in patients taking TAK-500, or if the severity of these side effects and risks will be the same, less, or greater from what was observed in animal studies.

It is not known what effects TAK-500 has on human pregnancy or development of the embryo or fetus. Female patients participating in this study should avoid becoming pregnant, breastfeeding a baby, or donating eggs for 180 days after the last dose of TAK-500. Male patients should avoid impregnating a female partner and donating sperm for 180 days after the last dose of TAK-500. Female patients of childbearing potential and male patients will be informed as to the potential risk of conception while participating in this study and will be advised that they must use effective contraception (ie, results in a low failure rate when used consistently and correctly), as specified below. A pregnancy test will be performed on each premenopausal female patient of childbearing potential at screening, on each day of TAK-500 administration, and again at treatment discontinuation during the EOT visit. A negative pregnancy test must be documented before the administration of study drug on C1D1.

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Female patients must meet one of the following:

- Postmenopausal (natural amenorrhea and not due to other medical reasons) for at least 1 year before the screening visit.
- Surgically sterile.
- If they are of childbearing potential, agree to practice the following 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time, from the time of signing of the ICF through 180 days after the last dose of study drug.

Highly Effective Methods	Other Effective Methods (Barrier Methods)
Intrauterine device Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Male condom Diaphragm with spermicide; cervical cap; sponge

- 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.)

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

- Agree to practice effective barrier contraception (eg, latex condom with a spermicidal agent) during the entire study treatment period and through 180 days after the last dose of study drug.

- 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.)

Before starting treatment, male patients should be advised to seek counseling on sperm storage, and female patients should be advised to seek counseling on egg storage, if these are desired.

It is not known whether TAK-500 passes into breast milk. Mothers should not breastfeed during the entire study treatment period and for 180 days after the last dose of study drug.

At the time of discharge from the hospital, patients and their caregivers will be educated about potential symptoms including but not limited to fever, edema, lightheadedness, dizziness, tachypnea, dyspnea, confusion, aphasia, dysphasia, ataxia, or tremor. If patients develop any of these symptoms, they should be instructed to immediately contact the principal investigator, who may recommend immediate medical attention.

As an additional safety measure, each patient will be required to carry a study information card detailing treatment site and investigator contact information, and clinical study information. This card is intended to provide relevant contact information should a patient be treated by a nonstudy health care provider or emergency medical services. It will also alert nonstudy health care providers to evaluate patients for the potential risks related to TAK-500 administration and provide them with the contact information of the treating site and/or obtain important study information relevant to the patient's care. This card will also remind patients of concerning signs or symptoms for which they should seek immediate medical attention.

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8.9 Management of Clinical Events

Evidence to support potential risks and effects is provided in Section 4.3.

There is no known antidote to TAK-500.

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 G-CSF, blood products (red blood cells and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology/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. If dose alterations are necessary because of the events detailed below, please refer to Section 8.5.

In Sections 8.9.1 to 8.9.9, guidance is provided for the management of some AEs that could be expected based on observations in nonclinical toxicology or because of the MOA of TAK-500. This guidance is not expected to replace investigator judgment in the management of AEs.

Notably, for any clinically significant Grade ≥3 AEs, referral to an appropriate subspecialist should be considered.

8.9.1 CRS

Evidence to support the potential risk of CRS is provided in Sections 4.1.2.3 and 4.3.1.1.

CRS should be graded following NCI CTCAE v5.0. Treatment guidelines are provided below; management of CRS requires close collaboration with specialists in neurology, pulmonology, cardiology, radiology, and/or critical care medicine, as necessary. Given the potential risk of CRS, the on-site pharmacy must confirm that [redacted] are on site and available should they be needed. In circumstances where [redacted] is not available, [redacted] will be considered acceptable treatment for CRS, under the condition that this is consistent with local institutional guidelines/practice and that the availability of the [redacted] is(are) confirmed with the site investigator before subject enrollment.

Investigators should differentiate CRS from other critical clinical conditions, including infusion-related reactions, sepsis, capillary leak syndrome, and hemophagocytic lympho-histiocytosis/macrophage activation syndrome. Fever is an important clinical sign that should raise the suspicion of impending CRS. If fever develops, institutional guidelines for management should be followed and patients should be frequently reassessed for signs of CRS. Strongly consider admission for close observation. For patients experiencing Grade ≥2 CRS, ECG telemetry is recommended. Echocardiogram could be obtained as clinically indicated. Early administration of IV fluids and tocilizumab is highly recommended for the management of CRS of Grade 2 or higher.

The diagnosis and management of CRS is based on clinical parameters as described in Table 8.d. Ferritin, C-reactive protein, and serum cytokine concentrations should NOT be used for clinical management decisions.

To further mitigate the risk of CRS during this study, vital signs will be measured frequently during and after infusion of TAK-500. Close monitoring of vital signs and clinical condition will continue if the patient experiences symptoms that could be consistent with CRS. During dose escalation, all patients will be hospitalized for approximately 24 (±4) hours after the first 2 doses of TAK-500 (C1D1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500). Regardless of the treatment cycle, if a Grade 2 CRS or infusion-related reaction occurs during or after administration of study drug, hospitalization is required for 24 hours after the end of the next 2 TAK-500 infusions. For patients without evidence of Grade 2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in the clinic for at least 6 hours after infusion. Patients who do not experience an infusion-related reaction or Grade 2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour. Should symptoms consistent with CRS develop, see Table 8.b for TAK-500 dose modification. In the combination arm, pembrolizumab will be held until TAK-500 is resumed.

The required hospitalization for the phase 2 dose expansion portion of the study may be decreased or removed if an adequate safety profile is demonstrated in the dose escalation phase of the study for the DL(s) and premedication regimen(s) included in expansion. If hospitalization

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is not required for dose expansion, outpatient monitoring will be required as outlined in the above paragraph.

In addition to in-patient and out-patient monitoring, patients will be asked to track oral temperature twice daily (first in the morning and last in the evening), and any time the patient feels febrile, on a patient diary throughout the first 42 days after initial dosing of TAK-500. If a patient experiences a temperature ≥100.4°F (38°C) at any time on study, they will be instructed to call the principal investigator immediately.

Table 8.d NCCN Guidelines v1.2021*: Management of CAR T-Cell–Related Toxicities

CYTOKINE RELEASE SYNDROME (CRS) [a, b]

Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the neutropenic patient. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. [c]

Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

CRS Grade	[redacted]	Additional Supportive Care
Grade 1: Fever (≥38°C)		• Empiric broad-spectrum antibiotics, consider G-CSF if neutropenic. [g] • Maintenance IV fluids for hydration. • Symptomatic management of organ toxicities.
Grade 2: Fever with hypotension not requiring vasopressors and/or hypoxia [h] requiring low-flow nasal cannula [i] or blow-by.		• IV fluid bolus as needed. • For persistent refractory hypotension after 2 fluid boluses [redacted]: start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. • Manage per Grade 3 if no improvement within 24 hours after starting [redacted]. • Symptomatic management of organ toxicities.

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Table 8.d NCCN Guidelines v1.2021*: Management of CAR T-Cell–Related Toxicities

CYTOKINE RELEASE SYNDROME (CRS) [a, b]

Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the neutropenic patient. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. [c]

Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

CRS Grade		Additional Supportive Care
Grade 3: Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[i] face mask, nonrebreather mask, or Venturi mask.	[redacted]	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring. • Supplemental oxygen. • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities.
Grade 4: Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation).		• ICU care and hemodynamic monitoring. • Mechanical ventilation as needed. • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities.

BiPAP: bilevel positive airway pressure; CAR: chimeric antigen receptor; CPAP: continuous positive airway pressure; CRRT: continuous renal replacement therapy; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony stimulating factor; HLH/MAS: hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICU: intensive care unit; [redacted]; IT: intrathecal; IV: intravenous; NA: not applicable; NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute.

All recommendations are category 2A unless otherwise indicated.

* Note that grading criteria outlined by NCCN for CRS management is different than detailed in this protocol for dose-reduction (Table 8.b) and NCI CTCAE v5.0 CRS grading.

Table 8.d NCCN Guidelines v1.2021*: Management of CAR T-Cell–Related Toxicities

CYTOKINE RELEASE SYNDROME (CRS) [a, b]

Prompt and urgent intervention to prevent progression of CRS is required; however, other causes of systemic inflammatory response should be ruled out, including infection and malignancy progression. Empiric treatment for infection is warranted in the neutropenic patient. Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading. [c]

Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

CRS Grade	[redacted]	Additional Supportive Care

[a] For HLH/MAS during CRS, treat per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and IT cytarabine for neurotoxicity.

[b] With permission from Elsevier (Lee et al. 2019).

[c] Organ toxicities should receive a thorough workup and appropriate management.

[redacted]

[g] GM-CSF is not recommended in the setting of CAR T-cell therapy.

[h] CRS grade is determined by the more severe event[redacted]

[i] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

[redacted]

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8.9.2 Pulmonary Edema

TAK-500 administration was associated with minimal to mild pulmonary edema in the GLP monkey toxicity study (see Section 4.3.1.2 for details).

To monitor for this potential side effect and minimize the clinical risk to patients, the following will occur:

- Patients will be hospitalized for at least the first 2 doses of TAK-500 or TAK-500 + pembrolizumab (C1D1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-

500), with monitoring for approximately 24 (±4) hours, allowing for close monitoring and timely management of symptoms.

- Vital signs will be collected no less frequently than every 6 hours, and additionally when clinically indicated, during hospitalization as specified in Section 8.1.1 and in the SOEs (Appendix A). Before discharge, a symptom-directed physical examination including assessment of the respiratory system will be required.
- Oxygenation should be carefully monitored and maintained as clinically indicated. Careful diagnosis and aggressive correction of pulmonary symptoms should occur quickly.
- Pulmonary imaging (eg, chest x-ray or chest CT) is recommended and investigators should have a low threshold to scan if the patient experiences any pulmonary or vascular symptoms.

As a general approach to established management of pulmonary toxicity, investigators may refer to "High dose interleukin-2 (Aldesleukin)-expert consensus on best management practices-2014" (see Table 8.e) (Dutcher et al. 2014) or local institution guidelines.

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Table 8.e Pulmonary Toxicity Clinical Management Recommendations

Considerations	Management
Tachypnea/dyspnea	**Typical Management**
Diagnose etiology and treat	Oxygen 2-4 L nasal cannula, increasing up to 35% rebreather
Hypoxic causes-Fluid overload, capillary leak, bronchospasm	Reassurance or sedative for anxiety, treat bronchospasm or acidosis if appropriate
Nonhypoxic causes	Hold TAK-500 dose if oxygen saturation <92%
Anxiety, fever, acidosis	**Variation Management**
Maintain oxygen saturation >92%-95%	Furosemide
	Bronchodilators
	Monitor bicarbonate

Investigators should differentiate pulmonary edema from other clinical conditions, including but not limited to, COVID-19 and capillary leak syndrome.

8.9.3 Skin Conditions/Rash

It is recommended that for all severity grades of cutaneous events, the diagnostic workup should include:

- Evaluation of a pertinent history and physical examination.
- Ruling out any other etiology of the skin problem (including infection, another drug side effect, a skin condition linked to another systemic disease or unrelated primary skin disorder).

- Evaluation of laboratory values, including a blood cell count, liver and kidney tests.
- Directed serologic studies if an autoimmune condition is suspected.
- Skin biopsy, consultation with dermatologist if indicated.
- Review full list of patient medications.

Further management of any noted skin toxicities should follow local management guidelines and evolving consensus guidelines for management of potentially immune-mediated skin toxicities (Brahmer et al. 2018).

8.9.4 Infusion Site Care

Lesions at the injection site, which may include inflammation or necrosis, represent a potential risk. No injection site findings were observed in nonclinical studies with TAK-500. Local institutional guidelines must be applied to stress proper administration and prevention of accidental extravasation of TAK-500. Usage of an IV port or central access is highly recommended. The IV line should be flushed as directed in the pharmacy manual at the end of each infusion accordingly to local procedures. Patients should be instructed to report any discomfort, pain, or swelling at the infusion site. Monitoring at the beginning and during the infusion for any discomfort, pain, or swelling must be ensured. If extravasation occurs, the infusion must be discontinued immediately, and supportive measures or institutional guidelines applied.

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8.9.5 Nausea and/or Vomiting

Nausea and/or vomiting is common in an oncology population; however, there is no evidence this is a risk of TAK-500.

This study will not initially use prophylactic antiemetics before the first dose of the study drug during dose escalation. However, a patient who develops nausea or vomiting will be actively managed by using optimal antiemetic treatment based on local standard practice. Additionally, antiemetics may be used prophylactically as clinically indicated after 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 uses a neuroleptic, a 5-HT3 antagonist, or an NK-1 antagonist may be added. Steroid use should be avoided unless it is a clinical necessity.

8.9.6 Fluid Deficit

Fluid deficit is common in an oncology population; however, there is no evidence this is a risk of TAK-500.

Fluid deficit should be corrected before initiation of study drug and during treatment. Patients on study should be advised to maintain adequate oral hydration.

8.9.7 Infusion-Related Reactions

Treatment and monitoring of patients until symptoms resolve should be consistent with institutional standards and guidelines, as appropriate. Infusion-related reactions should be diagnosed and managed following institutional guidelines and graded following NCI CTCAE v5.0. Table 8.b provides indications for dose modifications after an infusion-related reaction event.

The patient should be closely monitored until recovery of symptoms. Patients will be hospitalized for at least the first 2 doses of TAK-500 or TAK-500 + pembrolizumab (C1D1 and C2D1 for Q3W TAK-500; C1D1 and C1D15 for Q2W TAK-500), with monitoring for approximately 24 (±4) hours. The patient will be permanently discontinued from the study in case of a Grade 3 or 4 life-threatening reaction (except as noted in Section 8.2). All Grade 3 or 4 infusion-related reactions should be reported within 24 hours to the medical monitor and communicated as an SAE if criteria are met (see Section 10.1.3). Concomitant medications administered for infusion-related reaction treatment should be collected in the eCRF. If a patient develops signs and symptoms compatible with infusion-related reactions, and at investigator discretion, premedication can be instituted for the rest of the treatment.

Should emergency treatment be required in the event of life-threatening hypersensitivity or other acute infusion-related reaction, supportive therapy such as oxygen, bronchodilators, epinephrine, and antihistamines should be given according to local institutional guidelines. Corticosteroids should be avoided unless clinically indicated (ie, CTCAE Grade 3 or 4).

Regardless of the treatment cycle, if a Grade ≥2 CRS or infusion-related reaction occurs after the administration of study drug, hospitalization is required for 24 hours after the end of the next 2 TAK-500 infusions. For patients without evidence of Grade ≥2 CRS after 2 consecutive doses of TAK-500, subsequent administrations of TAK-500 may be performed in the outpatient setting with monitoring in the clinic for at least 6 hours after infusion. Patients who do not experience an infusion-related reaction or Grade 2 CRS after 4 consecutive administrations of TAK-500 may have their subsequent postinfusion in-clinic monitoring reduced to 1 hour.

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8.9.8 Management of Pembrolizumab Immune-Mediated AEs

Potential risks and effects of TAK-500 and pembrolizumab are listed in Section 4.3.2.

Based on nonclinical safety data for TAK-500 administered as an SA in monkeys, there is a potential for synergistic immune-related toxicity when TAK-500 is used in combination with pembrolizumab.

Pembrolizumab can cause immune-mediated reactions, as described in Section 4.3.2. Monitoring of these AEs is required through 90 days after the last dose of study drug or the start of subsequent anticancer therapy, whichever occurs first (Brahmer et al. 2018). Patients with AEs that are suspected to be related to pembrolizumab should be evaluated by appropriate methodology, including physical examinations, laboratory tests, and imaging. Dosing of pembrolizumab should be interrupted based on the guidance in Section 8.5.6. Treatment of these

AEs will be based on standard of care, local institutional guidance, the WARNINGS AND PRECAUTIONS section of the package insert, and the proper use guidance of pembrolizumab.

8.9.9 Management of COVID-19–Positive Patients

A consensus plan of action has been developed for the management of patients within the context of the COVID-19 pandemic. During the screening period, a patient who exhibits symptoms consistent with COVID-19 (eg, fever, shortness of breath, sore throat) will undergo COVID-19 testing per institutional guidelines. A patient with a negative test result will undergo further diagnostic work-up and management at the discretion of the site investigator. If a patient tests positive for COVID-19 during the screening period, enrollment should be paused during which time the investigator, in consultation with the sponsor, will determine the appropriate course of action for that patient. For patients with symptoms and/or requiring treatment, symptoms should have resolved to baseline, and treatment should be completed at least 7 days before enrollment. (A negative test result for severe acute respiratory syndrome coronavirus-2 [SARS CoV-2] by polymerase chain reaction (PCR) may also be documented, if required by local institutional guidelines.) Asymptomatic patients who test positive should wait at least 7 days from the positive test result to ensure they continue to remain asymptomatic before enrolling.

While on study treatment, a patient who exhibits symptoms consistent with COVID-19 (eg, fever, shortness of breath, sore throat) will undergo COVID-19 testing per institutional guidelines, in addition to a work-up for pulmonary toxicity related to the study intervention. A patient with a negative test result will undergo further diagnostic work-up and management at the discretion of the site investigator. If a patient tests positive for COVID-19 while on study, treatment should be withheld (up to 21 days), during which time the sponsor and investigator will determine the appropriate course of action for that patient.

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Suggested guidance is as follows:

- For patients with symptoms and/or requiring treatment, symptoms should have resolved to baseline and treatment should be completed at least 7 days before resuming study drug(s) (a negative test result for SARS-CoV-2 by PCR may also be documented if required by local institutional guidelines).
- Asymptomatic patients who test positive should wait at least 7 days from the positive test result to ensure they continue to remain asymptomatic before resuming study drug(s).

8.9.10 CV Toxicity

Evidence to support potential risks and effects is provided in Section 4.3.

Patients with medically managed hypertension should continue their antihypertensive medication before the administration of TAK-500 or TAK-500 + pembrolizumab. To monitor for potential CV toxicity, including transient hypertension of ≥160/100 mm Hg, patients will be hospitalized for monitoring after at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Vital signs will be measured

at least every 6 hours during hospitalization. Therapies that are required to manage CV toxicity are allowed based on standard clinical practice. Investigators should differentiate CRS/rigor-associated transient hypertension from other clinical conditions.

In all cases, consultation with the medical monitor should also be considered.

8.10 Blinding and Unblinding

This is an open-label study.

8.11 Description of Investigational Agents

8.11.1 TAK-500

TAK-500 drug product is provided as a sterile, frozen, liquid formulation contained in a single-use 10 mL glass vial with an aluminum seal with a plastic flip off cap. Each vial nominally contains 6 mg/3 mL of TAK-500. The excipients are listed in Table 8.f.

Table 8.f TAK-500 Drug Product Excipients

Excipient	Function
TAK-500 (Takeda)	Active ingredient
L-histidine (USP, Ph Eur, BP, JP)	Buffer
L-histidine monohydrochloride (Ph Eur, JP)	Buffer
L-arginine hydrochloride (USP, Ph Eur, BP, JP)	Stabilizer and tonicity agent
Polysorbate 80 (NF, JP, Ph Eur)	Stabilizer
Water for injection (USP, Ph Eur)	Solvent

BP: British Pharmacopoeia; JP: Japanese Pharmacopeia; NF: National Formulary; Ph Eur: European Pharmacopeia; USP: United States Pharmacopeia.

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Solution stabilizer (Polysorbate 80 IV) is composed of a sterile, aqueous solution consisting of excipients (L-histidine, L-arginine monohydrochloride) and polysorbate 80, all of which are also present in the TAK-500 drug product formulation. Solution stabilizer is supplied as 10 mL of solution filled into a single-use 20 R Type I glass vial. Solution stabilizer will be provided by the sponsor.

For dose preparation, solution stabilizer is added to diluent to obtain consistent levels of formulation excipients in the final dosing solution. TAK-500 drug product is then added to the diluent containing solution stabilizer. Specific dilution procedures are described in detail in the pharmacy manual.

For additional information, please refer to the pharmacy manual.

8.11.2 Pembrolizumab

Pembrolizumab will be sourced locally by sites whenever possible. Please refer to the most recent prescribing information for guidance on preparation, reconstitution, and administration instructions.

8.12 Preparation, Reconstitution, and Dispensation

8.12.1 TAK-500

Please refer to the pharmacy manual for preparation, reconstitution, and administration instructions.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

TAK-500 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-500.

Study drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

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8.12.2 Pembrolizumab

Please refer to the most recent pembrolizumab prescribing information as applicable to the specific country and the pharmacy manual for preparation, reconstitution, and administration instructions.

8.13 Packaging and Labeling

8.13.1 TAK-500

The TAK-500 drug product is provided in sterile, 10 mL, colorless, Type I borosilicate glass vials with a chloro-butyl rubber stopper and an aluminum seal with a plastic flip off cap. The TAK-500 drug product is provided as a sterile, frozen, liquid formulation contained in a single-use vial; each vial nominally contains 6.0 mg/3 mL of TAK-500 drug product.

The TAK-500 drug product will be labeled as investigational drug product. All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.13.2 Pembrolizumab

Pembrolizumab, if provided by sponsor, will be labeled as investigational drug product. All label information will fulfill requirements specified by local governing regulations. Additional details are provided in the pharmacy manual.

8.14 Storage, Handling, and Accountability

8.14.1 TAK-500

TAK-500 must be stored in a secure, limited-access location, according to conditions specified on the drug label and in the pharmacy manual. The investigator or designee must confirm that appropriate temperature conditions have been maintained and that any excursions are reported and resolved before use. Refer to the pharmacy manual for additional details.

Complete receipt, inventory, accountability, reconciliation, and destruction records will be maintained by authorized personnel at the study site for all used and unused study drug vials. A drug dispensing log, including records of drug received from the sponsor and drug dispensed to patients will be provided and kept at the study site. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for study drug accountability, return, and destruction. Instructions are provided in the pharmacy manual.

8.14.2 Pembrolizumab

Pembrolizumab must be stored in a secure, limited-access location, according to conditions specified on the drug label. The investigator or designee must confirm that appropriate temperature conditions have been maintained and that any excursions are reported and resolved before use. Refer to the pharmacy manual and the most recent pembrolizumab prescribing information as applicable to the specific country for additional details.

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8.15 Other Protocol-Specified Materials

Information on supplies required by the site for drug administration is provided in the pharmacy manual. Clinical supplies other than study drug to be provided by the sponsor or designee are specified in the study manual.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator, and other vendors participating in the study can be found in the study manual.

For 24-hour contact information, please refer to the study manual or equivalent.

9.2 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.

9.3 Treatment Group Assignments

The dose escalation and expansion phases of this study will not be randomized. Details for initiation of the SA and combination arms are described in Section 6.1. When TAK-500 SA and combination arms are both open to enrollment, patient assignment to a specific arm will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

Sites will be notified in advance when a different dosing frequency may be explored (eg, TAK-500 Q3W 21-day cycle vs TAK-500 Q3W 42-day cycle vs TAK-500 Q2W 42-day cycle dosing) or if certain tumor types are needed to complete an expansion cohort.

9.4 Study Procedures

Refer to the SOEs (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections below. Evaluations during the screening period are to be conducted within 28 days before administration of the first dose of the study drug. Unless otherwise noted, evaluations during the treatment period must occur before 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 SOEs (Appendix A).

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9.4.1 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.

9.4.2 Patient Demographics

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

9.4.3 Medical History

During the screening period, a complete medical history, including smoking/vaping history, will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it and the best response achieved by each one.

Available tumor genomic information obtained at the site will be collected.

9.4.4 Physical Examination

Physical examinations will be completed per standard of care at the times specified in the SOEs (Appendix A).

At screening, complete physical examinations will include an assessment of the following: height, skin, head, eyes, ears, nose, throat, respiratory system, CV system, gastrointestinal system, neurological condition, blood and lymphatic systems, and musculoskeletal system.

Symptom-directed physical examination will be conducted on Day 1 and as specified in the SOE (Appendix A) of each cycle before administration of the first dose of study treatment and any other time point during the 21- or 42-day cycle based on clinical need. This physical examination should include assessment of the respiratory system as well as evaluation of weight, and edema. Pulse oximetry will be required per Section 9.4.6.2. Evaluation of neurologic condition will also be performed on these days.

Safety follow-up call should be made with the patient as indicated in the SOEs to evaluate for overall AEs and general wellbeing.

9.4.5 ECOG Performance Status

Performance status is to be assessed using the ECOG scale (see Appendix G for a description of the scale) at the times specified in the SOEs (Appendix A).

9.4.6 Vital Signs

Vital sign measurements, including diastolic and systolic blood pressure while sitting (after approximately 5 minutes in this position), heart rate, respiratory rate, oxygen saturation, and temperature, as well as height and weight, will be assessed as specified in the SOEs (Appendix A).

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For administrations of TAK-500, vital signs will be measured immediately before the start of the infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vitals will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Vital signs should be measured and recorded at any time if the patient develops symptoms associated with potential risks of TAK-500 and/or pembrolizumab. The frequency and timing of vital sign monitoring may be modified based on emerging data and agreement between sponsor and investigators.

Vital signs should be measured and recorded any time the patient develops symptoms associated with potential risks of TAK-500 and/or pembrolizumab.

9.4.6.1 Patient Diary

Patients will be given a diary on which they will record oral temperature twice daily (first in the morning and last in the evening), and any time the patient feels febrile during the first 42 days of treatment (Cycles 1 and 2 for 21-day cycle and Cycle 1 for 42-day cycle), as specified in the SOEs (Appendix A). The diary should be brought to the site at each visit during this period and reviewed by study staff. If patients experience a temperature ≥100.4°F (38°C) at any time on study, they will be instructed to call the principal investigator. Sites will report clinically significant fever as AEs according to NCI CTCAE 5.0 guidelines, if clinically applicable.

9.4.6.2 Pulse Oximetry

Pulse oximetry should be obtained before each dose of TAK-500 and at any time a patient has any new or worsening respiratory symptoms – the requirement for subsequent dosing is based on O_2 saturation while at rest. A reading at rest and on exertion if clinically indicated should be obtained (O_2 saturation with exertion is not required to be >92%). Whether to measure O_2 saturation with exertion, should be based on the judgment of the investigator, but should remain consistent for each individual patient throughout the study. If O_2 saturation is measured with exertion, it is meant to (a) ensure that the patient is safe to treat and (b) monitor recovery of pulmonary status if decompensation occurred while on study. Instances where measuring O_2 saturation with exertion might be desirable include:

- Known underlying lung disease (ie, patients that potentially meet criteria described in exclusion criterion #8).
- Recent acute pulmonary injury (eg, from infection, aspiration, thrombosis).
- Patients who enrolled in the study without the need for supplemental O_2, but who subsequently had pulmonary decompensation and now require intermittent O_2 with exertion (monitoring for continued recovery).

If the patient's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a patient shows changes in pulse oximetry or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary AEs, the patient should be immediately evaluated to rule out pulmonary toxicity.

9.4.6.3 [redacted]

[redacted]

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9.4.7 Pregnancy Test

A serum choriogonadotropin beta pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. Women who are not of childbearing potential, surgically sterile, or postmenopausal (defined as amenorrhea for at least 12 months) and men do not need to have the test performed. The results must be negative within

4 days before the first dose of TAK-500 is administered (ie, within the 4 days before C1D1), or as otherwise required by local regulations.

Additional pregnancy testing (serum or urine; urine preferred) should be performed before each dose of TAK-500 and at EOT, as scheduled in Appendix A, and may be performed during the study at the discretion of the investigator, on request of an independent ethics committee (IEC)/institutional review board (IRB), or if required by local regulations.

9.4.8 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF from the time of informed consent signature through 30 days after the last dose of study drug or the start of subsequent systemic antineoplastic therapy, whichever occurs first. See Sections 8.6 and 8.7 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.9 AEs

Monitoring of all AEs, including SAEs, will be collected throughout the study as specified in the SOEs (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.4.10 Enrollment

Enrollment is defined as the time of initiation of the first dose of study drug. Procedures for completing enrollment information are described in the study manual.

9.4.11 Cardiac Monitoring

9.4.11.1 Safety 12-Lead ECGs and LVEF

The 12-lead standard safety ECGs will be performed to assess eligibility and throughout the study as specified in the SOEs (Appendix A). Safety ECGs will be compared with baseline screening ECGs. ECG assessments are to be performed with the patient supine and rested for 5 minutes. A qualified person will interpret the ECGs locally. When safety ECG collection times coincide with the collection times for triplicate ECGs, the triplicate ECGs may also be used by investigators on site for evaluation of safety. An additional safety ECG will not need to be performed in this setting. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. When the timing of ECG or vital signs measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling. The frequency and timing of ECG collection for safety may be modified based on emerging data and agreement between sponsor and investigators.

The assessment of LVEF measured by echocardiography or MUGA will be performed at screening and as clinically indicated. Any findings from LVEF determinations will be captured

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as AEs if, in the opinion of the investigator, there has been a clinically significant change from baseline.

9.4.11.2 Triplicate ECGs (With PK Sampling)

Triplicate 12-lead ECG recordings matched with PK sampling are required at time points specified in the SOEs (Appendix A) for a preliminary assessment of TAK-500 on QTc. The triplicate ECG will be stored and centrally read. Triplicate ECGs will be collected before PK sample collection. Triplicate 12-lead ECG measurements are performed using standard ECG equipment. Patients are required to be in supine position for 15 minutes, which is the ECG collection window (ie, at least 5 minutes before and up to 10 minutes during the 3 ECG collections for each planned time point). After the patient has been in supine position for at least 5 minutes, each triplicate ECG is to be collected on the ECG equipment. The actual time of triplicate ECG collections for each timepoint will be recorded on the eCRF.

When safety ECG collection times coincide with the collection times for triplicate ECGs, the triplicate ECGs may also be used by investigators on site for evaluation of safety. In these cases, the exact date/time and ECG parameters for the safety ECG reading should be recorded by the site in the clinical database. Meal consumption is known to alter ECG readings. For this reason, on Day 1 patients will abstain from eating food or having anything to drink except water from a minimum of 2 hours before the collection of the predose ECGs until after collection of the EOI triplicate ECGs. A low calorie and low sodium light meal is permitted immediately after the postinfusion ECG has been collected. Similarly, light meals are permissible immediately after collection of a scheduled triplicate ECG and approximately 1 hour before the next scheduled triplicate ECG collection time point.

When the timing of ECG or vital signs measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling.

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9.4.12 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the study manual.

During the COVID-19 public health emergency, if a study participant cannot access a clinical study site for unscheduled bloodwork collection as requested by the investigator, alternative Clinical Laboratory Improvement Amendments-certified sites may be used for laboratory tests that focus on the safety of study participants. Every effort should be made by the treating site to ensure laboratory normal ranges are collected from any such alternative locations.

Troponin I will be measured at screening and repeated on study if clinically indicated.

9.4.12.1 Clinical Chemistry, Hematology, Tumor Markers, Coagulation, and Thyroid Function

Blood samples for analysis of the clinical chemistry, hematology, coagulation, and thyroid function shown in Table 9.a will be obtained as specified in the SOEs (Appendix A).

Table 9.a Clinical Chemistry, Hematology, Tumor Markers, Coagulation, and Thyroid Function Tests

Hematology	**Serum Chemistry**	
Hematocrit	Protein (total)	Magnesium
Hemoglobin	Albumin	Phosphate
Leukocytes with differential	ALP	Potassium
Neutrophils (ANC)	ALT	Sodium
Platelets (count)	AST	Chloride
Erythrocytes (RBC)	Bilirubin (total)	Urate
MCH	Glucose (fasting not required)	
MCV	Lactate dehydrogenase	
MCHC	Calcium	
	Bicarbonate (if available as a part of blood chemistry panel of local laboratory)	
	C-reactive protein	
	Blood urea nitrogen	
	Creatinine	
Thyroid Function	**Coagulation**	
Thyrotropin	aPTT	
Thyroxine, free	PT or prothrombin international normalized ratio	
Tumor Markers	**Other**	
AFP (HCC)	Ferritin	
CA 27.29 (TNBC)	Creatine kinase	
	IL-6	
CA 19-9 (pancreatic adenocarcinoma)	Troponin I	
	HbA1c	

ANC: absolute neutrophil count; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; aPTT: activated partial thromboplastin time; HbA1c: glycosylated hemoglobin; HCC: hepatocellular carcinoma; IL-6: interleukin 6; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; RBC: red blood cell; TNBC: triple-negative breast cancer.

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If creatinine clearance is to be estimated, the Cockcroft-Gault formula (see Appendix H) will be used as follows:

> Estimated creatinine clearance = [(140 - age [years]) × (weight [kg])] / (72 × serum creatinine [mg/dL]).

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.13 Disease Assessment

For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of subsequent anticancer therapies). Tumor assessments for all patients should continue per protocol (scheduled from C1D1) even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. If a patient discontinues treatment for a reason other than documented PD, imaging is required at EOT if: (1) it has been more than 4 weeks since the most recent imaging, for patients within the first 6 months of treatment, or (2) it has been more than 6 weeks since the most recent imaging, for patients on study more than 6 months. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status, using RECIST v1.1 criteria.

For this study, CT and/or MRI scans should be acquired. CT scans of the chest, abdominal cavity, and pelvis will be obtained at screening. For patients with HNSCC or known cervical disease, a CT and/or MRI neck should also be obtained. The imaging modalities used for a patient should remain consistent throughout the study. If IV contrast is not available or contrast-enhanced CT scans are contraindicated for a particular patient, a noncontrast CT of the chest, in addition to contrast-enhanced abdomen and pelvis by MRI should be acquired, if possible. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation. In addition, nonmeasurable disease and new lesions will be documented and their statuses evaluated. X-rays and bone scans should be collected as clinically indicated. Deidentified copies of all imaging scans (including those from screening and any unscheduled scans) will be collected and transferred to the sponsor or designee (eg, central imaging vendor/imaging contract research organization) for storage. Determination of disease status will be based on local investigator assessment.

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9.4.13.1 RECIST v1.1 and Treatment Beyond Progression

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

- Measurable tumor size reduction may take longer treatment duration with immunotherapy than with a cytotoxic regimen.

- Response to immunotherapy may occur after appearance of PD, as assessed per conventional RECIST v1.1 (see Appendix I). In particular, small, new lesions may appear in the presence of other responsive target lesions (pseudo-progression).
- Durable SD may represent antitumor activity of immunotherapy.

Therefore, modifications to RECIST v1.1 will be implemented in this study as described below.

Accumulating data indicate it is possible that some patients treated with immunotherapy may derive clinical benefit beyond initial RECIST-defined PD. The protocol therefore accommodates an option to keep patients on treatment beyond such initial progression if specific criteria are met. Accordingly, patients treated with TAK-500 as an SA or in combination with pembrolizumab will be permitted to continue treatment beyond initial RECIST v1.1–defined PD if the following criteria are met:

- Investigator-assessed overall clinical benefit from continued treatment with pembrolizumab and/or TAK-500. The assessment of clinical benefit should consider whether the patient is clinically deteriorating and unlikely to receive further benefit from continued treatment.
- Tolerance of study drug(s).
- Stable performance status.
- Treatment beyond apparent progression will not delay an imminent intervention to prevent serious complications of PD (eg, CNS metastases).
- Patient-provided written informed consent describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

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The decision to continue treatment beyond initial RECIST v1.1–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 SOEs. Treatment should be discontinued permanently on documentation of further PD. If the patient experiences rapid clinical deterioration as perceived by the investigator before radiographic assessment within 6 weeks of original PD, the investigator can discontinue the study treatment without objective evidence of disease progression and report it as "symptomatic deterioration".

Patients who continue study therapy beyond initial RECIST v1.1–defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

9.4.14 Biomarker, Pharmacodynamics, and PK Samples

9.4.14.1 Primary Specimen Collection

Blood samples will be collected via venipuncture or indwelling catheter at the time points detailed in Appendix A for plasma concentration measurements of TAK-500 and biomarker assessments (except for tumor biopsy). These samples must be collected on their own dedicated

line, separate from the TAK-500/pembrolizumab administration line. The primary specimen collection is presented in Table 9.b.

If necessary, serum samples collected for PK assessments may also be used for exploration of pharmacodynamic biomarkers. These serum PK samples may only be used for this purpose after the final PK analysis has been completed.

Details on sample handling, storage, shipment, and analysis are provided in the laboratory manual.

Table 9.b [redacted]

[redacted]

9.4.14.2 Tumor Biopsies

9.4.14.2.1 [redacted]

[redacted].

9.4.14.2.2 [redacted]

[redacted].

9.4.15 PK Measurements

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual. Samples for PK will be collected at the time points specified in Appendix A. Serum samples should be collected from the contralateral arm (not the arm which was used for drug infusion).

The timing but not the total number of PK samples may be modified during the study based on emerging PK data if a change in sampling scheme is considered necessary to better characterize the PK of TAK-500, total antibody, and deconjugated TAK-676. A protocol amendment is not necessary for such modifications.

9.4.16 Biomarker and Pharmacodynamic Measurements

In this study, several biomarkers and pharmacodynamic measurements will be assessed to test for correlation with safety, PK, and, if possible, with antitumor activity. These biomarkers will be used to identify potential pharmacodynamic activity and patients who have a higher probability of response or of adverse reactions to TAK-500, including assessment of response or resistance to treatment that may emerge from this trial or future nonclinical or clinical trials. The biomarker sample analyses will be performed if or when required. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot be anticipated.

The biomarker and pharmacodynamic specimen collection time points are displayed in Appendix A. Details regarding the preparation, handling, and shipping of samples are provided in the laboratory manual.

The following biomarker and pharmacodynamic measures will be collected and may be tested.

9.4.16.1 [redacted]

[redacted].

9.4.16.2 [redacted]

[redacted].

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9.4.16.3 [redacted]

[redacted].

9.4.16.4 [redacted]

[redacted].

9.4.16.5 [redacted]

[redacted].

9.4.16.6 [redacted]

[redacted].

9.4.16.7 [redacted]

[redacted].

9.4.16.8 [redacted]

[redacted].

9.4.17 DNA Analyses

[redacted].

The data resulting from such analyses, if performed, may be pooled with similar data from other TAK-500 and TAK-676 clinical studies for eventual population PK analysis purposes and as such will be reported separately and not within the clinical study report for this study. This sample may be collected during the study if the sample cannot be collected at screening.

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9.4.18 Immunogenicity Sample Collection

Serum samples for the assessment of ADA will be collected at time points specified in the SOEs. Samples must be collected before study drug is administered on a dosing day, and optionally at unscheduled visits for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample will be assessed for neutralizing ADA if a positive ADA is detected. A final sample will be collected at EOT visit.

9.4.19 Collection, Storage, and Future Use of Biological Samples From Clinical Trial Subjects

The blood samples for standard clinical tests and PK analysis will be consumed or destroyed at or before the end of the study when all the test data have been analyzed. The archival tissue, biopsy tissue, and blood samples collected for the biomarker research part of this study will be assessed or stored by the sponsor with its long-term storage partners for up to 15 years from the end of the study; after that time, the samples will be destroyed. These leftover samples may be used for future research, which may be about diseases, conditions, or drugs that may not be included in this study, and the efficacy, design, and methods of future studies. These leftover samples may also be shared with researchers collaborating with the sponsor.

9.4.20 [redacted]

[redacted]

9.4.20.1 [redacted]

[redacted]

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9.4.20.2 [redacted]

[redacted]

9.4.20.3 [redacted]

[redacted]

[redacted]

[redacted]

9.4.20.4 [redacted]

[redacted]

[redacted]

[redacted]

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9.5 Documentation of Patient Screen Failures

Investigators must account for all patients who sign informed consent.

If the patient is found to be not eligible before the first dose, the investigator should complete the applicable eCRF.

The primary reason for patient screen failure is recorded in the eCRF using the following categories:

- Pretreatment event.
- Failed inclusion criteria or did meet exclusion criteria.
- Protocol deviation.
- Lost to follow-up.
- Withdrawal of consent by patient.
- Study terminated by sponsor.

Patient identification codes assigned to patients who fail screening should not be reused. Patients may be allowed to rescreen within 28 days of initial screening following discussion between investigator and sponsor.

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9.6 Completion of Study Treatment (EOT for Individual Patients), 90-Day Safety Check, and Crossover Option

Patients will be considered to have completed study treatment if they discontinue TAK-500 for any of the reasons outlined in Section 9.7. If the patient discontinues TAK-500 they will be required to discontinue all study treatment.

All patients will have a 90-day (±3 days) safety check after receiving last dose of TAK-500. This may occur by phone or in the clinic, at the investigator's discretion, and this contact will focus on any treatment-related immune-mediated AEs. If performed over the phone, only AE reporting is required. If patients have started on subsequent anticancer or radiation therapy during the interval, this will also be documented.

For patients who discontinue study treatment for reasons other than disease progression, they will continue to have imaging according to the following schedule: every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter, until PD or the start of alternative therapy. Date of disease progression and subsequent anticancer therapies will be documented.

In the setting of disease progression while on TAK-500 SA, crossover to the TAK-500 with pembrolizumab combination arm is optional and at the discretion of the investigator, in agreement with the sponsor. Patients in the TAK-500 SA treatment arm with objective evidence of PD may cross over to the TAK-500 and pembrolizumab combination arm into the last DL that is or was accruing patients. Crossover treatment should begin within 28 days of documented

disease progression and after the EOT visit; additionally, it is recommended that the first pembrolizumab dose be administered on a regularly scheduled TAK-500 dosing day. Crossover patients will proceed to a second EOT visit within 30 days of last TAK-500 dose after the combination treatment.

9.7 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 the first 21 days after enrollment (C1D21).
- Protocol deviation (after discussion with sponsor).
- PD (tumor progression documented as assessed per RECIST v1.1): As noted previously, patients who meet the criteria for PD per RECIST v1.1 may continue to stay on study if they are clinically benefiting (see Section 9.4.13). In these patients, treatment discontinuation should occur when a subsequent scan confirms the initial PD, unless there are earlier clear signs of rapid clinical progression (clinical progression is defined as no imaging test performed to assess tumor status, but the investigator considers that patient declining is caused by tumor progression).
- Symptomatic deterioration (the patient presents a decline in health that recommends terminating treatment, and tumor imaging is performed and does not qualify for PD).
- Initiation of another systemic anticancer treatment.
- Pregnancy (patient must be discontinued).
- Study terminated by sponsor.
- Withdrawal of consent by patient.
- Lost to follow-up.
- Other (after discussion with sponsor).

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Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOEs (Appendix A) 30 days (+7 days) after last dose, or before initiation of any subsequent treatment (if applicable). If a patient is not able to return for the EOT visit, the EOT assessments may be performed at the time of treatment discontinuation. The primary reason for study drug discontinuation will be recorded on the eCRF.

Patients are also to be contacted for a safety check 90 days after the last dose.

During the dose escalation phase, patients not receiving all required doses in the first 21 days after initiation of TAK-500 for reasons other than DLT (eg, informed consent withdrawn) may be replaced.

In the case of study termination by the sponsor, eligible patients may have continued poststudy access to TAK-500 as described in Section 6.3.5.

9.8 Posttreatment Follow-up Assessments

Some patients may discontinue study drug for reasons other than PD; these patients will remain in the study for follow-up and will be followed every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter with imaging until PD or the start of alternative therapies. Date of disease progression based on available local data, and subsequent anticancer therapies will be collected during this follow-up period. The EOS eCRF is to be completed when the patient discontinues from the follow-up period.

NOTE: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths or SAEs that the investigator considers related to study drug that occur during posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

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9.9 Completion of Study (for Individual Patients)

Patients will be considered to have completed the study if they discontinue study drug for any of the reasons outlined in Section 9.7, including PD, and have also completed the following:

- EOT visit.
- Day 90 (±3 days) safety follow-up (visit or telephonic call).
- For patients without PD at time of discontinuation of therapy:
  - Follow-up imaging as outlined in Section 9.8 to continue until PD or initiation of subsequent anticancer therapy, and
  - Documentation of PD or initiation of subsequent anticancer therapy.

In the dose expansion phase of the study, patients will be considered to have completed the study when they complete an EOT visit and posttreatment follow-up (including OS), as applicable, or discontinue from the study for any of the reasons outlined in Section 9.7.

9.10 Withdrawal of Patients From Study/Early Termination or EOS

All patients will have an EOS form completed. A patient may end study participation for any of the following reasons:

- Completed study (as defined in Section 9.9).
- Death.
- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.

- Study closed and patient continuing with treatment in poststudy access (see Section 6.3.5).
- 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.

9.11 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.

Tests and procedures should be performed on schedule; however, unless otherwise specified, occasional changes are allowable within a 3-day window for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor. Allowable windows on dosing days are described in Section 8.1.

A maximum of 1 TAK-500 dose can be skipped, otherwise TAK-500 must be permanently discontinued. A patient can have up to 2 DL reductions of TAK-500 as an SA or in combination due to AEs but further reductions are not permitted (the patient should discontinue study drug in this case).

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10.0 AEs

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient 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.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient 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.

All abnormal laboratory values will be reviewed by the investigator but only those abnormal values that lead to discontinuation or delay in treatment, dose modification, therapeutic

intervention, or are considered by the investigator to be a clinically significant change from baseline will be assessed as AEs.

10.1.3 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 10.2 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, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one 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.

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In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE v5.0. 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/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Special Situation Report Definition

A special situation report (SSR) is defined as any of the following events:

- Abuse: persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful or physical or psychological effects.
- Misuse: situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or within the legal status of its supply.
- Medication Error: an unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor quality administration) of a medicinal product while in the control of health care provider, patient, or consumer, which leads to harm or has the potential to lead to harm.
- Overdose: the administration of a quantity of medicinal product given per administration or per day, which is above the maximal dose according to the protocol.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient 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 10.3 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 a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If faxing a paper-based SAE form, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Fax Numbers:

- US and Canada: + 1-800-963-6290.
- Rest of World: + 1-202-315-3560.

Email submission of SAE forms with a PDF attachment should only be used in the case where fax is not possible, and EDC is not feasible within 24 hours of receiving the event. If using email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

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Email Address:

- PVsafetyoncologyAmer@takeda.com.

If SAEs are reported via fax or by email, EDC/Rave must be updated as soon as possible with the appropriate information.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

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

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug and/or the AxMP administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE v5.0. The criteria are provided in the study manual.

Relationship of the event to study drug and/or the AxMP administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug/s and/or the AxMP?

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10.2.1 Recording and Reporting AEs and SAEs Related to AxMPs

The use of AxMPs is required in this study for both the prevention (premedication before TAK-500 dosing; Section 6.1.1) and acute management of CRS (Section 8.9.1, and Table 8.d) (Lee et al. 2019). The causality for all AEs must be assessed against the AxMPs. Any SAE deemed related to AxMP will follow the SAE reporting procedures described in Section 10.2. All non-serious AEs assessed as related to the authorized AxMP should be reported to the sponsor within 7 days by transmitting an EDC report. If transmission of the EDC report is not feasible, a paper AE/SAE report form must be sent.

10.3 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 the time of signing of the informed consent through 30 days after the administration of the last dose of study drug(s) (eg, EOT) or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRFs.

- AEs ongoing at EOT should be monitored until they are resolved, return to baseline, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), the start of 2L alternative therapy, or 6 months after PD has occurred, whichever comes first.
- AEs that the investigator considers to be immune-mediated will be reported from the time of initiation of study drug(s) through 90 days after the administration of the last dose of study drug(s) or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRFs.
- SAEs and AxMP-related AEs and SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of signing of informed consent through last study visit or before initiation of new anticancer therapy (whichever comes first) and recorded in the eCRF.
- SAEs will be monitored until they have resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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10.4 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 must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. 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 sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Pregnancies are to be reported through 180 days after the last dose of study drug.

10.5 Procedures for Reporting Product Complaints or SSRs

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 report this via the phone numbers or email addresses provided in the study manual.

SSRs (see Section 10.1.4) are defined as medication errors and uses outside what is foreseen in the protocol, including overdose, misuse, and abuse of the product. SSRs may or may not be associated with an AE/SAE. SSRs must be reported to Takeda Global Patient Safety Evaluation, using a paper SSR form, within 7 calendar days of awareness via the contact information provided in the study manual. If a SSR is associated with an SAE, the SAE must be reported to Takeda Global Patient Safety Evaluation within 24 hours of awareness.

Product complaints and SSRs in and of themselves are not AEs. If a product complaint or a SSR results in an SAE, the SAE should be reported.

For product complaints related to pembrolizumab sourced locally by the clinical site, use standard methods to contact product manufacturer or regulatory agency per standard site process.

10.6 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, investigators, and IRBs and 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 expedited reports within 7 days for fatal and life-threatening events and within 15 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.

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11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Data Monitoring Committee

For phase 2 dose expansion only:

An independent data monitoring committee (IDMC) will review safety data and the interim analysis data for futility as detailed in the IDMC charter. The charter of the IDMC will specify that this committee is charged with providing periodic reports to the sponsor that contain recommendations that include, but are not limited to, (a) continuation of the study, (b) continuation with modification, and (c) termination of the study.

12.0 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, 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.

12.1 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, contract

research organization 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 designee) 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 the 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 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.

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12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 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 copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or 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 for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan 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.

13.1.1 Analysis Sets

The analysis sets will include the following:

- **Safety analysis set:** Patients who have received at least 1 dose, even if incomplete, of study drug will be used for all safety analyses and for some antitumor activity analyses.
- **PK analysis set:** Patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.
- **DLT-evaluable analysis set:** The DLT-evaluable analysis set will include patients who receive all required doses of TAK-500 with or without pembrolizumab and remain on study for 21 days from first dosing of TAK-500 (through C1D21) without experiencing a DLT or who have a DLT during the first 21 days after study drug administration. The DLT-evaluable population in the TAK-500 SA and the TAK-500 + pembrolizumab combination dose escalation cohorts will be used to determine the MTD (specific premedication regimens to be evaluated separately).
- **Response-evaluable analysis set:** The response-evaluable analysis set, a subset of the safety analysis set including patients with measurable disease at baseline and at least 1 posttreatment evaluation, will be used for analyses of response.
- **Peripheral pharmacodynamic analysis set:** The peripheral pharmacodynamic analysis set will include those patients from the safety population who have been on study for at least 1 week and have baseline and at least 1 postbaseline peripheral sample assessment.
- **Tumor biopsy analysis set:** The tumor biopsy analysis set will include those patients from the safety population who have baseline and at least 1 postbaseline tumor biopsy sample assessments.
- **Immunogenicity analysis set:** The immunogenicity analysis set consists of patients who receive at least 1 dose of TAK-500 and have an ADA status assessment at baseline, and at least 1 postbaseline sample.

Patients in the SA arm who cross over to the combination arm will be analyzed separately using all the post-crossover data, repeating the main analyses as appropriate, to show long-term safety and antitumor activity. As described in Section 8.5.2, these crossover patients will still be included in the main analyses, in which their post-crossover data will be excluded.

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Patients treated with a specific premedication regimen will be analyzed separately from cohorts treated without premedication or with other premedication regimens.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.

Baseline values for patients who cross over from the SA arm to the combination arm are defined as the last valid value before exposure to the combination drug.

13.1.3 Efficacy Analysis

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For the dose escalation phase, antitumor activity is not the primary endpoint; secondary antitumor activity endpoints include ORR, DCR, DOR, and TTR. In the dose expansion phase, ORR is the primary endpoint; secondary antitumor activity endpoints include DCR, DOR, TTR, PFS, and OS. No formal statistical tests will be performed for these efficacy endpoints in the study.

ORR is defined as the proportion of patients who achieve cPR or cCR (determined by the investigator) during the study in the response-evaluable analysis set.

DCR is defined as the proportion of patients who achieve SD or better (determined by the investigator) >6 weeks during the study in the response-evaluable analysis set.

DOR is defined as the time from the date of first documentation of a cPR or better to the date of first documentation of PD or death for responders (cPR or better) in the response-evaluable analysis set. Responders without documentation of PD will be censored at the date of last response assessment that is SD or better.

TTR is defined as the time from the date of first dose administration to the date of first documented cPR or better (determined by the investigator) in the response-evaluable analysis set.

PFS is defined as the time from date of study treatment to the first documented disease progression based on RECIST v1.1, or death due to any cause, whichever occurs first, in the safety analysis set.

OS is defined as the time from the date of first dose administration to the date of death.

ORR and DCR will be summarized using descriptive statistics with 95% CI. DOR and TTR will be analyzed using Kaplan-Meier method for response-evaluable analysis set. PFS and OS will be analyzed using Kaplan-Meier method for the safety analysis set in dose expansion cohorts only.

Responses achieved in the crossover patients and long-term durability of response will be presented separately from the main study data.

13.1.4 PK Analysis

13.1.4.1 PK Noncompartmental Analysis

PK parameters for TAK-500 and total antibody will be estimated using noncompartmental methods with WinNonlin software. The PK parameters will be estimated from the concentration-time profiles for the PK population.

The following PK parameters will be determined, as permitted by data:

- C_{max}.
- t_{max}.
- AUC_t.
- AUC_∞.
- $t_{1/2z}$.
- CL.
- V_{ss}.

PK parameters will be summarized using descriptive statistics. Individual TAK-500 concentration-time data and individual PK parameters will be presented in listings and tabulated using summary statistics by dose cohort. Individual and mean concentration-time profiles will be plotted by dose cohort. A summary of deconjugated TAK-676 concentration-time data will be included (if measurable).

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13.1.4.2 PK Sampling Intended for Population PK Analysis

The PK data collected in this study are intended to contribute to future population PK analyses of TAK-500. These population PK analyses may additionally include data collected in other TAK-500 clinical studies. The plan for the population PK analysis will be defined separately and the results reported separately.

13.1.5 Immunogenicity Analysis

Immunogenicity parameters (ADA-negative, transiently and persistently ADA-positive, low or high ADA titer) will be analyzed using descriptive statistics in the safety analysis set and immunogenicity analysis set. The relationship of immunogenicity responses to PK, antitumor activity, and safety may be explored.

13.1.6 Pharmacodynamic Analysis

The [redacted] will be evaluated in peripheral blood and/or tumor samples collected at baseline and after administration of TAK-500. The change [redacted] will be calculated and used to establish evidence of pharmacodynamic modulation. The relationship between [redacted] may also be explored. The analysis will be performed in the pharmacodynamic population.

13.1.7 PK/Pharmacodynamic Analysis

The relationship between TAK-500, total antibody, and/or deconjugated TAK-676 exposure and pharmacodynamic response ([redacted]) will be explored on an ongoing basis as PK and pharmacodynamic data become available to understand the PK-pharmacodynamic relationship of TAK-500 and to help in estimation of the PAD range. Data permitting, mathematical models may be used to describe this relationship and such models may be used to predict the dose/schedule of TAK-500 that provides the desired exposure and pharmacological response for future evaluation. These data may be presented graphically as well as summarized in the clinical study report. The analysis will be performed in the pharmacodynamic population.

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13.1.8 PK/QTc Analysis

The PK-time matched triplicate ECG data collected in each patient will be pooled to understand the PK-QTc relationship of TAK-500. The relationship between TAK-500 serum concentration and effects on heart rate and QTcF will be analyzed using mixed effects modeling. These population PK-QTc analyses may include data collected in other TAK-500 clinical studies. As such, the analysis plan for the population PK-QTc analysis will be separately defined, and the results of these analyses will be reported separately and not presented in the clinical study report for this study.

13.1.9 Safety ECG Analysis

A summary of ECG abnormalities will be presented by visit. ECG parameters (QT, QTcF, PR interval, QRS, and heart rate) will be summarized at each scheduled time point, along with mean change from baseline to each posttreatment time point.

13.1.10 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set.

Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study and through 30 days after the last dose of study drug will be tabulated.

Related immune-mediated AEs as determined by the investigator that occur after administration of the first dose of study drug and through 90 days after administration of the last dose of study drug or before initiation of new anticancer therapy (whichever comes first) will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those reported by ≥10% of all patients).
- Treatment-emergent SAEs (related and regardless of relationship).
- TEAEs leading to study drug modification and discontinuation.

The incidence of DLTs will be tabulated using the DLT-evaluable analysis set.

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 the changes from baseline) of vital signs and weight will be tabulated by scheduled time point. ECOG Performance Status will be summarized using a shift table.

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Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline vs worst postbaseline values, may be used to understand the TAK-500 safety profile.

All concomitant medications collected from the first dose of study drug throughout 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 to further define the safety profile of TAK-500.

13.1.11 [redacted]

[redacted]

[redacted].

13.1.12 [redacted]

13.1.12.1 [redacted]

[redacted]

13.1.12.2 [redacted]

[redacted]

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13.2 Interim Analysis and Criteria for Early Termination

In the dose escalation phase, although no formal interim analysis is planned, investigators and sponsor representatives will review all available data to determine dose escalation and number of patients per cohort in the dose escalation phase.

In the dose expansion phase, an interim futility analysis will be performed, as detailed in Sections 6.1.3 and 13.3.

13.3 Determination of Sample Size

Approximately 313 patients will be enrolled in the study, including approximately 82 in the dose escalation phase and approximately 231 in the dose expansion phase (assuming only 1 dose schedule will be expanded).

In the phase 1 dose escalation phase, approximately 52 patients will be enrolled to achieve about 46 DLT-evaluable patients in the SA arm, and approximately 30 patients will be enrolled to achieve a maximum of 27 DLT-evaluable patients in the combination arm (assuming a drop-out rate of 10%). In the SA arm, a maximum of 42 DLT-evaluable patients is planned for BOIN

escalation to cover 8 DLs and additionally 4 DLT-evaluable patients for the two 1 + 2 + 3 escalation DLs. In the combination arm, the number of patients will depend on the starting DL. Assuming the escalation starts at 80 μg/kg, a maximum of 27 DLT-evaluable patients will be enrolled. Additional patients may be enrolled for the evaluation of Q2W administration of TAK-500 if this schedule is explored in the dose escalation phase (in either the SA or combination arm).

In the phase 2 dose expansion phase, each cohort's sample size is based on Simon's 2-stage design or an exact binomial 1-stage design with ORR as the endpoint, a 1-sided alpha equal to 0.1, and an assumed dropout rate of 10%. In the following cohort-specific design specifications, H_0 represents the "null hypothesis," H_A represents the "alternative hypothesis," RE represents "response-evaluable," and power represents "statistical power." Additionally, specific design scenarios are dependent on the results from preceding scenarios and may or may not be realized.

- *2L NSCLC TAK-500 + pembrolizumab RDE 1 versus RDE 2 [2:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 39 patients will be enrolled in the RDE 1 cohort, allowing for 35 RE patients. H_0: ORR ≤ 23%, H_A: ORR ≥40%, and power = 80%. The futility analysis will occur at 21 RE patients, where ≥5 responders are required for successfully passing futility.
  - Approximately 20 patients will be enrolled in the RDE 2 cohort, allowing for 18 RE patients. If the futility analysis in RDE 1 fails, additional enrollment will be initiated to increase the RDE 2 RE sample size to 21 patients and Simon's 2-stage design will be applied in the same manner as planned for RDE 1. Given this, the total number of RE patients for RDE 2 may be 18, 21, or 35.
- *3L NSCLC TAK-500 SA RDE 1 versus RDE 2 [1:1 randomization]:*
  - Based on a single-stage exact binomial design, approximately 24 patients will be enrolled each in the RDE 1 cohort and the RDE 2 cohort allowing for 21 RE patients per cohort. For each cohort, H_0: ORR ≤ 5%, H_A: ORR ≥20%, and power = 82%. The total RE sample size across the 2 cohorts will be 42 patients.
- *2L pancreatic adenocarcinoma TAK-500 + pembrolizumab RDE 1 versus 2L pancreatic adenocarcinoma TAK-500 SA RDE 1 [1:1 randomization]:*
  - Based on Simon's 2-stage design, approximately 45 patients will be enrolled each in the combination cohort and the SA cohort, allowing for 40 RE patients per cohort. For each cohort, H_0: ORR ≤ 16%, H_A: ORR ≥30%, and power = 80%. For each cohort, a futility analysis will occur at 25 RE patients, where ≥4 responders are required for successfully passing futility.
- *3L RCC TAK-500 + pembrolizumab RDE 1:*
  - Based on a single-stage exact binomial design, approximately 34 patients will be enrolled allowing for 30 RE patients. H_0: ORR ≤ 8%, H_A: ORR ≥25%, and power = 90%.

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14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 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 (contract research organization) and by the IRB or IEC.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and permitted by the IRB/IEC.

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, 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.

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14.2 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 IEC, 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 the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it is mandatory to be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 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, US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] 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 14.1.

15.0 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.

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15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable 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 because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US 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 investigator's brochure, a copy of the ICF, and, if applicable, patient recruitment materials and 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 its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the

competent authority to begin the study. Until the site receives 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 designee).

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

15.2 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, and 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.

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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 before 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. If the patient is not capable of rendering adequate written informed consent, then the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that 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, or the patient's legally acceptable representative, at the time of

consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters 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 or the relevant patient's legally acceptable representative 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.

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15.3 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 be linked to the sponsor's clinical study database or documentation only 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, US FDA, UK MHRA, Japan PMDA), 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 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study participants, this would be done through the investigator.

Takeda applies certain measures to protect participants' personal data and prevent data breaches, detailed in a separate document (Compliance with National Requirements on Data Protection).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

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 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.

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15.4.2 Clinical Trial Registration

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 on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by 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.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov, ClinicalTrialsRegister.eu, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 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.

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Appendix A SOEs

The SOEs are provided for:

- SOE for TAK-500 Q3W treatment (21-day cycle).
- SOE for TAK-500 Q3W treatment (42-day cycle).
- SOE for TAK-500 Q2W treatment (42-day cycle).

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SOEs for TAK-500 Q3W Treatment (21-Day Cycle)

For the SOEs when administered TAK-500 Q3W on a 21-day cycle, as an SA or in combination with pembrolizumab, see:

- Table A-1 for Cycle 1.
- Table A-2 for Cycle 2 through EOS.
- Table A-3 for serial PK and ECG sampling.
- Table A-4 for pharmacodynamic biomarkers collection.

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Table A-1 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15
Study Procedures							
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Medical history [c]	X	X					
Physical examination [c]	X	X	X		X	X	X
Height	X						
Weight		X			X	X	X
Vital signs [d]	X	X	X		X	X	X
[redacted]							
ECOG Performance Status	X	X					
Safety 12-lead ECG [f]	X	X					
ECHO or MUGA	X						
Tumor assessment [g]	X						
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF						
AE reporting	Recorded from the signing of ICF						
	SAEs will be reported from signing of the ICF						
Patient diary review [h]					X	X	X
Safety follow-up call [i]				X			
Dosing							
Pembrolizumab administration [j]		X					
TAK-500 administration [j]		X					
Premedication [k]		X					
Samples/Laboratory Assessments							
Pregnancy test [l]	X	X					
Hematology/chemistry [m]	X	X				X	X

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Table A-1 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15
Tumor markers [n]		X					
Thyroid function tests [m]	X						
C-reactive protein [m]	X	X				X	X
Creatine kinase	X						
Ferritin	X	X				X	X
Coagulation	X						
Troponin I	X						
HbA1c	X						
IL-6 [o]		X					
PK and triplicate ECG sampling schedule for TAK-500 Q3W treatment (21-day cycle): Table A-3							
Biomarker sample collection for TAK-500 Q3W treatment (21-day cycle): Table A-4							

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; CT: computed tomography; cPR: confirmed partial response; CTCAE: Common Terminology Criteria for Adverse Events; CxDx: Cycle x Day x; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; HbA1c: glycosylated hemoglobin; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IL: interleukin; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition scan; PD: progressive disease; PD-1: programmed cell death protein 1; PK: pharmacokinetic(s); Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to administration of TAK-500 unless otherwise specified.

[a] Unless otherwise noted, the screening procedures must occur within 28 days before the day of the first dose of study drug (C1D1).

[b] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles.

[c] Medical history will include smoking/vaping history and available baseline disease characteristics, such as disease type, staging, PD-1 expression, etc. Complete physical examination (including assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, neurological condition, blood and lymphatic, and musculoskeletal) and medical history will be collected at screening and the time points indicated. The C1D1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1). Postscreening physical examinations will be symptom- or finding-directed and will be performed at any time point based on clinical need. Before discharge from the clinic or

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Table A-1 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15

hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

[d] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vital signs will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[redacted]

[f] Safety ECGs should be performed at screening and C1D1 predose, EOI (+1 hour), and 2 (+1 hour) and 3 (+1 hour) hours postdose. A qualified person will interpret the ECGs locally. ECG assessments are to be performed with the patient supine and rested for 5 minutes. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. When the timing of ECG or vital signs measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling. The frequency and timing of ECG collection for safety may be modified based on emerging data and agreement between sponsor and investigators.

[g] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status, using RECIST v1.1 criteria. Refer to Section 9.4.13 for details.

[h] For 6 weeks (42 days) after C1D1, on nondosing days or when patient is not hospitalized, patients will be asked to record oral temperature twice daily (first in the morning and last in the evening) and any time the patient feels febrile on a patient diary that should be brought to the site at each Cycle 1 and 2 visit. Please report clinically significant fever as AEs according to CTCAE v5.0 guidelines.

[i] The principal investigator (or appropriate designee, subinvestigator, study nurse) is required to call the patient on the days specified to assess the patient for overall AEs and general well-being.

[j] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before administration of TAK-500 on Day 1. Detailed infusion instructions are provided in the pharmacy manual.

[k] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500 in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[l] A serum choriogonadotropin beta pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-500 is administered (ie, within the 4 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing (serum or urine; urine preferred) will be performed before each dose

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Table A-1 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15

of TAK-500 and may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations.

[m] The hematology and chemistry blood samples for C1D1 may be collected within 4 days before dosing to ensure patient eligibility on C1D1. If screening clinical laboratory testing was performed within 4 days before the C1D1 dose, it need not be repeated on C1D1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets, erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[n] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 2 cycles (6 weeks) thereafter: TNBC, CA 27.29; HCC, AFP; pancreatic adenocarcinoma, CA 19-9.

[o] IL-6 levels to be measured for the first 2 doses (C1D1 and C2D1) predose and 12 hours postdose (±30 minutes).

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Table A-2 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles				EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [c]	Follow-up [c]
	Day 1 [a]	Day 2	Day 8 [b]	Day 21			
Study Procedures							
Symptom-directed physical examination [d]	X	X	X [b]		X	X	
Weight	X		X [b]		X	X	
Vital signs [e]	X	X	X [b]		X	X	
[redacted]							
ECOG Performance Status	X				X	X	
Safety 12-lead ECG [g]	X				X	X	
Tumor assessment [h]				X [h]	X		X
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through EOT						
AE reporting	Recorded from the signing of ICF through EOT (and 90 (±3) days after last dose of the study drug for any immune-mediated events)					X	
	SAEs will be reported from signing of the ICF through 30 days after the last dose of study drug (through 90 days for any immune-mediated events)					X	
Patient diary review [i]	X		X [b]				
Safety follow-up call [j]						X	
Dosing							
Pembrolizumab administration [k]	X						
TAK-500 administration [k]	X						
Premedication [l]	X						
Samples/Laboratory Assessments							
Pregnancy test [m]	X				X		
Hematology/chemistry [n]	X		X [b]		X		
Tumor markers [o]	X						

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Table A-2 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles				EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [c]	Follow-up [c]
	Day 1 [a]	Day 2	Day 8 [b]	Day 21			
Thyroid function tests [p]	X						
C-reactive protein [p]	X		X [b]				
Ferritin [p]	X		X [b]				
HbA1c [p]	X						
IL-6 [q]	X						
PK and triplicate ECG sampling schedule for TAK-500 Q3W treatment (21-day cycle): Table A-3							
Biomarker sample collection for TAK-500 Q3W treatment (21-day cycle): Table A-4							

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; cPR: confirmed partial response; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; CxDx: Cycle x Day x; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOS: end of study; EOT: end of treatment; HbA1c: glycosylated hemoglobin; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IL: interleukin; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; PD: progressive disease; PK: pharmacokinetic(s); Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 plus pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles. If a patient has had 2 consecutive administrations of TAK-500 without Grade ≥2 CRS, they may be treated as an outpatient with at least 6 hours of in-clinical observation after infusion; patients who do not experience infusion-associated symptoms or symptoms consistent with CRS during or after 4 consecutive infusions of TAK-500 may have their postinfusion monitoring reduced to 1 hour for subsequent cycles.

[b] Day 8 clinic visit and associated laboratory tests and procedures are only required for Cycle 2. Additional cycles will not require clinic visits and procedures on Day 8.

[c] Patients who discontinue study treatment for reasons other than PD will continue follow-up imaging every 6 weeks (±3 days) from first dose for the first 6 months and then every 12 weeks (±3 days) thereafter, until the occurrence of PD, loss to follow-up, consent withdrawal, the start of subsequent systemic antineoplastic therapy, study termination, or death, whichever occurs first. Date of disease progression and subsequent anticancer therapies will be documented. Ninety days (±3 days) after last dose, all patients will have a safety check, which can occur by phone or in the clinic, at the investigator's discretion and this contact will focus on any treatment-related immune-mediated AEs. If performed over the phone, only AE reporting is required. An EOS page will be completed for all patients.

[d] The symptom-directed physical examination may be performed at additional visits during the treatment cycle at the discretion of the investigator. Before discharge from the

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Table A-2 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles				EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [c]	Follow-up [c]
	Day 1 [a]	Day 2	Day 8 [b]	Day 21			

clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

[e] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[redacted]

[g] Single safety ECGs will be collected predose on days of treatment and at EOT as shown. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[h] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status using RECIST v1.1 criteria. If a patient is discontinuing treatment for a reason other documented PD, imaging is required at EOT if: (1) it has been more than 4 weeks since the most recent imaging, for patients within the first 6 months of treatment, or (2) it has been more than 6 weeks since the most recent imaging, for patients on study more than 6 months. Refer to Section 9.4.13 for details.

[i] For 6 weeks (42 days) after C1D1, on nondosing days or when patient is not hospitalized, patients will be asked to record oral temperature twice daily (first in the morning and last in the evening) and any time the patient feels febrile on a patient diary that should be brought to the site at each Cycle 1 and 2 visit. Please report clinically significant fever as AEs according to CTCAE v5.0 guidelines.

[j] The principal investigator (or appropriate designee, subinvestigator, study nurse) is required to call the patient on the days specified to assess the patient for overall AEs and general well-being.

[k] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before administration of TAK-500 on Day 1. Detailed infusion instructions are provided in the pharmacy manual.

[l] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500 in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[m] Pregnancy testing (serum or urine; urine preferred) will be performed before each dose of TAK-500 and at EOT. Additional pregnancy testing (serum or urine; urine preferred) may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations.

[n] Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets,

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Table A-2 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles				EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [c]	Follow-up [c]
	Day 1 [a]	Day 2	Day 8 [b]	Day 21			

erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[o] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 2 cycles (6 weeks) thereafter: TNBC, CA 27.29; HCC, AFP; pancreatic adenocarcinoma, CA 19-9.

[p] C-reactive protein and ferritin to be measured every cycle. HbA1c and thyroid function tests to be performed every 12 weeks and if clinically indicated. Additional laboratory, including troponin, tests will only be repeated if clinically indicated while on study.

[q] IL-6 levels to be measured around the first 2 doses (C1D1 and C2D1) predose and 12 hours postdose (±30 minutes).[p] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour before administration of TAK-500 in the SA arm and immediately before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

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Table A-3 Serial PK and ECG Sampling for TAK-500 Q3W Treatment (21-Day Cycle)

	Cycle 1						Cycle 2					Cycles 3, 4, 9, 15
	Day 1 [a]		Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 1 [a]		Day 2	Day 8	Day 15	Day 1 [a]
	Triplicate ECG [b]	PK	PK	PK	PK	PK	Triplicate ECG [b]	PK	PK	PK	PK	PK
Predose (<90 min before dose) [a]	X3	X1					X3	X1				X1
EOI (±10 min)	X3	X1					X3	X1				X1
6 h postdose (±30 min)	X3	X1					X3	X1				X1
12 h postdose (± 1 h)	X3	X1					X3	X1				
24 h postdose (±1 h)	X3		X1				X3		X1			X1 (if hospitalized) [c]
Day 4 postdose (±4 h)				X1								
Day 8 postdose (±4 h)					X1					X1		
Day 15 postdose (±4 h)						X1						

CxDx: Cycle x Day x; ECG: electrocardiogram; EOI: end of infusion; PK: pharmacokinetic(s); Q3W: once every 3 weeks.
The schedule for ECG sampling may be modified based on data from previous cohorts. The triplicate ECG data are to be collected using standard ECG equipment. On days/times when safety ECG collections coincide with triplicate ECG collections, the triplicate ECGs may be used by the investigators on site for the safety ECG assessment. 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. The triplicate ECG measurements should be completed immediately before the corresponding PK blood draw.
During the expansion phase, for Cycle 1 and Cycle 2 only, no more than 5 PK samples will be collected after each cycle. For later cycles (Cycles 3, 4, 9, and 15), no more than 3 PK samples will be collected after each cycle. The sample collection timepoints will be determined based on emerging data from the dose escalation phase.
X1 = 1 PK sample will be collected for analysis of TAK-500, total antibody, and deconjugated TAK-676 at each time point.
X3 = three 12-lead ECG measurements will be performed at each time point.
All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.
[a] The timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle. To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.
[b] Triplicate 12-lead ECG measurements are to be performed with the patient supine, after a 5-minute rest period, and will be recorded at 2- to 5-minute intervals.
[c] Only required if a patient is hospitalized for administration of TAK-500. To be obtained at 24 hours postdose with a ± 6-hour window.

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Table A-4 Pharmacodynamic Biomarkers Collection for TAK-500 Q3W Treatment (21-Day Cycle)

	S	Cycle 1								Cycle 2								Cycles 3, 4, 9, 15			EOT
		Day 1				Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 1				Day 2	Day 3	Day 8	Day 15	Day 1			30 Days After Last Dose
		Predose ≤90 m Before Dose [a]	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	12 h Post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]	DPV [b]	DPV [b]	DPV [b]	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	12 h Post-EOI ±1h [a]	24 h Post-EOI ±1 h [a]		DPV [b]	[b]	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	
[redacted]																					
Serum Sample for Immunogenicity [e]	X									X								X			X

Table A-4 Pharmacodynamic Biomarkers Collection for TAK-500 Q3W Treatment (21-Day Cycle)

		Cycle 1								Cycle 2								Cycles 3, 4, 9, 15			EOT
	S	Day 1				Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 1				Day 2	Day 3	Day 8	Day 15	Day 1			30 Days After Last Dose
		Predose ≤90 m Before Dose [a]	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	12 h Post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]	DPV [b]	DPV [b]	DPV [b]	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	12 h Post-EOI ±1h [a]	24 h Post-EOI ±1 h [a]		DPV [b]	[b]	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 m	

ADA: antidrug antibodies; AE: adverse event; CxDx: Cycle x, Day x; DPV: during planned visit; [redacted]; EOI: end of infusion; EOT: end of treatment; [redacted]; Q3W: once every 3 weeks; S: screening.

For the combination arm, the predose sample collections will be conducted before pembrolizumab and TAK-500 administration. All other timeframes within the table should be relative to TAK-500 administration, not pembrolizumab.

All times mentioned are relative to TAK-500 administration unless otherwise specified.

[a] To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.

[b] While these pharmacodynamic collections will be performed during dose escalation, during dose expansion these pharmacodynamic collections will only be mandated if the patient is hospitalized or is seen at the clinic as part of their posttreatment care or at the same time as other blood collections.

[redacted].

[e] Immunogenicity (ADA) samples must be collected before study drug is administered on a dosing day. Additional unscheduled collections should be obtained for patients who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample will be assessed for neutralizing ADA if a positive ADA is detected.

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SOEs for TAK-500 Q3W Treatment (42-Day Cycle)

For the SOEs when administered TAK-500 Q3W on a 42-day cycle, as an SA or in combination with pembrolizumab, see:

- Table A-5 for Cycle 1.
- Table A-6 for Cycle 2 through EOS.
- Table A-7 for serial PK sampling.
- Table A-8 for pharmacodynamic biomarkers collection.

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Table A-5 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15	Day 22 [b]	Day 29	Day 42
Study Procedures										
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history [c]	X	X								
Physical examination [c]	X	X	X		X	X	X	X	X	
Height	X									
Weight		X			X	X	X	X	X	
Vital signs [d]	X	X	X		X	X	X	X	X	
ECOG Performance Status	X	X						X		
Safety 12-lead ECG [e]	X	X						X		
ECHO or MUGA	X									
Tumor assessment [f]	X									X
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF									
AE reporting	Recorded from the signing of ICF									
	SAEs will be reported from signing of the ICF									
Patient diary review [g]					X	X	X	X	X	
[redacted]										
Safety follow-up call [i]				X						
Dosing										
Pembrolizumab administration [j]		X						X		
TAK-500 administration [j]		X						X		
Premedication [k]		X						X		
Samples/Laboratory Assessments										
Pregnancy test [l]	X	X						X		

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Table A-5 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15	Day 22 [b]	Day 29	Day 42
Hematology/chemistry [m]	X	X				X	X	X	X	
Tumor markers [n]		X								
Thyroid function tests	X									
C-reactive protein	X	X				X		X	X	
Creatine kinase	X									
Ferritin	X	X				X		X	X	
Coagulation	X									
Troponin I	X									
HbA1c	X									
IL-6 [o]		X						X		
PK sampling schedule for TAK-500 Q3W treatment (42-day cycle): Table A-7										
Biomarker sample collection for TAK-500 Q3W treatment (42-day cycle): Table A-8										

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; cPR: confirmed partial response; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; CxDx: Cycle x Day x; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; [redacted]; HbA1c: glycosylated hemoglobin; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IL: interleukin; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition scan; PD: progressive disease; PD-1: programmed cell death protein 1; PK: pharmacokinetic(s); [redacted]; Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] Unless otherwise noted, the screening procedures must occur within 28 days before the day of the first dose of study drug (C1D1).

[b] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles. Before discharge from the clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

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Table A-5 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15	Day 22 [b]	Day 29	Day 42

[c] Medical history will include smoking/vaping history and available baseline disease characteristics, such as disease type, staging, PD-1 expression, etc. Complete physical examination (including assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, neurological condition, blood and lymphatic, and musculoskeletal) and medical history will be collected at screening and the time points indicated. The C1D1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1). Postscreening physical examinations will be symptom- or finding-directed and will be performed at any time point based on clinical need. Before discharge from the clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

[d] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vital signs will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[e] Safety ECGs should be performed at screening; C1D1 predose, EOI (+1 hour), and 2 (+1 hour) and 3 (+1 hour) hours postdose; and C1D22 predose. A qualified person will interpret the ECGs locally. ECG assessments are to be performed with the patient supine and rested for 5 minutes. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. When the timing of ECG or vital signs measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling. The frequency and timing of ECG collection for safety may be modified based on emerging data and agreement between sponsor and investigators.

[f] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status, using RECIST v1.1 criteria. Refer to Section 9.4.13 for details.

[g] For 6 weeks (42 days) after C1D1, on nondosing days or when patient is not hospitalized, patients will be asked to record oral temperature twice daily (first in the morning and last in the evening) and any time the patient feels febrile on a patient diary that should be brought to the site at each Cycle 1 visit. Please report clinically significant fever as AEs according to CTCAE v5.0 guidelines.

[redacted]

[i] The principal investigator (or appropriate designee, subinvestigator, study nurse) is required to call the patient on the days specified to assess the patient for overall AEs and general well-being.

[j] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before the administration of TAK-500 on Day 1 and Day 22. Detailed infusion instructions are provided in the pharmacy manual.

[k] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500

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Table A-5 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15	Day 22 [b]	Day 29	Day 42

in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[l] A serum choriogonadotropin beta pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-500 is administered (ie, within the 4 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing (serum or urine; urine preferred) will be performed before each dose of TAK-500 and may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations.

[m] The hematology and chemistry blood samples for C1D1 may be collected within 4 days before dosing to ensure patient eligibility on C1D1. If screening clinical laboratory testing was performed within 4 days before the C1D1 dose, it need not be repeated on C1D1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets, erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[n] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 6 weeks thereafter: TNBC, CA 27.29; HCC, AFP; pancreatic adenocarcinoma, CA 19-9.

[o] IL-6 levels to be measured during C1D1 and C1D22 predose and 12 hours postdose (±30 minutes).

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Table A-6 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]			EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose	Follow-up [b]
	Day 1	Day 22	Day 42			
Study Procedures						
Symptom-directed physical examination [c]	X	X		X	X	
Weight	X	X		X	X	
Vital signs [d]	X	X		X	X	
ECOG Performance Status	X	X		X	X	
Safety 12-lead ECG [e]	X	X		X	X	
Tumor assessment [f]			X	X		X
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through EOT					
AE reporting	Recorded from the signing of ICF through EOT (and 90 (±3) days after last dose of the study drug for any immune-mediated events)				X	
	SAEs will be reported from signing of the ICF through 30 days after the last dose of study drug (through 90 days for any immune-mediated events)				X	
[redacted]						
Safety follow-up call					X	
Dosing						
Pembrolizumab administration [h]	X	X				
TAK-500 administration [h]	X	X				
Premedication [i]	X	X				
Samples/Laboratory Assessments						
Pregnancy test [j]	X	X		X		
Hematology/chemistry [k]	X	X		X		
Tumor markers [l]	X					
Thyroid function tests [m]	X					

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Table A-6 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]			EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose	Follow-up [b]
	Day 1	Day 22	Day 42			
C-reactive protein [m]	X	X				
Ferritin [m]	X	X				
HbA1c [m]	X					
PK sampling schedule for TAK-500 Q3W treatment (42-day cycle): Table A-7						
Biomarker sample collection for TAK-500 Q3W treatment (42-day cycle): Table A-8						

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; cPR: confirmed partial response; CRS: cytokine release syndrome; CT: computed tomography; CxDx: Cycle x Day x; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; EOT: end of treatment; [redacted]; HbA1C: glycosylated hemoglobin; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; PD: progressive disease; PK: pharmacokinetic(s); [redacted]; Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles. If a patient has had 2 consecutive administrations of TAK-500 without Grade ≥2 CRS, they may be treated as an outpatient with at least 6 hours of in-clinical observation after infusion; patients who do not experience infusion-associated symptoms or symptoms consistent with CRS during or after 4 consecutive infusions of TAK-500 may have their postinfusion monitoring reduced to 1 hour for subsequent cycles.

[b] Patients who discontinue study treatment for reasons other than PD will continue follow-up imaging every 6 weeks (±3 days) from first dose for the first 6 months and then every 12 weeks (±3 days) thereafter, until the occurrence of PD, loss to follow-up, consent withdrawal, the start of subsequent systemic antineoplastic therapy, study termination, or death, whichever occurs first. Date of disease progression and subsequent anticancer therapies will be documented. Ninety days (±3 days) after last dose, patients will have a safety check, which can occur by phone or in the clinic, at the investigator's discretion and this contact will focus on any treatment-related immune-mediated AEs. If performed over the phone, only AE reporting is required. An EOS page will be completed for all patients.

[c] The symptom-directed physical examination may be performed at additional visits during the treatment cycle at the discretion of the investigator. Before discharge from the clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

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Table A-6 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]			EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose	Follow-up [b]
	Day 1	Day 22	Day 42			

[d] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vitals will also be measured at 3 and 6 hours after dosing of TAK-500; measurement should be obtained in a ±30-minute window. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[e] Single safety ECGs will be collected predose on days of treatment and at EOT as shown. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[f] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status using RECIST v1.1 criteria. If a patient is discontinuing treatment for a reason other documented PD, imaging is required at EOT if: (1) it has been more than 4 weeks since the most recent imaging, for patients within the first 6 months of treatment, or (2) it has been more than 6 weeks since the most recent imaging, for patients on study more than 6 months. Refer to Section 9.4.13 for details.

[redacted]

[h] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before the administration of TAK-500 on Day 1 and Day 22 of each cycle. Detailed infusion instructions are provided in the pharmacy manual.

[i] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500 in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[j] Pregnancy testing (serum or urine; urine preferred) will be performed before each dose of TAK-500 and at EOT. Additional pregnancy testing (serum or urine; urine preferred) may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations.

[k] Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets, erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

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Table A-6 SOE for TAK-500 Q3W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]			EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose	Follow-up [b]
	Day 1	Day 22	Day 42			

[l] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 6 weeks hereafter: TNBC, CA 27.29; HCC, AFP; pancreatic adenocarcinoma, CA 19-9.

[m] C-reactive protein and ferritin to be measured on Day 1 and Day 22 of every cycle. HbA1c and thyroid function tests to be performed every 12 weeks and if clinically indicated. Additional laboratory, including troponin, tests will only be repeated if clinically indicated while on study.

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Table A-7 Serial PK Sampling for TAK-500 Q3W Treatment (42-Day Cycle)

	Cycle 1									Cycles 2, 3, 4, 9, 15
	Day 1 [a]	Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 22 [a]	Day 23	Day 29	Day 36	Day 1 [a]
Predose (<90 min before dose) [a]	X1					X1				X1
EOI (±10 min)	X1					X1				X1
6 h postdose (±30 min)	X1					X1				X1
12 h postdose (± 1 h)	X1					X1				X1
24 h postdose (±1 h)		X1					X1			X1 (if hospitalized) [b]
Day 4 postdose (±4 h)			X1							
Day 8 postdose (±4 h)				X1				X1		
Day 15 postdose (±4 h)					X1				X1	

CxDx: Cycle x Day x; EOI: end of infusion; PK: pharmacokinetic(s); Q3W: once every 3 weeks.

X1 = 1 PK sample will be collected for analysis of TAK-500, total antibody, and deconjugated TAK-676 at each time point.

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

During the expansion phase, for Cycle 1 and Cycle 2 only, no more than 5 PK samples will be collected after each cycle. For later cycles (Cycles 3,4, 9, and 15), no more than 3 PK samples will be collected after each cycle. The sample collection timepoints will be determined based on emerging data from the dose escalation phase.

[a] The timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle. To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.

[b] Only required if a patient is hospitalized for administration of TAK-500. To be obtained at 24 hours postdose with a ± 6-hour window.

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Table A-8 Pharmacodynamic Biomarkers Collection for TAK-500 Q3W Treatment (42-Day Cycle)

		Cycle 1																Cycles 2, 3, 4, 9, 15			EOT
	S	Day 1				Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 22				Day 23	Day 24	Day 29	Day 36	Day 1			
		Pre dose ≤90 m Before Dose [a]	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	12 h post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]	DPV [b]	DPV [b]	DPV [b]	Pre dose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	12 h Post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]		DPV [b]		Pre dose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	30 Days After Last Dose
[redacted]																					
Serum Sample for Immunogenicity [e]	X									X								X			X

only

Table A-8 Pharmacodynamic Biomarkers Collection for TAK-500 Q3W Treatment (42-Day Cycle)

	S	Cycle 1																Cycles 2, 3, 4, 9, 15			EOT
		Day 1				Day 2	Day 4 (±1 day)	Day 8	Day 15	Day 22				Day 23	Day 24	Day 29	Day 36	Day 1			
		Pre dose ≤90 m Before Dose [a]	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	12 h post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]	DPV [b]	DPV [b]	DPV [b]	Pre dose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	12 h Post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]		DPV [b]		Pre dose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ±30 min	30 Days After Last Dose

ADA: antidrug antibodies; AE: adverse event; CxDx: Cycle x, Day x; DPV: during planned visit; [redacted]; EOI: end of infusion; EOT: end of treatment; [redacted]; Q3W: once every 3 weeks; S: screening.

For the combination arm, the predose sample collections will be conducted before pembrolizumab and TAK-500 administration. All other timeframes within the table should be relative to TAK-500 administration, not pembrolizumab.

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.

[b] While these pharmacodynamic collections will be performed during dose escalation, during dose expansion these pharmacodynamic collections will only be mandated if the patient is hospitalized or is seen at the clinic as part of their posttreatment care or at the same time as other blood collections.

[redacted].

[e] Immunogenicity (ADA) samples must be collected before study drug is administered on a dosing day. Additional unscheduled collections should be obtained for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample will be assessed for neutralizing ADA if a positive ADA is detected.

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SOEs for TAK-500 Q2W Treatment (42-Day Cycle)

For the SOEs when administered TAK-500 Q2W on a 42-day cycle, as an SA or in combination with pembrolizumab, see:

- Table A-9 for Cycle 1.
- Table A-10 for Cycle 2 through EOS.
- Table A-11 for serial PK sampling.
- Table A-12 for pharmacodynamic biomarkers collection.

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Table A-9 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15 [b]	Day 16	Day 22	Day 29 [b]	Day 30	Day 42
Study Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical history [c]	X	X										
Physical examination [c]	X	X	X		X	X	X		X	X		
Height	X											
Weight		X			X	X	X		X	X		
Vital signs [d]	X	X	X		X	X	X		X	X		
ECOG Performance Status	X	X					X		X	X		
Safety 12-lead ECG [e]	X	X					X			X		
ECHO or MUGA	X											
Tumor assessment [f]	X											X
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF											
AE reporting	Recorded from the signing of ICF											
	SAEs will be reported from signing of the ICF											
Patient diary review [g]					X	X	X		X	X		
[redacted]												
Safety follow-up call [i]				X								
Dosing												
Pembrolizumab administration [j]		X							X			
TAK-500 administration [j]		X					X			X		
Premedication [k]		X					X			X		

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Table A-9 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15 [b]	Day 16	Day 22	Day 29 [b]	Day 30	Day 42
Samples/Laboratory Assessments												
Pregnancy test [l]	X	X					X			X		
Hematology/chemistry [m]	X	X				X	X		X	X		
Tumor markers [n]		X										
Thyroid function tests	X											
C-reactive protein	X	X				X	X		X	X		
Creatine kinase	X											
Ferritin	X	X				X	X		X	X		
Coagulation	X											
Troponin I	X											
HbA1c	X											
IL-6 °		X					X					
PK sampling schedule for TAK-500 Q2W treatment (42-day cycle): Table A-11												
Biomarker sample collection for TAK-500 Q2W treatment (42-day cycle): Table A-12												

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; cPR: confirmed partial response; CRS: cytokine release syndrome; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; CxDx: Cycle x Day x; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; [redacted]; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IL: interleukin; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition scan; PD: progressive disease; PD-1: programmed cell death protein 1; PK: pharmacokinetic(s); [redacted]; Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) with permission of the medical monitor for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] Unless otherwise noted, the screening procedures must occur within 28 days before the day of the first dose of study drug (C1D1).

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Table A-9 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15 [b]	Day 16	Day 22	Day 29 [b]	Day 30	Day 42

[b] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles. If a patient has had 2 consecutive administrations of TAK-500 without Grade ≥2 CRS, they may be treated as an outpatient with at least 6 hours of in-clinical observation after infusion; patients who do not experience infusion-associated symptoms or symptoms consistent with CRS during or after 4 consecutive infusions of TAK-500 may have their postinfusion monitoring reduced to 1 hour for subsequent cycles.

[c] Medical history will include smoking/vaping history and available baseline disease characteristics, such as disease type, staging, PD-1 expression, etc. Complete physical examination (including assessment of the following systems: skin, head, eyes, ears, nose, throat, respiratory, cardiovascular, gastrointestinal, neurological condition, blood and lymphatic, and musculoskeletal) and medical history will be collected at screening and the time points indicated. The C1D1 physical examination and medical history are not required if the screening physical examination was conducted and medical history obtained within 4 days before administration of the first dose of study drug (C1D1). Postscreening physical examinations will be symptom- or finding-directed and will be performed at any time point based on clinical need. Before discharge from the clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

[d] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hours post infusion (±10 minutes). On C1D1 vital signs will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[e] Safety ECGs should be performed at screening; C1D1 predose, EOI (+1 hour), and 2 (+1 hour) and 3 (+1 hour) hours postdose; C1D15 predose; C!D22 predose and C1D29 predose. A qualified person will interpret the ECGs locally. ECG assessments are to be performed with the patient supine and rested for 5 minutes. Additional ECGs may be obtained as clinically indicated at any time during the study at the discretion of the investigator. When the timing of ECG or vital signs measurements coincides with the timing of a blood draw (eg, PK sample), the ECG measurements and vital signs measurements should be completed first, followed by blood sampling. The frequency and timing of ECG collection for safety may be modified based on emerging data and agreement between sponsor and investigators.

[f] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status, using RECIST v1.1 criteria. Refer to Section 9.4.13 for details.

[g] For 6 weeks (42 days) after C1D1, on nondosing days or when patient is not hospitalized, patients will be asked to record oral temperature twice daily (first in the morning and last in the evening) and any time the patient feels febrile on a patient diary that should be brought to the site at each Cycle 1 visit. Please report clinically significant fever as AEs according to CTCAE v5.0 guidelines.

[redacted]

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Table A-9 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 1

	Screening [a]	Day 1 [b]	Day 2	Day 3	Day 4	Day 8	Day 15 [b]	Day 16	Day 22	Day 29 [b]	Day 30	Day 42

[i] The principal investigator (or appropriate designee, subinvestigator, study nurse) is required to call the patient on the days specified to assess the patient for overall AEs and general well-being.

[j] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before the administration of TAK-500 on Day 1. Detailed infusion instructions are provided in the pharmacy manual.

[k] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500 in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[l] A serum choriogonadotropin beta pregnancy test will be performed only for patients of childbearing potential during screening and again at C1D1 (baseline) if the screening test was performed more than 4 days before the first dose of any study drug. The results must be negative within 4 days before the first dose of TAK-500 is administered (ie, within the 4 days before C1D1), or as otherwise required by local regulations. Additional pregnancy testing (serum or urine; urine preferred) will be performed before each dose of TAK-500 and may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations.

[m] The hematology and chemistry blood samples for C1D1 may be collected within 4 days before dosing to ensure patient eligibility on C1D1. If screening clinical laboratory testing was performed within 4 days before the C1D1 dose, it need not be repeated on C1D1. Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets, erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[n] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 6 weeks thereafter: TNBC, CA 27.29; HCC, AFP; Pancreatic adenocarcinoma, CA 19-9.

[o] IL-6 levels to be measured during C1D1 and C1D15 predose and 12 hours postdose (±30 minutes).

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Table A-10 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]					EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [b]	Follow-up [b]
	Day 1	Day 15	Day 22	Day 29	Day 42			
Study Procedures								
Symptom-directed physical examination [c]	X	X	X	X		X	X	
Weight	X	X	X	X		X	X	
Vital signs [d]	X	X	X	X		X	X	
ECOG Performance Status	X	X	X	X		X	X	
Safety 12-lead ECG [e]	X	X		X		X	X	
Tumor assessment [f]					X	X		X
Monitoring of concomitant medications and procedures	Recorded from the signing of ICF through EOT							
AE reporting	Recorded from the signing of ICF through EOT (and 90 (±3) days after last dose of the study drug for any immune-mediated events)						X	
	SAE will be reported from signing of the ICF through 30 days after the last dose of study drug (through 90 days for any immune-mediated events)						X	
[redacted]								
Safety follow-up call							X	
Dosing								
Pembrolizumab administration [h]	X		X					
TAK-500 administration [h]	X	X		X				
Premedication [i]	X	X		X				

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Table A-10 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]					EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [b]	Follow-up [b]
	Day 1	Day 15	Day 22	Day 29	Day 42			
Samples/Laboratory Assessments								
Pregnancy test [j]	X	X		X		X		
Hematology/chemistry [k]	X	X	X	X		X		
Tumor markers [l]	X							
Thyroid function tests [m]	X							
C-reactive protein [m]	X		X					
Ferritin [m]	X		X					
Troponin I [m]	X							
PK sampling schedule for TAK-500 Q2W treatment (42-day cycle): Table A-11								
Biomarker sample collection for TAK-500 Q2W treatment (42-day cycle): Table A-12								

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AE: adverse event; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; cCR: confirmed complete response; cPR: confirmed partial response; CRS: cytokine release syndrome; CT: computed tomography; CxDx: Cycle x Day x; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; EOT: end of treatment; [redacted]; HbA1C: glycosylated hemoglobin; HCC: hepatocellular carcinoma; ICF: informed consent form; IEC: independent ethics committee; IRB: institutional review board; IV: intravenous; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; MRI: magnetic resonance imaging; PD: progressive disease; PK: pharmacokinetic(s); [redacted]; Q2W: once every 2 weeks; Q3W: once every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors; SA: single agent; SAE: serious adverse event; SOE: schedule of events; TNBC: triple-negative breast cancer; v: Version; WBC: white blood cell.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) for holidays, vacations, and other administrative reasons. **If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the medical monitor.**

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

Table A-10 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]					EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [b]	Follow-up [b]
	Day 1	Day 15	Day 22	Day 29	Day 42			

[a] Patients will be hospitalized for at least the first 2 administrations of TAK-500 or TAK-500 + pembrolizumab, with monitoring for approximately 24 (±4) hours. Subsequent monitoring will be determined based on the presence of Grade 2 CRS in prior cycles. If a patient has had 2 consecutive administrations of TAK-500 without Grade ≥2 CRS, they may be treated as an outpatient with at least 6 hours of in-clinical observation after infusion; patients who do not experience infusion-associated symptoms or symptoms consistent with CRS during or after 4 consecutive infusions of TAK-500 may have their postinfusion monitoring reduced to 1 hour for subsequent cycles.

[b] Patients who discontinue study treatment for reasons other than PD will continue follow-up imaging every 6 weeks (±3 days) from first dose for the first 6 months and then every 12 weeks (±3 days) thereafter, until the occurrence of PD, loss to follow-up, consent withdrawal, the start of subsequent systemic antineoplastic therapy, study termination, or death, whichever occurs first. Date of disease progression and subsequent anticancer therapies will be documented. Ninety days (±3 days) after last dose, patients will have a safety check, which can occur by phone or in the clinic, at the investigator's discretion and this contact will focus on any treatment-related immune-mediated AEs. If performed over the phone, only AE reporting is required. An EOS page will be completed for all patients.

[c] The symptom-directed physical examination may be performed at additional visits during the treatment cycle at the discretion of the investigator. Before discharge from the clinic or hospital on treatment days, a physical examination will include an assessment of the respiratory and neurologic systems as well as a complete set of vital signs.

[d] Vital signs will be measured immediately before the start of the TAK-500 infusion (within 30 minutes), 30 minutes after start of infusion (±5 minutes), at the EOI (±10 minutes), 1 hour after infusion (±10 minutes), any time when clinically indicated, and before discharge. For infusion times of less than 30 minutes, vital signs will be measured immediately before the start of the infusion (within 30 minutes), at the EOI (±5 minutes), 30 minutes after EOI (±5 minutes), and at 1 hour after infusion (±10 minutes). On C1D1 vitals will also be measured at 3 and 6 hours after dosing of TAK-500 (measurement should be obtained in a ±30-minute window). Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[e] Single safety ECGs will be collected predose on days of treatment with TAK-500 and at EOT as shown. A qualified person will interpret the ECGs locally. Additional ECGs may be obtained as clinically indicated at the discretion of the investigator. ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[f] Radiological evaluations (contrast-enhanced CT scan or MRI as clinically indicated) will be used to assess the status of the patient's underlying disease. An evaluation of lesions will be performed during screening (within 28 days before the first dose of study drug). For all patients, radiographic assessments of the disease burden will be performed locally at screening/baseline (within 28 days before the first study drug administration), then every 6 weeks (±3 days) for the first 6 months from date of first dose, then every 12 weeks (±3 days) thereafter (until PD or the start of alternative therapies). Tumor assessments for all patients should continue, scheduled from C1D1, even if dosing is interrupted. Patients with an initial CT or MRI scan showing either a PR or CR should have repeat imaging in 6 weeks to confirm response. If the patient has had an appropriate CT or MRI scan performed within 28 days of C1D1, the results of that scan may be used for tumor lesion measurements at screening. Patients will undergo CT or MRI with IV contrast, as appropriate to monitor and assess response status, using RECIST v1.1 criteria. If a patient is discontinuing treatment for a reason other documented PD, imaging is required at EOT if: (1) it has been more than 4 weeks since the most recent imaging, for patients within the first 6 months of treatment, or (2) it has been more than 6 weeks since the most recent imaging, for patients on study more than 6 months. Refer to Section 9.4.13 for details.

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Table A-10 SOE for TAK-500 Q2W Treatment (42-Day Cycle) Cycle 2 Through EOS

	Cycle 2 and Subsequent Cycles [a]					EOT 30 (+7) Days After Last Dose or Before Subsequent Therapy	Safety Follow-up 90 (±3) Days After Last Dose [b]	Follow-up [b]
	Day 1	Day 15	Day 22	Day 29	Day 42			
[redacted]								

[h] For the combination arm only, pembrolizumab will be administered IV with completion of pembrolizumab infusion 1 hour before the administration of TAK-500 on Day 1. Detailed infusion instructions are provided in the pharmacy manual.

[i] For patients in cohorts where premedication with [redacted] is assigned, [redacted] will be administered 1 hour (50-120 min) before administration of TAK-500 in the SA arm and 1 hour (50-120 min) before pembrolizumab in the combination arm. [redacted] premedication will begin with C1D1 dosing and continue in subsequent cycles.

[j] Pregnancy testing (serum or urine; urine preferred) will be performed before each dose of TAK-500 and at EOT. Additional pregnancy testing (serum or urine; urine preferred) may be performed during the study at the discretion of the investigator, on request of an IEC/IRB, or if required by local regulations

[k] Hematology includes complete blood cell count with differential consisting of the following: hemoglobin, hematocrit, leukocytes (WBCs), differential WBC count, platelets, erythrocytes, MCH, MCV, and MCHC. Machine counts are acceptable. The chemistry panel consists of the following: protein (total), sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, bilirubin, ALP, AST, ALT, lactate dehydrogenase, albumin, glucose, urate, calcium, phosphate, and magnesium.

[l] The following tumor markers for the associated select tumors will be assessed at baseline before treatment on C1D1 and then every 6 weeks thereafter: TNBC, CA 27.29; HCC, AFP; pancreatic adenocarcinoma, CA 19-9.

[m] C-reactive protein and ferritin to be measured on Day 1 and Day 22 of every cycle. HbA1c and thyroid function tests to be performed every 12 weeks and if clinically indicated. Additional laboratory, including troponin, tests will only be repeated if clinically indicated while on study.

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Table A-11 Serial PK Sampling for TAK-500 Q2W Treatment (42-Day Cycle)

	Cycle 1									Cycles 2, 3, 4, 9, 15
	Day 1 [a]	Day 2	Day 4 (±1 day)	Day 8	Day 15 [a]	Day 16	Day 22	Day 29 [a]	Day 30	Day 1 [a]
Predose (<90 min before dose) [a]	X1				X1			X1		X1
EOI (±10 min)	X1				X1			X1		X1
6 h postdose (±30 min)	X1				X1			X1		X1
12 h postdose (±1 h)	X1									X1
24 h postdose (±1 h)		X1				X1			X1	X1 (if hospitalized) [b]
Day 4 postdose (±4 h)			X1							
Day 8 postdose (±4 h)				X1			X1			

CxDx: Cycle x Day x; EOI: end of infusion; PK: pharmacokinetic(s); Q2W: once every 2 weeks.

X1 = 1 PK sample will be collected for analysis of TAK-500, total antibody, and deconjugated TAK-676 at each time point.

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

During the expansion phase, for Cycle 1 and Cycle 2 only, no more than 5 PK samples will be collected after each cycle. For later cycles (Cycles 3, 4, 9, and 15), no more than 3 PK samples will be collected after each cycle. The sample collection timepoints will be determined based on emerging data from the dose escalation phase.

[a] The timing of the morning visits should occur at approximately the same time as the morning dosing times on previous days of the cycle. To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.

[b] Only required if a patient is hospitalized for administration of TAK-500. To be obtained at 24 hours postdose with a ± 6-hour window.

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Table A-12 Pharmacodynamic Biomarkers Collection for TAK-500 Q2W Treatment (42-Day Cycle)

	S	Cycle 1																	
		Day 1				Day 2	Day 4 (±1 day)	Day 8	Day 15				Day 16	Day 22	Day 24	Day 29				Day 30
		Predose ≤90 m Before Dose [a]	0.5 h Post-EOI ±15 m	6 h Post-EOI ± 30 min	12 h Post-EOI ±1 h [b]	24 h Post-EOI ±1 h [b]	DPV [b]	DPV [b]	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	6 h Post-EOI ± 30 min	12 h Post-EOI ±1h [b]	DPV [b]	DPV [b]		Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	3 h Post-EOI ±30 m	6 h Post-EOI ±1 h	
[redacted]																				
Serum Sample for Immunogenicity [e]	X								X							X				

Table A-12 Pharmacodynamic Biomarkers Collection for TAK-500 Q2W Treatment (42-Day Cycle)

	Cycles 2, 3, 4, 9, 15					EOT
	Day 1					30 (+7) Days After Last Dose
	Predose ≤30 m Before Dose	0.5 h Post-EOI ±15 m	3 h Post-EOI ±30 m		6 h Post-EOI ±1 h	
[redacted]						
Serum Sample for Immunogenicity [d]	X					X

ADA: antidrug antibodies; AE: adverse event; CxDx: Cycle x, Day x; DPV: during planned visit; [redacted]; EOI: end of infusion; EOT: end of treatment; [redacted]; Q2W: once every 2 weeks; S: screening.

For the combination arm, the predose sample collections will be conducted before pembrolizumab and TAK-500 administration. All other timeframes within the table should be relative to TAK-500 administration, not pembrolizumab.

All timepoints mentioned are relative to TAK-500 administration unless otherwise specified.

[a] To coincide with PD biomarker timing, sample should be obtained at least 15 minutes after C1D1 premedication dose, if applicable.

[b] While these pharmacodynamic collections will be performed during dose escalation, during dose expansion these pharmacodynamic collections will only be mandated if the patient is hospitalized or is seen at the clinic as part of their posttreatment care or at the same time as other blood collections.

[redacted].

[c] Immunogenicity (ADA) samples must be collected before study drug is administered on a dosing day. Additional unscheduled collections should be obtained for a patient who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample will be assessed for neutralizing ADA if a positive ADA is detected.

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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 a 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. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (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 or the patient's legally acceptable representative.
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

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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. This responsibility lies on the appropriate individual.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, 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.

The 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 the 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.

The 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 the investigator's own country.

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

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Appendix D Clinical Inhibitors of OATP1B1 and OATP1B3

Drug Class	Medication Name (Brand Name)	Required Washout Period Before First Dose
Antiviral	Atazanavir (Reyataz)	14 days before first dose of study drug(s)
	Lopinavir (Kaletra)	
	Ritonavir (Norvir)	
	Simeprevir (Olysio)	
	Remdesivir (Veklury)	
Antibiotic	Clarithromycin (Biaxin, Biaxin XL)	
	Erythromycin (E.E.S. Granules, E.E.S.-400 Filmtab, EryPed 200, EryPed 400, Ery-Tab, Erythrocin Lactobionate, Erythrocin Stearate Filmtab, PCE Dispertab)	
	Rifampin (single dose)/rifampicin (Rifadin, Rifadin IV, Rimactane)	
Immunosuppressant	Cyclosporine (Gengraf, Neoral, SandIMMUNE)	
Antilipemic/ hypercholesterolemia	Gemfibrozil (Lopid)	

Source: fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

DDI: drug-drug interaction; FDA: Food and Drug Administration; OATP: organic anion transporting polypeptide.

Note the list of clinical inhibitors of OATP1B1 and OATP1B3 is not exhaustive and is based on the FDA Draft DDI Guidance.

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Appendix E Potential Risks of TAK-676

Several potential risks and target organs were identified in in vitro and in vivo toxicology studies with TAK-676 and are discussed below. Increase in pro-inflammatory cytokines were observed in an in vitro human whole blood cytokine release assay and in serum from rats and monkeys administered TAK-676. The predominant microscopic finding in rats was single-cell necrosis across multiple organs that was most consistent with death of lymphocytes and leukocytes. Additional targets in rats included bone marrow, lymph nodes, thymus, GIT, hematopoietic system (spleen), soleus muscle, and liver. The target organ in the monkey was the lungs.

Effects on Lung Vasculature

Administration of TAK-676 resulted in pulmonary changes in monkeys, but not rats, that were considered consistent with vascular leak and the cause of the moribundity and/or death observed in monkeys at doses ≥0.13 mg/kg (bolus and infusion).

In the non-GLP single-dose study in monkeys, macroscopic observations at necropsy in the monkeys removed early included fluid accumulation in the thoracic cavity and at 0.2 mg/kg only, discoloration (diffuse, dark red, mottled) and fluid accumulation in the lungs. Microscopic findings in the lung included interstitial/alveolar edema in all monkeys removed early from study, with histiocytes in the alveolar space at 0.2 mg/kg only.

In the 2-week repeat-dose GLP study twice weekly, macroscopic observations were limited to monkeys that were found dead or removed moribund on Day 2 at 0.13 mg/kg (infusion) and included fluid accumulation in the thoracic cavity and mottled discoloration in the lungs. Microscopic findings (limited to lung) were observed in monkeys receiving 0.13 mg/kg TAK-676 via bolus or infusion administration that were found dead, removed moribund, or that underwent early scheduled euthanasia on Days 4, 8, or 11 and included minimal to moderate congestion, minimal to mild alveolar/interstitial edema and histiocytic alveolar infiltration, and/or minimal hemorrhage. These findings correlated with the mottled discoloration of the lung observed macroscopically, were considered to be consistent with vascular leak, and were considered directly related to the poor clinical tolerability and early mortality at this dose. In addition, minimal alveolar/interstitial edema was observed in 1 female that survived (with no notable clinical observations) to scheduled necropsy on Day 16 at 0.13 mg/kg (slow bolus). These findings were not observed in monkeys evaluated after the 2-week postdose period.

Effects on the Immune and Lymphoid Systems

TAK-676–related effects on the immune and lymphoid systems were limited to the rat.

In the exploratory studies in rats, single-cell necrosis of lymphocytes and/or decreases in lymphocyte cellularity were observed in the Peyer's patches and in the cecal, mesenteric, and mandibular lymph nodes. These findings correlated with decreases in circulating lymphocytes.

In the repeat-dose (GLP) study in rats, decreases in thymic and increases in splenic weights were observed and correlated with decreased cellularity and necrosis of lymphocytes in the thymus, and increased extramedullary hematopoiesis in the spleen (related to decreased red cell mass on hematology). In addition, sinus erythrocytosis and congestion/hemorrhage were noted in lymph

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nodes and thymus that generally correlated with gross observations of discoloration. In animals found dead or removed early at ≥20 mg/kg changes in circulating lymphocytes and leukocytes included minimal to marked increases in neutrophil counts; moderate to marked decreases in lymphocytes; mild increase in monocytes. Additional changes at 40 mg/kg in these animals included moderate to marked decreases in eosinophils, increased basophils and decreased large unstained cells with low to many pyknotic cells noted on blood smears. In surviving animals at ≥10 mg/kg, minimal decreases in total white blood cell counts, a minimal to moderate increase in neutrophil counts, a moderate to marked decrease in lymphocyte counts, and a minimal increase in monocyte counts (20 mg/kg only) were noted. At ≥10 mg/kg, the predominant microscopic finding was single cell necrosis most consistent with death of lymphocytes and leukocytes that was observed across multiple tissues including: lymph nodes; spleen; gut-associated lymphoid tissue; bronchus-associated lymphoid tissue; thymus; in perivascular and interstitial areas in skeletal muscle; and in the epididymis. At ≥20 mg/kg, single-cell necrosis of presumptive lymphocytes and leukocytes was also observed in the portal interstitium of liver; the lamina propria and submucosa of the GIT (stomach, duodenum, jejunum, ileum, colon, cecum, and rectum), that was occasionally associated with degeneration of adjacent mucosal cells admixed with associated neutrophilic infiltrates; in the bone marrow; and in the perivascular and interstitial areas of the lung. At 40 mg/kg, single-cell necrosis of presumptive lymphocytes and leukocytes as noted in the cervix. These findings recovered after a 2-week postdose period.

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Effects on the Liver

In a non-GLP liver microtissue (LiMT) cytotoxicity assay, TAK-676 had no effect on cell viability in dog, monkey, or human LiMT (50% inhibitory concentration [IC_{50}] >100 μM), suggesting a low drug-induced liver injury (DILI) risk was detected in vitro. In contrast, incubation of rat LiMT with 100-μM TAK-676 resulted in a moderate decrease in cell viability (60%, IC_{50} = 88.3 μM), suggesting that rats may have a species-specific DILI hazard.

In vivo, TAK-676–related effects on the liver were limited to the rat. In the GLP-compliant repeat-dose study, bile duct hyperplasia, single-cell hepatocyte necrosis, and increased hepatocellular mitosis with corresponding changes in serum chemistry parameters (ALT, AST, glutamate dehydrogenase, and gamma glutamyl transferase activities and alpha-2-macroglobulin) were observed at ≥20 mg/kg. Except for bile duct hyperplasia associated with mild mixed cell infiltrates in the liver of 1 male at 20 mg/kg, findings recovered after a 2-week postdose period.

Effects on the Bone Marrow

TAK-676–related effects on the bone marrow were limited to the rat. In the GLP-compliant repeat-dose study, decreased cellularity of mature granulocytes in the bone marrow that was associated with increased immature granulocytes and sometimes with the presence of pyknotic cells presumed to be granulocytes in the bone marrow were observed microscopically at ≥20 mg/kg. These findings correlated with increases in neutrophils on hematology. These findings recovered after a 2-week postdose period.

Effects on the Skeletal Muscle (Soleus)

TAK-676–related effects on the skeletal muscle (soleus) were limited to the rat. In the GLP-compliant repeat-dose study, at ≥10 mg/kg occasional degeneration and necrosis of myocytes was associated with single-cell necrosis of presumptive lymphocytes and leukocytes in perivascular and interstitial areas and mixed cell infiltrates were noted. These findings recovered after a 2-week postdose period.

Effects on GIT

TAK-676–related effects on the GIT were limited to the rat. In the GLP-compliant repeat-dose study, dose-dependent submucosal edema was noted in the colon, cecum, and rectum at ≥20 mg/kg. In addition, discoloration of the stomach, jejunum, and ileum were observed at ≥20 mg/kg and generally correlated with congestion, hemorrhage, and single-cell necrosis of presumptive lymphocytes and leukocytes within the lamina propria and submucosa. Feces changes (loose, soft, liquid, or mucoid) were observed in moribund animals. In addition, decreases in body weight and weight gain were also observed in animals found dead or removed from the study early, and correlated with decreases in food consumption, and required food supplementation starting on Days 5 for some animals and Day 8 for additional animals at 40 mg/kg (bolus and infusion). The gross and microscopic findings noted in the GIT could not be directly correlated with the clinical observations in the rats.

Effects at the Injection Site

There were no injection site findings noted after IV bolus or infusion administration in the GLP-compliant repeat-dose toxicity study in rats or in the exploratory or GLP-compliant studies in monkeys. In the exploratory repeat-dose toxicity study in rats, microscopic changes at the injection site included perivascular minimal to mild hemorrhage and minimal to moderate inflammation in all groups (including controls) that had an increased incidence and severity in animals administered TAK-676 and was accompanied by minimal to mild vascular degeneration and necrosis at ≥2.1 mg/kg twice weekly.

Potential for CRS

Increases in pro-inflammatory cytokines were observed in an in vitro human whole blood cytokine release assay and suggest a potential TAK-676–related risk for CRS and inflammatory and immune-related toxicities in humans.

There were no clinical signs or increases in body temperature suggestive of a CRS after administration of TAK-676 in the GLP-compliant toxicity studies in rats and monkeys. However, in rats, increases in TNF-α and IL-6 were observed at ≥10 mg/kg on Days 1, 11, and 15. In monkeys, increases in IL-6 were observed at 0.13 mg/kg (bolus and infusion) on Day 1 only. The relationship between IL-6 and the toxicity observed at 0.13 mg/kg in the monkey is unclear. In addition, there was clinical pathology evidence of an acute phase response in both species.

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Appendix F BOIN Design

The BOIN design (Liu and Yuan 2015) will be used to guide the dose escalation decisions and MTD estimation. This study was designed and will be conducted using the software BOIN that is available at trialdesign.org.

Target toxicity rate is 0.3. During the study, if the observed DLT rate at the current dose is ≤0.236, the next cohort of patients will be treated at the next higher DL; if it is ≥0.358, the next cohort will be treated at the next lower DL; if it is within 0.236 and 0.358, additional patients will be enrolled in this DL. For the purpose of overdose control, a DL and all the DLs above it will be eliminated from further examination if its posterior probability of exceeding the target toxicity rate is greater than 0.95. If the lowest DL is eliminated, stop the escalation for safety. Unless such early stop happens, dose escalation will continue until either: (1) the maximum sample size is reached, or (2) the number of patients treated at the current dose reaches 9 and the recommendation is to retain at the current DL.

The dose escalation algorithm is described as the following steps:

1. Patients in the first cohort are treated at lowest DL.
2. Decide the DL for the next cohort according to the rule shown in Table F-1, noting the following:
   a) "Eliminate" means that the current DL and all higher DLs are eliminated to prevent treating any future patients at these overly toxic DLs.
   b) When a DL is eliminated, automatically de-escalate to the next lower DL. When the lowest DL is eliminated, stop the dose escalation for safety. In this case, no DL should be selected as the MTD.
   c) If none of the actions (ie, escalation, de-escalation or elimination) is triggered, the next cohort will be treated with the current dose.
   d) If the current dose is the lowest DL and the rule indicates a de-escalation, treat the next cohort at the lowest DL unless the number of DLTs reaches the elimination boundary, at which point the dose escalation should be terminated for safety.
   e) If the current dose is the highest dose and the rule indicates an escalation, treat the next cohort at the highest dose.
3. Repeat Step 2 until either: (1) the maximum sample size is reached, or (2) 9 patients have been treated with the current DL and the recommendation is to retain at the current DL.

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Table F-1 Dose Escalation/De-escalation Rule for the BOIN Design

Number of patients treated at the current dose	1	2	3	4	5	6	7	8	9
Escalate if number of DLT ≤	0	0	0	0	1	1	1	1	2
De-escalate if number of DLT ≥	1	1	2	2	2	3	3	3	4
Eliminate if number of DLT ≥	NA	NA	3	3	4	4	5	5	5

BOIN: Bayesian Optimal Interval; DLT: dose-limiting toxicity; NA: not applicable.
Number of DLT is the number of patients with at least 1 DLT.

After the dose escalation is complete, the MTD is selected based on isotonic regression, as specified in Liu and Yuan (Liu and Yuan 2015). Specifically, the dose is selected as the MTD for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, the higher DL is selected when the isotonic estimate is lower than the target toxicity rate; the lower DL is selected when the isotonic estimate is greater than or equal to the target toxicity rate.

The operating characteristics of the BOIN design are evaluated with simulations assuming various distributions of toxicity across DLs shown in Table F-2.

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Table F-2 Simulation Scenarios

Dose Level (TAK-500)	True DLT Rate							
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
8 µg/kg	0.21	0.15	0.10	0.06	0.04	0.02	0.015	0.01
16 µg/kg	**0.30**	0.21	0.15	0.10	0.07	0.05	0.04	0.03
24 µg/kg	0.42	**0.30**	0.18	0.13	0.08	0.06	0.05	0.04
40 µg/kg	0.45	0.40	**0.30**	0.15	0.10	0.08	0.07	0.05
80 µg/kg	0.49	0.46	0.45	**0.30**	0.12	0.11	0.10	0.08
160 µg/kg	0.55	0.53	0.51	0.45	**0.30**	0.14	0.13	0.10
240 µg/kg	0.62	0.59	0.57	0.51	0.47	**0.30**	0.15	0.13
360 µg/kg	0.68	0.64	0.62	0.57	0.53	0.48	**0.30**	0.15
480 µg/kg	0.72	0.68	0.65	0.64	0.59	0.53	0.47	**0.30**

DLT: dose-limiting toxicity.

For the SA escalation, we assume the BOIN escalation starts at 16 µg/kg, and a maximum of 42 DLT-evaluable patients can be enrolled after the BOIN escalation starts. Each cohort enrolls 3 patients.

For the combination escalation, we assume the BOIN escalation starts at 80 μg/kg and a maximum of 27 DLT-evaluable patients can be enrolled after the BOIN escalation starts (Scenarios 1 and 2 are not included in the simulation because it is unlikely for 24 μg/kg or less to be the MTD if 80 μg/kg has been cleared for safety in the SA arm). Each cohort enrolls 3 patients.

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Table F-3 Operating Characteristics for the SA Escalation

	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5		Scenario 6		Scenario 7		Scenario 8	
Dose Level (TAK-500)	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**	**Selection %**	**% Pts Treated**
8 µg/kg	20.4	17.0	5.7	6.3	1.6	2.3	0.3	0.6	0.0	0.2	0.0	0.1	0.0	0.0	0.0	0.0
16 µg/kg	**51.4**	**47.3**	30.9	35.2	11.7	22.8	4.1	16.0	1.7	12.4	0.5	10.7	0.3	9.8	0.2	9.4
24 µg/kg	20.0	25.7	**39.8**	**33.4**	25.4	27.2	8.0	17.3	2.0	12.6	0.9	11.1	0.6	10.0	0.3	9.6
40 µg/kg	5.5	**7.7**	18.0	18.1	**44.6**	**29.3**	21.8	22.4	3.7	13.6	2.6	11.9	1.6	10.9	0.6	10.1
80 µg/kg	1.1	2.0	4.7	5.7	13.7	14.6	**47.5**	**26.9**	20.5	20.0	5.6	13.4	4.4	12.3	2.4	11.2
160 µg/kg	0.2	0.3	0.6	1.1	2.6	3.1	15.5	13.5	**54.4**	**26.1**	21.8	18.2	7.6	13.2	4.2	12.0
240 µg/kg	0.0	0.0	0.1	0.1	0.3	0.6	2.5	2.7	15.2	12.5	**52.5**	**22.3**	21.9	16.0	7.2	12.8
360 µg/kg	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.4	2.2	2.2	13.8	10.5	**47.2**	**18.6**	22.7	15.7
480 µg/kg	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	2.2	1.8	16.4	9.2	**62.4**	**19.0**
% Early stopping	1.3		0.3		0.0		0.0		0.0		0.0		0.0		0.0	
Expected no. of pts	18.6		21.1		23.8		27.4		30.8		33.3		35.2		35.2	

Pts: patients; SA: single agent.

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Table F-4 Operating Characteristics for the Combination Escalation

Dose Level (TAK-500)	Scenario 3		Scenario 4		Scenario 5		Scenario 6		Scenario 7		Scenario 8	
	Selection %	% Pts Treated	Selection %	% Pts Treated	Selection %	% Pts Treated	Selection %	% Pts Treated	Selection %	% Pts Treated	Selection %	% Pts Treated
8 µg/kg	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
16 µg/kg	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
24 µg/kg	13.8	11.5	0.7	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
40 µg/kg	**47.5**	**34.7**	17.4	16.7	0.8	1.6	0.4	1.0	0.2	0.7	0.1	0.4
80 µg/kg	32.1	41.2	**58.8**	**49.9**	19.8	32.2	5.3	20.6	4.2	18.4	2.0	16.5
160 µg/kg	5.0	10.0	19.1	25.6	**60.0**	**42.0**	22.7	27.5	7.7	19.8	4.1	17.7
240 µg/kg	0.4	1.4	3.5	5.7	16.3	19.6	**53.4**	**33.0**	23.4	23.4	7.8	18.9
360 µg/kg	0.0	0.1	0.3	0.9	2.7	4.1	15.1	15.2	**47.2**	**25.7**	25.1	21.5
480 µg/kg	0.0	0.0	0.0	0.1	0.4	0.5	3.0	2.7	17.4	12.2	**60.9**	**25.0**
% Early stopping	0.0		0.0		0.0		0.0		0.0		0.0	
Expected no. of pts	18.2		17.8		20.1		22.2		23.7		24.1	

Pts: patients.

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Appendix G 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, 1982 (Oken et al. 1982).
ECOG: Eastern Cooperative Oncology Group.

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Appendix H Cockcroft-Gault Equation

For male patients:

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

For female patients:

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

Source: Cockcroft and Gault, 1976.

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Appendix I RECIST v1.1

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 based on size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target site of measurable lesions.

Table I-1 Disease Response Criteria for Target and Nontarget Lesions

Evaluation of target lesions	
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
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 1 or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
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	
CR	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Unequivocal progression of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Source: (Eisenhauer et al. 2009).

CR: complete response; LD: longest diameter; PD: progressive disease; PR: partial response; SD: stable disease.

The following table summarizes the overall response status calculation at each time point for patients who have measurable disease per RECIST v1.1 at baseline.

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Table I-2 Disease 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 et al. 2009).

CR: complete response; NE: not evaluable; PD: progressive disease; PR: partial response; SD: stable disease.

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

Table I-3 Disease 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 et al. 2009).

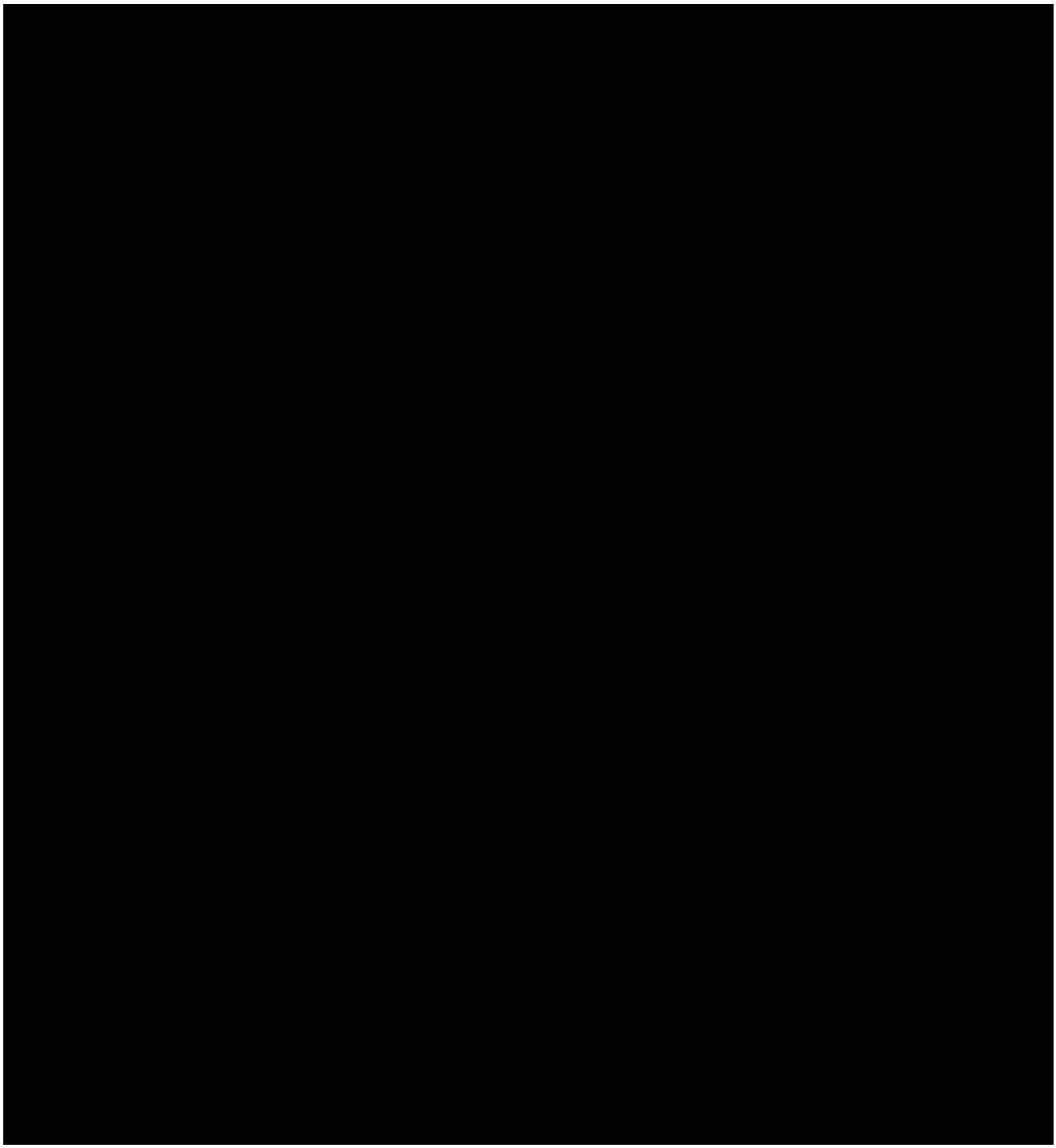
CR: complete response; NE: not evaluable; PD: progressive disease; SD: stable disease.

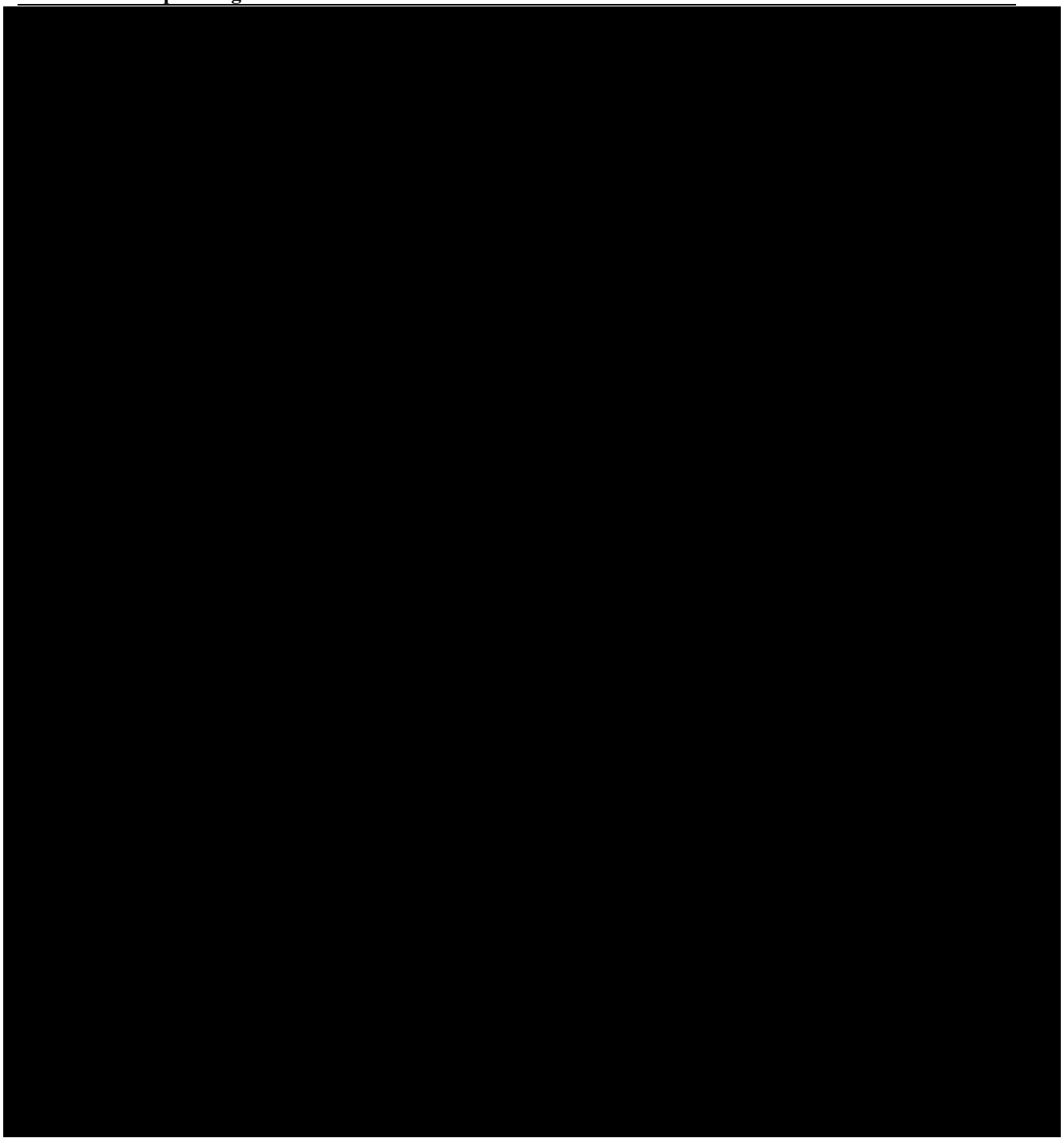
[a] Non-CR/non-PD is preferred over SD for nontarget disease because SD is increasingly used as endpoint for assessment of antitumor activity in some studies, so to assign this category when no lesions can be measured is not advised.

RECIST v1.1 and treatment beyond progression: As described in Section 9.4.13.1, accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients will be permitted to continue study treatment beyond initial RECIST v1.1 defined PD as long as they meet the criteria outlined in this section. All decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

Appendix J [redacted]

[redacted]





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Appendix K [redacted]

[redacted]

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Appendix L [redacted]

[redacted]

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Appendix M [redacted]

[redacted]

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Appendix N Protocol History

Date	Amendment Number	Region
13 June 2023	Amendment 3	North America, Europe
25 October 2022	Amendment 2	United States
21 September 2021	Amendment 1	United States
15 July 2021	Initial Protocol	United States

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2.

The primary reasons for this amendment are to:

- Transition the initiation of the combination TAK-500 plus pembrolizumab dose escalation arm to the safety clearance of the 80 µg/kg dose level (DL) or determination of pharmacologically active dose (PAD) to be ≤40 µg/kg in the single agent (SA) TAK-500 dose escalation cohort.
- Add 2 indications: renal clear cell carcinoma (RCC) and nasopharyngeal carcinoma (NPC).
- Clarify the number of patients to be enrolled to potentially explore the once every 2 weeks (Q2W) TAK-500 dosing schedule in dose escalation.
- Add a cytokine release syndrome (CRS) mitigation strategy.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 4.2 Rationale for the Proposed Study Section 4.2.1.8 RCC Section 4.2.1.9 NPC Section 5.1.1 Primary Objectives Section 6.1 Overview of Study Design Section 7.1 Inclusion Criteria	Included patients with renal clear cell carcinoma (RCC) and nasopharyngeal carcinoma (NPC).	RCC and NPC are tumors with high cysteine-cysteine chemokine receptor type 2 expression in the tumor immune microenvironment and have high unmet need in later lines of therapy.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2.	Section 2.0 STUDY SUMMARY Section 4.2.2.4 Dose Range Section 4.2.2.5 Dosing Schedule of TAK-500 Section 6.1 Overview of Study Design Section 6.1.1 TAK-500 Dose Escalation Section 6.1.1.1 TAK-500 SA Dose Escalation Section 6.1.1.2 TAK-500 in Combination With Pembrolizumab Dose Escalation Section 6.1.1.3 General Rules for Dose Escalation Section 6.1.2 TAK-500 in Combination With Pembrolizumab Dose Expansion Section 6.1.3 Study Assessments Section 8.1.1 TAK-500 Section 8.1.3 TAK-500 in Combination With Pembrolizumab Section 8.3.1 BOIN Dose Escalation Section 8.5.3 Criteria for Administering a Subsequent Dose/Starting a New Treatment Cycle Section 8.5.4 Criteria for Dose Modification Appendix A SOEs	Adjusted aspects of the study design related to dose escalation of TAK-500 single agent and in combination with pembrolizumab.	The changes optimize the approach for balancing potential antitumor activity and safety.
3.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives Section 5.2.2 Secondary Endpoints Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures	Updated language for evaluation of dose-responsive impact on T-cell infiltration of the tumor following TAK-500 administration.	Changed in order to more accurately represent the intended analysis of TAK-500 on the tumor.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints	Removed pharmacologically active dose (PAD) range and the dose for further development as secondary endpoints.	Endpoints are generally subject-level variables, while PAD and the dose for further development are population level.
5.	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures	Removed the following secondary endpoint: "[redacted]"	The modified biomarker endpoint is of an exploratory nature rather than a secondary nature.
6.	Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Design Section 6.2 Number of Patients Section 13.3 Determination of Sample Size	Increased the number of patients to 118.	Number of patients increased to account for additional once-every-2-weeks cohorts in dose escalation.
7.	Section 2.0 STUDY SUMMARY Section 6.1.1.1 TAK-500 SA Dose Escalation	Changed wording from "2 subsequent DLs [dose levels]" to "2 consecutive DLs" for confirmation of minimum PAD.	Changed for clarification.
8.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Changed inclusion criterion #4 from "evaluable" to "measurable" lesion.	Evaluation of tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1, requires measurement of lesions.
9.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Removed inclusion criterion #6.	While investigators are still expected to use their best judgment in enrolling patients who they expect could remain on study reasonably long enough to assess safety and efficacy of study treatments, it was determined performance status is a less subjective evaluation of overall health.
10.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added pre-existing conditions to exclusion criterion #16.	A pre-existing condition may affect patient safety.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
11.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Changed exclusion criterion #20 to reduce the washout period from 14 days to 7 days.	Seven days should be sufficient to taper a patient on systemic corticosteroids.
12.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria Section 8.6 Excluded Concomitant Medications and Procedures Section 8.7 Permitted Concomitant Medications and Procedures	Added an exception for nonsystemic corticosteroids.	Nonsystemic corticosteroids should not affect the pharmacology of TAK-500 or present any safety concerns.
13.	Section 2.0 STUDY SUMMARY Section 6.1.3 Study Assessments Section 8.2 Definitions of DLT Section 8.5.5 Criteria for Discontinuation of TAK-500 Section 8.6 Excluded Concomitant Medications and Procedures	Updated definitions of dose-limiting toxicity (DLT).	Updated to clarify and to ensure patient safety.
14.	Section 2.0 STUDY SUMMARY Section 6.1.1.1 TAK-500 SA Dose Escalation Section 8.4 Definition of PAD	Updated the definition of PAD.	The definition was updated to reflect the latest understanding of what PAD should be for this study.
15.	Section 2.0 STUDY SUMMARY Section 13.1.1 Analysis Sets Appendix A SOEs	Added an option for [redacted] premedication. Specified that patients treated with [redacted] premedication will be evaluated separately from those without premedication.	This change made for increased patient safety and increased clarity in statistical analysis.
16.	Section 4.1.2.2 TAK-676	Updated background information about TAK-676.	This was updated to reflect the latest data for TAK-676.
17.	Section 4.1.2.3 TAK-500	Added background information about TAK-500.	This section added to reflect the latest data for TAK-500.
18.	Section 4.2.2.2 Recommended Starting Dose Based on MABEL	Added clarification regarding preclinical models and cytokine release syndrome (CRS).	Updated to reflect the latest data.
19.	Section 4.2.3.1 Tumor Biopsies	Removed reference to bayesian logistic regression modeling.	This reference is not necessary.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
20.	Section 4.3 Potential Risks and Benefits	Updated section to indicate that TAK-500 is currently being evaluated in a first-in-human study.	This section was updated to reflect the latest data.
21.	Section 4.3.1.1 CRS	Updated background information about CRS.	This was updated to reflect the latest data.
22.	Section 6.1.1.1 TAK-500 SA Dose Escalation Section 6.1.1.2 TAK-500 in Combination With Pembrolizumab Dose Escalation Section 6.1.1.4 Corticosteroid Premedication Section 8.1.1 TAK-500 Section 8.5.4 Criteria for Dose Modification Section 8.9.1 CRS Section 8.9.7 Infusion-Related Reactions Appendix A SOEs	Updated the study design to include a CRS-mitigation strategy.	CRS has been observed in patients, and a strategy has been developed to mitigate CRS for continued dose escalation.
23.	Section 8.1.1 TAK-500 Section 9.4.6 Vital Signs Appendix A SOEs	Clarified that measurement of vital signs on Cycle 1 Day 1 should be obtained 3 and 6 hours after dosing of TAK-500, within a ±30-minute window.	This was changed for clarification.
24.	Section 8.5.3 Criteria for Administering a Subsequent Dose/Starting a New Treatment Cycle	Removed albumin.	Patients do not need to have a certain level of albumin before having a subsequent dose of TAK-500 or starting a new treatment cycle.
25.	Section 8.5.4 Criteria for Dose Modification	Updated dose-modification guidelines.	This was updated to increase patient safety.
26.	Section 8.9.2 Pulmonary Edema	Updated guidelines for management of pulmonary edema.	This was updated to increase patient safety.
27.	Section 8.9.7 Infusion-Related Reactions	Updated guidelines for management of infusion-related reactions.	This was updated to increase patient safety.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
28.	Section 8.9.9 Management of COVID-19–Positive Patients	Updated guidelines for the management of coronavirus disease 2019 (COVID-19)–positive patients.	This was updated to be consistent with most recent understanding of COVID-19 risks and management.
29.	Section 8.9.10 CV Toxicity	Added guidelines for management of cardiovascular toxicity.	This was added to increase patient safety.
30.	Section 9.4.4 Physical Examination Section 9.4.6.2 Pulse Oximetry	Added clarification regarding the assessment of O_2 saturation using pulse oximetry.	To harmonize the previous contradictions between the 2 sections.
31.	Section 9.4.12.1 Clinical Chemistry, Hematology, Tumor Markers, Coagulation, and Thyroid Function Appendix A SOEs	Added the interleukin-6 test.	This laboratory test was added to increase patient safety.
32.	Section 9.4.13 Disease Assessment	Added an option to obtain an intravenous (IV) contrast scan.	IV contrast and contrast-enhanced computed tomography scans (if available) are preferable to reduce patient burden.
33.	Section 9.4.14.2 Tumor Biopsies Appendix A SOEs	Changed PD, biomarker, and PK sampling timepoints. Increased the biopsy collection window to 28 days. Specified that biopsy collection will be 48 hours after dosing.	The collection window was increased to reduce patient burden. Sampling timepoints changed to more appropriately reflect PD activity profile.
34.	Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Updated the discontinuation criteria.	This was updated for increased patient safety.
35.	Section 13.1.1 Analysis Sets	Updated the definition of DLT-evaluable set.	The change made for increased clarity in statistical analysis.
36.	Section 13.1.3 Efficacy Analysis	Changed antitumor “analysis” to antitumor “activity.”	Change made for increased clarity in statistical analysis.
37.	Section 13.1.3 Efficacy Analysis	Added death to the definition of duration of response.	This change was made to clarify that all-cause death is also considered an event.

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Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
38.	Section 13.1.3 Efficacy Analysis	Added "PFS [progression-free survival] will be analyzed using Kaplan-Meier method for the safety analysis set in dose expansion cohorts only."	This was added for clarity.
39.	Section 13.2 Interim Analysis and Criteria for Early Termination	Added "In the dose expansion phase, an interim futility analysis will be performed,"	To clarify that an interim futility analysis for the expansion cohort will be performed.
40.	Appendix A SOEs	Clarification that ECGs will be done on dosing days.	Update made for clarification.
41.	Appendix A SOEs	Updated footnote "I" in Table A-1 SOE for TAK-500 Q3W Treatment (21-Day Cycle) Cycle 1.	Update made for clarification.

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Protocol Amendment 1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 1.

The primary reason for this amendment is to:

Address the changes requested by United States (US) Food and Drug Administration (FDA) during Investigational New Drug (IND) application review.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 STUDY SUMMARY Section 6.1.1 TAK-500 SA Dose Escalation Section 6.1.4 Study Assessments Section 8.9.1 CRS Section 8.9.7 Infusion-Related Reactions SOEs	Increased patient monitoring time in the clinic to at least 4 hours after TAK-500 infusion during the second infusion and beyond. Patients who do not experience infusion-associated symptoms or symptoms consistent with cytokine release syndrome (CRS) during or after the first 3 infusions of TAK-500 may have their subsequent post-infusion monitoring reduced to 1 hour.	Changes made in response to an FDA request for additional safety monitoring of patients after TAK-500 infusions.
2.	Section 2.0 STUDY SUMMARY Section 6.1.1 TAK-500 SA Dose Escalation Section 6.1.2 TAK-500 in Combination With Pembrolizumab Dose Escalation Section 8.3.1 BOIN Dose Escalation	Modified enrollment rule by staggering the dosing between the first patient of any new dose level (DL) and subsequent patients enrolled at the same DL by 24 hours.	Changes made in response to an FDA request to ensure there is a 24-hour gap in dosing between the first patient of any new DL and subsequent patients.
3.	Section 2.0 STUDY SUMMARY Section 8.1.1 TAK-500 Section 8.9.1 CRS	Highlighted the option to use other anti–interleukin (IL)-6 agents for CRS treatment due to limited availability of tocilizumab.	Due to the limited supply of tocilizumab, which has been publicly stated by the manufacturer, FDA requested that an alternative for tocilizumab in treatment of CRS be noted.

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Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
4.	Section 2.0 STUDY SUMMARY Section 8.2 Definitions of DLT	Revised the definitions of dose-limiting toxicity (DLT): 1. Removed the following exception: "Isolated elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), that is ≤10 × upper limit of normal (ULN) in the absence of significant bilirubin elevation (Grade <3), excluding elevations meeting Hy's Law." 2. The following exceptions are to be resolved/corrected within 3 days instead of 5 days: • Grade 3 asymptomatic laboratory changes (other than renal function). • Grade 3 nausea and/or emesis. • Grade 3 diarrhea.	Changes made in response to FDA request to modify DLT definitions.
5.	Section 13.1.9 Safety ECG Analysis	Changed the QT interval correction method from Bazette to Fridericia.	Changed to correct a typographical error. Initial intent was only to include QT interval with Fridericia correction method (QTcF) as this is the more established standard for QT correction.

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Signature Page for TAK-500-1001 Protocol Amendment 3 2023-06-13

Title: TAK-500-1001 Protocol Amendment 3 2023-06-13

Approval	[redacted] Clinical 19-Jun-2023 12:43:17 GMT+0000
Approval	[redacted] Statistics 19-Jun-2023 12:44:54 GMT+0000
Approval	[redacted] Research 19-Jun-2023 13:02:02 GMT+0000

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