# CONTRATTO DI RICERCA PER SPERIMENTAZIONE CLINICA SU INIZIATIVA DELLO SPERIMENTATORE

Il presente contratto s'intende stipulato alla data dell'ultima sottoscrizione di esso, tra:

**Fondazione IRCCS Istituto Nazionale dei Tumori** con sede legale in via Venezian n. 1, 20133, Milano, Italia, Codice Fiscale 80018230153 e Partita I.V.A. 04376350155 nella persona del Direttore Generale, Dott.ssa Maria Teresa Montella, di seguito indicato come "**Istituzione**",

e

**MSD Italia S.r.l.,** con socio unico, soggetta a direzione e coordinamento di Merck & Co., Inc., con sede in Roma, via Vitorchiano 151, P.IVA n. 00887261006 C.F. n. 00422760587, *rappresentata dal Dr. Giorgio Ursillo nella sua qualità di Procuratore Speciale in virtù della Procura Speciale rilasciata in data 24.11.23 munito dei necessari poteri*, in nome proprio e per conto di **MERCK SHARP & DOHME LLC**, con sede in 126 East Lincoln Avenue, Rahway, New Jersey, 07065 USA, di seguito indicata come "**MSD**".

Da qui in avanti anche, singolarmente, "Parte" e, collettivamente, "Parti" del presente accordo

**PREMESSO CHE:**

- l'Istituzione (di seguito anche "**Promotore)** e lo Sperimentatore Responsabile (come definito nel successivo articolo 2) hanno progettato e intendono sostenere e condurre in maniera autonoma e indipendente uno studio denominato "Activity of Pembrolizumab plus Enfortumab Vedotin in Collecting Duct and Renal Medullary Carcinoma" (lo "**Studio**"), "numero EuCTR 2024-511587-93-00, rif. MISP n° 101404, concernente la sicurezza e l'efficacia del farmaco in sperimentazione (il "**Medicinale Sperimentale**") mediante una serie di ricerche cliniche;

- MSD, in coerenza con il proprio impegno nel campo della ricerca clinica, intende apportare il proprio contributo a favore dell'Istituzione nei termini ed alle condizioni previste nel presente contratto (il "**Contratto**"), dichiarando per sé e per conto delle consociate, controllate e collegate del gruppo MSD, di avere interesse esclusivamente scientifico ai risultati dello Studio e rimanendo invece esclusa ogni finalità di lucro o collegata allo sviluppo industriale o commerciale del Medicinale Sperimentale;
- non esistono tra le Parti rapporti o cointeressenze che possono pregiudicare l'indipendenza dello Studio ed influenzarne i risultati.

- il Promotore si impegna a comunicare/ha comunicato ad AIFA e al Comitato Etico

competente nella domanda di autorizzazione e richiesta di parere la propria volontà circa l'utilizzo del finanziamento di MSD, depositando copia del presente contratto e di ogni eventuale ulteriore accordo ai sensi dell'art. 2, comma 6 del D.M. 30.11.2021.

**TUTTO CIÒ PREMESSO**, le Parti convengono quanto segue.

## 1. Oggetto

L'Istituzione e lo Sperimentatore Responsabile (definito ed indicato all'articolo 2 che segue) condurranno, lo Studio secondo quanto previsto nel Contratto nonché nel protocollo (e sue eventuali modifiche apportate a norma del Contratto) "Activity of Pembrolizumab plus Enfortumab Vedotin in Collecting Duct and Renal Medullary Carcinoma " (di seguito il "**Protocollo**") numero EuCTR 2024-511587-93-00 , rif. di Registro MISP 101404, che viene allegato sub "A" a formare parte integrante del Contratto.
L'Istituzione assicura che, per quanto di sua conoscenza, le proprie strutture e la popolazione dei pazienti sono idonee alla conduzione dello Studio.
L'Istituzione e lo Sperimentatore Responsabile convengono che lo Studio verrà condotto in ogni suo aspetto a norma delle leggi e dei regolamenti vigenti, ivi incluse in particolare le norme ICH di Buona Pratica Clinica (D.M. 15.07.1997 e s.m.i.).
L'Istituzione e lo Sperimentatore Responsabile convengono inoltre di non condurre nell'ambito dello Studio attività di ricerca con il Medicinale Sperimentale in contrasto con il Protocollo ovvero al di fuori dell'ambito di esso.
L'Istituzione condurrà lo Studio in qualità di promotore a sensi di legge ed adempirà agli obblighi e doveri del promotore nel corso dello Studio stesso. Pertanto, l'Istituzione provvederà ad ottenere tempestivamente tutte le approvazioni necessarie per effettuare lo Studio (a titolo esemplificativo: approvazione del proprio Comitato Etico, accettazione dei Comitati Etici dei Centri in caso di Studio multicentrica, autorizzazione della sperimentazione da parte dell'Autorità Competente), e a richiedere eventuali proroghe che dovessero rendersi necessarie, informandone tempestivamente MSD. L'Istituzione fornirà ad MSD una dichiarazione scritta attestante la positiva conclusione della procedura autorizzativa (i.e. indicazione della data di presentazione della domanda autorizzativa, data di avvio della procedura comunicata dall'Autorità Competente, assenza di obiezioni motivate nei termini di legge)**.**
In caso di interruzione temporanea, sospensione, revoca o modifica del parere del Comitato Etico o dell'autorizzazione dell'Autorità Competente, lo Sperimentatore Responsabile e l'Istituzione dovranno darne notizia a MSD entro 24 (ventiquattro) ore da tale evento con precisa indicazione dei motivi del verificarsi di ognuna delle descritte ipotesi.
L'Istituzione e lo Sperimentatore Responsabile convengono che l'Istituzione sarà l'unico centro di ricerca a condurre lo Studio.

## 2. Sperimentatore Responsabile

Lo sperimentatore responsabile dello Studio presso l'Istituzione sarà il Dott. Giuseppe Procopio (lo "**Sperimentatore Responsabile**"). Lo Sperimentatore Responsabile sarà responsabile della direzione e della supervisione dello Studio, secondo il Protocollo e il

Contratto. Lo Sperimentatore Responsabile e l'Istituzione svolgeranno lo Studio tramite personale dotato di competenze adeguate allo svolgimento dei compiti assegnati e vincolato al rispetto del Protocollo e del Contratto. Per "Personale" si intende (i) i dipendenti e i dirigenti dell'Istituzione, incluso lo "Sperimentatore Principale" e (ii) qualsiasi consulente o collaboratore dell'Istituzione.

Nel caso in cui lo Sperimentatore Responsabile dovesse lasciare l'Istituzione o venirne allontanato, l'Istituzione stessa dovrà dare di ciò comunicazione scritta a MSD non oltre 10 (dieci) giorni dal momento in cui ne sia venuto a conoscenza. Il successore dello Sperimentatore Responsabile dovrà essere accettato per iscritto da MSD, dovrà accettare tutti i termini e condizioni di cui al Contratto e al Protocollo e sottoscrivere detti documenti a conferma di tale accettazione (la mancata sottoscrizione non esimerà tuttavia detto successore dall'osservanza del Contratto e del Protocollo).
L'Istituzione assicura e garantisce di non coinvolgere in alcuna attività connessa allo Studio persone che siano state radiate da o comunque limitate nell'esercizio delle attività di laboratorio o di sperimentazione clinica o escluse da programmi sanitari in conseguenza della applicazione di norme o regolamenti applicabili allo Studio.
L'Istituzione si obbliga ad informare immediatamente per iscritto MSD , nel caso venisse a conoscenza (i) di provvedimenti di radiazione o limitazione di attività del tipo su accennato adottati nei confronti di soggetti coinvolti a qualsivoglia titolo nello Studio, ovvero (ii) di azioni, vertenza, inchiesta, indagine o procedimento legale o amministrativo dovesse risultare pendente o, per quanto a conoscenza dell'Istituzione, incombere in relazione alla radiazione, dequalificazione o espulsione dell'Istituzione ovvero di qualsiasi persona che svolga incarichi a norma del Contratto.
Lo Sperimentatore Responsabile assicura e garantisce che nessuna azione, inchiesta, vertenza, indagine o procedimento legale o amministrativo risulta pendente o minacciato con riferimento alla sua radiazione o dequalificazione come sopra indicato e si impegna ad informare senza indugio MSD per iscritto nel caso in cui qualsiasi azione, vertenza, indagine o procedimento legale o amministrativo dovesse essere pendente o minacciato al riguardo.
L'Istituzione e lo Sperimentatore Responsabile danno atto che il mancato rispetto dei requisiti etici e di condotta di cui al presente articolo 2 costituisce grave inadempimento tale da legittimare la risoluzione ex art. 1456 c.c. del Contratto con gli effetti di cui all'art. 5.
L'Istituzione e lo Sperimentatore Responsabile si obbligano ad ottenere, ove previsto dalla legislazione in vigore, i necessari consensi dalle persone i cui dati personali dovessero essere comunicati da parte dell'Istituzione e dello Sperimentatore Responsabile a MSD in vista dell'uso e della comunicazione degli stessi da parte di MSD per fini correlati all'adempimento del Contratto ovvero a autorità sanitarie coinvolte o a seguito di indagini o richieste obbligatorie. Resta inteso che non saranno trasmessi a MSD dati personali dei soggetti arruolati nello Studio.
Lo Sperimentatore Responsabile assicura e garantisce di non trovarsi, e che i membri della sua famiglia e parenti stretti (compresi il consorte, sposato o meno, i consanguinei, i figli, i genitori, i nonni) non si trovano, in situazioni di conflitto di interessi ai sensi di qualsiasi normativa applicabile, in particolare, ed a titolo non limitativo: (a) essendo alle dipendenze di pubbliche amministrazioni, rivestendo qualità di funzionari pubblici od avendo

incarichi, gratuiti o a pagamento, che possano consentire all'interessato di influire sulle attività di MSD o sue consociate (incluse le relazioni con dipendenti o funzionari pubblici che possano consentire all'interessato di influire sulle attività di MSD o sue consociate); (b) essendo componente titolare o consulente di qualsiasi comitato per la rimborsabilità, comitato di controllo sui prezzi, comitato di autorizzazione dei farmaci o comitati del genere; (c) rivestendo un incarico governativo o pubblico, inclusi gli incarichi in organizzazioni sanitarie governative internazionali, quali WHO (World Health Organization) o UNICEF. Lo Sperimentatore Responsabile dovrà informare MSD nel caso in cui la sua situazione ovvero quella di altri membri della sua cerchia familiare dovesse mutare rispetto a quella sopra descritta nel corso della durata del Contratto.
Senza che ciò comporti deroga all'obbligo di riservatezza, lo Sperimentatore Responsabile si obbliga a comunicare la natura dei rapporti intercorrenti tra lo Sperimentatore Responsabile stesso e MSD alle entità dianzi descritte nonché a qualsiasi ulteriore entità del genere ed a conformarsi alle normative proprie di tali entità in tema di conflitto di interessi. Lo Sperimentatore Responsabile dovrà inoltre, come stabilito da MSD: (a) astenersi dal contribuire a decisioni che possano aver conseguenze rispetto alle attività di MSD o delle sue sussidiarie per il periodo di tempo all'uopo determinato; (b) ottenere la preventiva approvazione da parte della entità interessata alla stipulazione del Contratto; e/o (c) comunicare il rapporto di collaborazione con MSD a tale entità prima di contribuire a qualsiasi decisione che possa aver conseguenze rispetto alle attività di MSD o delle sue consociate.

## 3. Svolgimento dello Studio

L'Istituzione e lo Sperimentatore Responsabile gestiranno lo Studio in modo indipendente, nella piena osservanza del Protocollo, delle normative nazionali e comunitarie applicabili (tra cui in particolare, a titolo esemplificativo ma non limitativo, le Linee Guida di Buona Pratica Clinica CPMP/ICH/135/95, recepite con D.M. 15.07.1997; il Regolamento UE 536/2014, il D.Lgs n. 211/03 e il D. Lgs. n. 200/2007 ove applicabili; il D.M. 12.05.2006; il DM 14.7.2009, D.M. 08.02.2013 ove applicabili, D.M del 30.11.2021 e di ogni altra normativa applicabile allo Studio. In accordo al D.M. del 30.11.21, lo Studio sarà condotto in piena autonomia scientifica, tecnica e procedurale da parte del Promotore, senza alcuna partecipazione o responsabilità di MSD.
L'Istituzione e lo Sperimentatore Responsabile si impegnano ad ottenere tutte le autorizzazioni prescritte per lo svolgimento dello Studio nei tempi previsti ed a far sì che tutti i partecipanti allo Studio le osservino e le facciano osservare. L'Istituzione e lo Sperimentatore Responsabile si assicureranno che tutti i soggetti chiamati a prestare la loro attività per conto dell'Istituzione o dello Sperimentatore Responsabile si attengano ai termini ed alle condizioni del Contratto. Ogni e qualsiasi documento (in particolare, consenso informato od informativa a fini privacy) che dovesse fare riferimento a MSD non dovrà indicare la stessa quale promotore dello Studio od attribuirle diritti od obblighi diversi da quelli previsti nel Contratto, e dovrà essere comunicato in copia a MSD per opportuna informazione.
Il Promotore potrà provvedere autonomamente ad effettuare le modifiche al Protocollo che dovessero rendersi necessarie ai fini della buona condotta dello Studio. Le modifiche dovranno essere sempre comunicate a MSD, in particolare quando siano state richieste dal Comitato Etico. Le eventuali modifiche del Protocollo non comporteranno modificazioni

del Contributo, come di seguito definito, né alcun obbligo aggiuntivo a carico di MSD, fatta salva la facoltà di quest'ultima di prendere in considerazione richieste, adeguatamente documentate, del Promotore in tal senso.

## 4. Durata del Contratto

La durata del Contratto decorrerà dalla data di ultima sottoscrizione e si protrarrà, salvo anticipato scioglimento a norma dell'articolo 5, sino al completamento dello Studio prevista per il 01/07/2029, e all'avvenuta pubblicazione inerente i risultati dello Studio sul sito www.clinicaltrial.gov (in accordo a quanto previsto nella tranche "Pagamento Finale" dell'Allegato B).

Ove in qualsiasi momento lo Sperimentatore Responsabile o l'Istituzione avessero motivo di ritenere che lo Studio non possa essere iniziato o completato secondo le tempistiche inizialmente previste, MSD dovrà essere informata per iscritto e potrà recedere dal Contratto a norma dell'articolo 5, fermo restando che anche ove MSD non receda, ciò non comporterà alcun obbligo di MSD di provvedere alle eventuali spese aggiuntive, salvo diverso accordo delle Parti. Resta altresì inteso che ove il mancato o ritardato avvio, svolgimento e/o completamento dello Studio rispetto alle tempistiche inizialmente previste sia imputabile alla inerzia colpa o al dolo dell'Istituzione e/o dello Sperimentatore, MSD potrà risolvere il Contratto ex art. 1456 c.c. fermo il risarcimento del danno, con restituzione immediata delle somme già corrisposte da parte di MSD.

## 5. Risoluzione e recesso

5A. Facoltà di Recesso

Le Parti potranno recedere in qualunque momento dal Contratto mediante preavviso scritto di trenta (30) giorni. Nel caso in cui MSD eserciti il diritto di recesso ai sensi della presente disposizione e tale preavviso fosse ritenuto non congruo da parte dell'Istituzione, tenute presenti le conseguenze della somministrazione del Medicinale Sperimentale sui soggetti arruolati, le Parti concorderanno le tempistiche da seguire al fine di sospendere il trattamento di tali soggetti nel modo più sicuro, ma in nessun caso l'obbligo di MSD relativo alla fornitura del Medicinale Sperimentale potrà estendersi oltre un ragionevole lasso di tempo.

L'Istituzione potrà interrompere, sospendere o cessare lo Studio in via anticipata rispetto a quanto indicato nel Protocollo qualora, sulla base di un suo insindacabile ed indipendente giudizio, reputi la sua prosecuzione incompatibile con la tutela della salute e della sicurezza dei pazienti.

5B. Clausola Risolutiva Espressa

Nel caso in cui MSD abbia notizia o accerti: (i) che lo Studio non è condotto in conformità con la normativa applicabile o le norme di buona pratica clinica o (ii) la violazione dell'art. 2 (Sperimentatore Responsabile), 6 (Informazioni) e 22 (Disciplina sull'Anticorruzione), MSD avrà la facoltà di risolvere con effetto immediato il Contratto ai sensi dell'art. 1456 c.c., fermo il risarcimento del danno, incluso l'eventuale danno alla reputazione o all'immagine di MSD, con restituzione immediata delle somme già corrisposte da parte di

MSD per la parte non utilizzata.

5C. Effetti derivanti dalla cessazione del Contratto

Nel caso di cessazione per qualsiasi motivo del Contratto (ivi incluso, a titolo esemplificativo, il caso di completamento dello Studio):

(i) l'Istituzione dovrà distruggere le rimanenze del Medicinale Sperimentale nell'osservanza delle linee guida della Conferenza per la Armonizzazione/Buona Pratica Clinica (ICH/GCP) ed inoltre fornire a MSD, su richiesta da parte di quest'ultima, copia della documentazione comprovante la distruzione in conformità alle previsioni delle linee guida della Conferenza per la Armonizzazione / Buona Pratica Clinica (ICH/GCP) e di ogni altra normativa applicabile, nonché la documentazione relativa alle quantità di Medicinale Sperimentale usato.

(ii) L'Istituzione e lo Sperimentatore Responsabile restituiranno a MSD a richiesta di quest'ultima tutte le Informazioni Riservate (come definite all'articolo 8) in possesso dello Sperimentatore Responsabile o dell'Istituzione che siano di proprietà o nella disponibilità di MSD.

(iii) Salvo il caso in cui il Contratto sia risolto per il grave inadempimento dell'Istituzione o dello Sperimentatore Principale ai sensi dell'art. 5B e, o qualora altrimenti concordato per iscritto dalle parti, L'Istituzione avrà diritto a percepire esclusivamente il corrispettivo maturato sino alla data della cessazione del Contratto, nonché il rimborso delle spese e i costi sostenuti e documentati e gli oneri e spese derivanti da impegni assunti verso terzi dall'Istituzione medesimo per l'esecuzione del Protocollo e non revocabili..

Le seguenti disposizioni sopravvivranno alla cessazione, per qualunque motivo o ragione del Contratto:

(i) mantenere la riservatezza circa le Informazioni Riservate (come definite all'articolo 8);

(ii) osservare gli obblighi di tenuta dei rapporti (come previsto all'articolo 6);

(iii) osservare gli obblighi di pubblicazione (come previsti all'articolo 9) e ottenere le approvazioni ed i consensi in relazione a campagne informative (come previste all'articolo 17);

(iv) il Contributo per le prestazioni eseguite alla data della cessazione del Contratto, salvo quanto indicato al precedente art.5 lett. B);

(v) obbligazioni relative al Medicinale Sperimentale e a qualsiasi altro materiale fornito da MSD;

(vi) obbligazioni relative a risarcimenti e assicurazioni (come previsto all'articolo 11);

(vii) obblighi in materia di Invenzioni e assistenza nell'ottenimento di protezioni brevettuali (come previsto all'articolo 12).

## 6. Informazioni

A. Tenuta della documentazione e corrispondenza

Lo Sperimentatore Responsabile e l'Istituzione avranno l'obbligo di predisporre e tenere con diligenza tutta la documentazione inerente lo Studio ed obbligatoria ai sensi di legge, nonché renderla disponibile su eventuale richiesta delle Autorità amministrative

competenti e delle Autorità giudiziarie
In considerazione delle finalità dello Studio e pertanto dell'opportunità per MSD di accrescere le proprie conoscenze nel campo del trattamento dei tumori rari del rene quali il carcinoma dei dotti collettori e il carcinoma midollare del rene, le Parti convengono che:

(i) per tutta la durata del Contratto, MSD riceverà ogni 3 (tre) mesi circa aggiornamenti periodici sull'andamento dello Studio nel formato di cui all'Allegato C;
(ii) entro 1 anno dalla conclusione dello Studio per qualsiasi causa, MSD riceverà una relazione clinica finale ("**CSR**") o manoscritto dello studio conforme alle prescrizioni di MSD. Il CSR definitivo dovrà contenere dati aggregati e/o descrittivi, tavole ed elenchi di dati e fare menzione degli eventi avversi non seri in forma di tavola o di elenco. Tutti i dati dello Studio forniti a MSD saranno previamente resi anonimi nel pieno rispetto della normativa europea e nazionale sulla privacy.

Senza pregiudizio dei diritti del Promotore di cui all'art. 8, le Parti dichiarano ed accettano che i dati inclusi dei rapporti preliminari e nella CSR potranno essere oggetto di utilizzo da parte di MSD ma non a fini registrativi e, comunque, sempre in accordo al D.M. del 30.11.21.

Quanto sopra, anche a conferma dell'effettivo svolgimento dello Studio.

B. Procedure relative alla comunicazione di Eventi Avversi.

(i) Ai fini del Contratto i termini sotto indicati saranno definiti come di seguito:

- Per "**Evento Avverso**" o "**AE**" si intende una condizione clinica avversa riscontrata in un soggetto cui sia stato somministrato il Medicinale Sperimentale, indipendentemente dalla correlazione con il Medicinale Sperimentale stesso. Un AE può consistere in una manifestazione sfavorevole e non prevedibile (un anomalo risultato di analisi, ad esempio), sintomo, o malattia connessa temporalmente all'uso del Medicinale Sperimentale.

- Per "**Carenza del Dispositivo**" si intende una inadeguatezza di un dispositivo medico correlata all'identità, alla qualità, alla durevolezza, all'affidabilità, alla sicurezza o alle prestazioni del medesimo, come un malfunzionamento, un uso scorretto o un errore di utilizzo e un'etichettatura inadeguata.

- Per "**Incidente**" si intende un qualsiasi malfunzionamento o deterioramento delle caratteristiche e/o prestazioni di un dispositivo in studio, nonché qualsiasi inadeguatezza nell'etichettatura o nelle istruzioni d'uso che, direttamente o indirettamente, potrebbe provocare o aver provocato il decesso di un paziente, dell'utilizzatore o di altre persone, oppure un serio deterioramento dello stato di salute.

- Per "**Evento da Dispositivo Medico**" si intende un qualsiasi malfunzionamento o deterioramento delle caratteristiche e/o delle prestazioni di un dispositivo in studio, nonché qualsiasi inadeguatezza riguardante l'etichettatura o le istruzioni d'uso che

ha determinato o potrebbe aver determinato un evento sfavorevole per l'utilizzatore o eventuali altre persone.

- Per "**Evento Avverso Serio**" o "**SAE**" si intende una condizione clinica avversa riscontrata in un soggetto cui sia stato somministrato il Medicinale Sperimentale che comporti la morte, un evento pericoloso per la vita, un evento che porti all'ospedalizzazione del paziente o che causi il prolungamento di un'ospedalizzazione già in corso, un evento che causi invalidità/inabilità persistente o significativa, che causi un'anomalia congenita o un difetto alla nascita, il cancro o un nuovo cancro in un paziente già affetto da cancro, o un sovradosaggio. Altre condizioni clinicamente rilevanti che possano compromettere la sicurezza del paziente o che rendano necessario intervenire al fine di evitare alcuno degli eventi sopradescritti, dovranno pure essere considerate "seri".

- Per "**Sospetta Reazione Avversa Seria Inattesa**" o "**SUSAR**" si intende qualsiasi Evento Avverso Serio la cui natura, intensità o frequenza non sia in linea con quanto riportato nella versione più aggiornata della Confidential Investigational Brochure (CIB) del prodotto, o, se riferita ad un prodotto in commercio, non sia in linea con il Riassunto delle Caratteristiche del Prodotto (RCP) o Foglio Illustrativo.

(ii) Segnalazione degli Eventi Avversi Seri (SAEs), delle Sospette Reazioni Avverse Serie Inattese (SUSARs), degli Eventi da Dispositivo Medico, delle Carenze del Dispositivo o degli Incidenti.
Lo Sperimentatore Responsabile invierà al Reparto di Farmacovigilanza di MSD Italia, qualsiasi informazione relativa ad un SAE (indipendentemente dalla correlazione con un farmaco MSD) o ad una SUSAR, Evento da Dispositivo Medico, Carenza del Dispositivo o Informazioni su Incidente, incluse, ma non limitate a, tutte le informazioni inziali e di follow-up che coinvolgano qualsiasi paziente incluso nello studio. La notifica avverrà entro due (2) giorni lavorativi e non più di 3 giorni di calendario dalla data di conoscenza delle informazioni. Tali informazioni dovranno essere trasmesse al Reparto di Farmacovigilanza di MSD Italia, in inglese, mediante il modulo "Global Safety Intake Form" (Allegato D) e dovranno includere il nome dello Sperimentatore ed il codice identificativo del paziente coinvolto.
Se la terapia dello studio era in cieco, le informazioni sulle SUSARs saranno riportate in aperto. I codici di randomizzazione per tutti gli altri SAEs saranno forniti ad MSD (all'attenzione Reparto di Farmacovigilanza di MSD Italia: FAX : 06 /3339327 ) alla fine dello studio, se la terapia era in cieco.

(iii) MSD potrebbe definire alcuni Eventi Avversi Non-Seri di Interesse. Se vengono definiti degli Eventi Avversi Non-Seri di Interesse, MSD fornirà tali informazioni per iscritto allo Sperimentatore Responsabile al momento dell'approvazione del Protocollo, al momento della firma di questo contratto od in qualsiasi momento successivo. La segnalazione dei definiti Eventi Avversi Non-Seri di Interesse sarà gestita nello stesso modo dei SAEs, salvo diverso accordo scritto tra le Parti.

(iv) A MSD dovranno altresì essere segnalate, agli stessi contatti ed in accordo con le tempistiche definite per la segnalazione dei SAE/SUSAR, tutte le esposizioni al Medicinale Sperimentale durante la gravidanza o l'allattamento (inclusi i casi di partner femminile di soggetto maschile trattato con il Medicinale Sperimentale), siano le stesse associate o meno ad un evento avverso. Lo Sperimentatore Responsabile seguirà le gravidanze fino al compimento, al fine di accertarsi del loro esito. L'esito della gravidanza verrà segnalato al Reparto di Farmacovigilanza di MSD.

(v) lo Sperimentatore Responsabile e il Promotore dovranno osservare le rispettive obbligazioni di segnalazione sussistenti nei confronti delle autorità regolatorie/competenti con riferimento a ciascun AE, SAE o SUSAR che si verifichi nel corso della Ricerca.

(ii) (vi) Le segnalazioni di SAEs, nonché le altre relative segnalazioni concernenti la sicurezza, dovranno essere trasmesse in inglese al numero di fax del reparto di Farmacovigilanza di MSD Italia: 06 /3339327 e corredate con la copertina Fax "Safety Fax Form" allegata al Contratto (Allegato E). MSD confermerà la ricezione del rapporto entro un (1) giorno lavorativo. Se la conferma non viene ricevuta entro un (1) giorno lavorativo, lo Sperimentatore Principale/Istituto contatterà MSD per determinare se il rapporto originale deve essere inviato nuovamente. Lo sperimentatore principale/istituzione manterrà una registrazione della conferma.

C. lo Sperimentatore Responsabile e il Promotore, nel caso in cui venissero a conoscenza di un difetto o di un possibile difetto del Medicinale Sperimentale (oppure del placebo fornito da MSD o del farmaco utilizzato come farmaco di confronto nello Studio) od in generale di prodotti di MSD, si impegnano ad informarne immediatamente per iscritto MSD.

D. Lo Sperimentatore Responsabile e l'Istituto si impegnano inoltre a condurre lo Studio e a mantenere aggiornati le registrazioni e i dati nel corso del Contratto nonché successivamente alla sua scadenza o risoluzione anticipata in osservanza dei requisiti di cui a tutte le norme legislative e regolamentari applicabili.

E. Lo Sperimentatore Responsabile si impegna a segnalare a MSD entro 24 (ventiquattro) ore eventuali notifiche ricevute da parte delle competenti autorità di controllo e ad inviare, entro lo stesso termine, copia delle comunicazioni scritte, pervenute presso il sito di Studio da parte di autorità di controllo, concernenti ispezioni o verifiche, che riguardino il Medicinale Sperimentale, lo Studio ovvero la capacità dell'Istituzione di condurre ricerche cliniche. L'Istituzione, tramite lo Sperimentatore Responsabile si impegna ad eseguire le suddette segnalazioni e comunicazioni tempestivamente e, comunque, entro un termine congruo che non pregiudichi eventuali facoltà/diritti esercitabili da MSD finalizzati a tutelare la propria posizione soggettiva nei confronti delle autorità di controllo.

F. Una copia di tutte le SUSARs e delle Relazioni Annuali sulla conduzione dello Studio dovranno essere presentate da parte dello Sperimentatore Responsabile come richiesto

dall'Agenzia Regolatoria. Lo Sperimentatore Responsabile si impegna ad includere nella documentazione presentata, in accordo alle leggi locali, il numero identificativo del Medicinale Sperimentale (IND, CSA, etc.), se disponibile, valido al momento del deposito della presentazione. In aggiunta lo Sperimentatore Responsabile accetta di inviare entro 15 giorni copia di queste informazioni ad MSD (all'attenzione: MSD Italy Pharmacovigilance Dept FAX : 06 /3339327 ) al momento della sottomissione all'appropriata agenzia regolatoria e tutti i rapporti annuali sullo stato di avanzamento devono essere inviati via e-mail a **pharmacovigilance.italy@msd.com** dallo sperimentatore principale al momento della presentazione all'agenzia regolatoria appropriata.

G. MSD dovrà fornire allo Sperimentatore Responsabile e all'Istituzione, all'inizio dello Studio e nel corso di esso, informazioni relative al Medicinale Sperimentale, includendo, ma non limitandosi, alle informazioni relative alla sicurezza. Dette informazioni dovranno essere considerate riservate da parte dello Sperimentatore Responsabile e dell'Istituzione. Lo sperimentatore principale è responsabile della registrazione dello studio sul sito **https://eudract.ema.europa.eu/**, compresa, ma non solo, l'accurata compilazione del modulo EUDRACT e la comunicazione tempestiva di eventuali modifiche al modulo a MSD. Qualsiasi modifica dovrà essere valutata per determinare l'impatto sulla disponibilità delle forniture.

## 7. Finanziamenti

MSD provvederà ad erogare il contributo per il finanziamento dei costi dello Studio, indicato all'Allegato B (il "**Contributo**"): le tempistiche di erogazione sono indicate all'Allegato C. L'Istituzione trasmetterà a MSD fattura, ovvero la documentazione necessaria a giustificare la corresponsione delle somme secondo le scadenze pure indicate all'Allegato C. Il pagamento dell'ultima tranche verrà effettuato a seguito della ricevuta di notifica di Protocol Registration and Result System di clinicaltrial.gov attestante che l'Istituzione ha sottomesso i Risultati finali dello Studio Qualora lo Studio venisse concluso anticipatamente o interrotto, MSD non sarà tenuta ad erogare le *tranches* di contributo successive all'interruzione, essendo il medesimo erogato ai fini esclusivi di esecuzione e copertura dei costi dello Studio.
Nel caso in cui le attività di ricerca non dovessero risultare iniziate o completate entro il termine indicato all'art. 4, i finanziamenti dovranno essere restituiti in tutto o in parte a discrezione di MSD, fatto salvo il raggiungimento di obiettivi intermedi da parte dell'Istituzione e dello Sperimentatore Responsabile se il ritardo non è imputabile a un inadempimento dell'Istituzione o salvo che sia stata concessa una proroga per iscritto. Le Parti danno espressamente atto che i pagamenti qui previsti da parte di MSD relativi non sono in alcun modo collegati al numero di pazienti arruolati nello Studio né costituiscono o possono essere interpretati come indebito incentivo alla prescrizione o uso di prodotti MSD. Le Parti dichiarano che il Contributo (i) è da ritenersi in linea con l'equo valore di mercato per le attività in esso comprese (ii) non è definito sulla base del volume o valore di prescrizioni o comunque in riferimento a tali prescrizioni o altre attività economiche che si generino fra le Parti.

# 8. Informazioni riservate

A. Obbligo di riservatezza

Per un periodo di dieci (10) anni successivo alla scadenza o alla risoluzione anticipata del Contratto, l'Istituzione e lo Sperimentatore Responsabile manterranno il riserbo in relazione al materiale, ai dati, al know-how e/o informazioni confidenziali o documenti riservati eventualmente forniti o altrimenti resi noti da MSD nell'ambito o ai fini dello Studio, ivi inclusi, a titolo non limitativo, il Dossier per lo Sperimentatore (IB) e qualsiasi altra informazione o materiale messi a disposizione in virtù di contratti in precedenza stipulati tra le Parti ed ivi indicati come aventi natura riservata (le "**Informazioni Riservate**"). Detti vincoli non saranno applicabili alle Informazioni Riservate che:

(i) siano o divengano di pubblico dominio (ma non per colpa dell'Istituzione o dello Sperimentatore Responsabile); o

(ii) vengano rivelate all'Istituzione o allo Sperimentatore Responsabile da parte di terzi estranei che non siano obbligati da vincoli di riservatezza nei confronti di MSD riguardo alle stesse (ed il cui legittimo diritto possa essere debitamente dimostrato da parte dell'Istituzione o dello Sperimentatore Responsabile); o

(iii) siano già a conoscenza dell'Istituzione o dello Sperimentatore Responsabile al momento della ricezione degli stessi da parte di MSD (e detta preventiva conoscenza possa essere debitamente dimostrata da parte dell'Istituzione o dello Sperimentatore Responsabile); o

(iv) vengano pubblicate in conformità a previsioni esplicite di cui al Contratto.

B. Ipotesi di non violazione dell'obbligo di riservatezza

L'Istituzione potrà rivelare le Informazioni Riservate nei limiti previsti dalla legge o da atti o decreti di autorità o enti governativi. In tali ipotesi, l'Istituzione informerà tempestivamente per iscritto MSD e fornirà ad essa piena collaborazione nell'approntare le necessarie difese, in particolare qualora MSD intendesse proporre azioni cautelari o sospensive. Lo Sperimentatore Responsabile e/o l'Istituzione dovranno in ogni caso rivelare unicamente quanto sia strettamente necessario al fine di ottemperare ad eventuali ordini delle competenti autorità, indipendentemente dal fatto che MSD abbia ottenuto un provvedimento di tutela o altro provvedimento

C. Obbligo di custodia e restituzione delle Informazioni Riservate

L'Istituzione e lo Sperimentatore Responsabile si obbligano a restituire senza indugio a MSD, a richiesta di quest'ultima, e nel rispetto delle norme legislative e regolamentari applicabili, tutte le Informazioni Riservate ricevute da MSD ovvero di proprietà di MSD a norma del Contratto; restando tuttavia inteso che l'Istituzione potrà conservare copia delle Informazioni Riservate in luogo sicuro al fine di adempiere gli obblighi di legge in materia di conservazione dei documenti.

D. Diffusione delle Informazioni Riservate

L'Istituzione e lo Sperimentatore Responsabile limiteranno la diffusione delle Informazioni Riservate ottenute in virtù del presente alle sole persone che siano vincolate da un accordo di riservatezza in termini equivalenti o più restrittivi rispetto al Contratto e che siano direttamente interessati allo Studio e comunque solo limitatamente a quanto necessario.

## 9. Dati, pubblicazioni ed altri diritti

A. Dati e Risultati dello Studio
Le Parti concordano che tutti i dati di ricerca ed i risultati ottenuti nel corso dello Studio apparterranno in via esclusiva all'Istituzione e potranno essere liberamente utilizzati a qualsivoglia fine legittimo. L'Istituzione, oltreché per la pubblicazione di cui al presente articolo, utilizzerà i dati di ricerca ed i risultati ottenuti nel corso dello Studio esclusivamente a fini non commerciali di istruzione e di ricerca. Lo Sperimentatore Responsabile e l'Istituzione, salvo che per la pubblicazione di cui al presente articolo, si obbligano a non consentire l'accesso o il diritto di utilizzo a favore di terzi quanto ai dati ed ai risultati per finalità estranee a quelle di cui al D.M. del 30.11.21. Qualora lo Sperimentatore Responsabile e/o l'Istituzione intendessero autonomamente utilizzare in qualsiasi modo i dati ed i risultati dello Studio a fini commerciali, si applica quanto previsto nel successivo art. 12.

B. Pubblicazioni e Presentazioni Pubbliche
Nei termini di cui al D.M. 08.02.2013, lo Sperimentatore Responsabile si impegna a pubblicare i risultati dello Studio e a presentare una pubblicazione a tale riguardo a un periodico scientifico, sulla base di una *peer review*, entro un anno dalla visita finale sull'ultimo soggetto sottoposto a esame o che abbia subito un intervento rilevante ai fini della raccolta dati dello Studio, indipendentemente dai risultati dello Studio stesso. MSD avrà facoltà di esaminare e commentare qualsiasi pubblicazione e/o presentazione pubblica (ivi inclusi, a titolo non limitativo, diapositive e testi delle presentazioni orali o di altro tipo nonché testi destinati alla trasmissione su supporto elettronico, con accesso via computer ad esempio a Internet, World Wide Web e simili, di seguito, cumulativamente "**Presentazioni Pubbliche**"), da inviarsi alla stessa almeno quarantacinque (45) giorni prima della consegna per la pubblicazione o la presentazione. Lo Sperimentatore Responsabile e l'Istituzione si impegnano a tenere in considerazione eventuali indicazioni o suggerimenti formulati per iscritto da MSD.

Nessuna Informazione Riservata di MSD (come definite all'articolo 8), dovrà essere contenuta in una Presentazione Pubblica. Nel caso in cui le Parti fossero in disaccordo circa l'accuratezza o l'adeguatezza della analisi dei dati e della presentazione, e/o in merito alla riservatezza delle Informazioni Riservate di MSD, l'Istituzione e lo Sperimentatore Responsabile si obbligano ad incontrare i rappresentanti di MSD presso il centro clinico di Studio o come altrimenti convenuto, prima dell'effettuazione di qualsiasi Presentazione Pubblica, allo scopo di discutere in buona fede e dirimere le divergenze o disaccordi.

Ove MSD dovesse riscontrare elementi brevettabili in una Presentazione Pubblica, MSD indicherà immediatamente all'Istituzione tali elementi e le Parti concorderanno in buona fede come procedere a seconda che si tratti di Invenzioni dell'Istituzione, Invenzioni Comuni o Invenzioni della Società. In questi ultimi due casi, qualora ciò potesse nuocere a diritti di MSD e in particolare pregiudicare i suoi diritti di proprietà intellettuale od industriale, MSD avrà facoltà di richiedere motivatamente e per iscritto che dette indicazioni vengano espunte dalla Presentazione Pubblica o di farne rinviare la pubblicazione o presentazione per un periodo non superiore a 90 (novanta) giorni successivi al periodo di esame originario, onde provvedere all'adeguata tutela dei suoi

diritti.

Lo Sperimentatore Responsabile si impegna a menzionare MSD in tutte le presentazioni Pubbliche utilizzando la seguente formula: "*Finanziato in parte mediante un contributo di ricerca concesso nell'ambito del Programma di Ricerca per Sperimentazioni ad iniziativa dello Sperimentatore di MSD Italia S.r.l. Le opinioni espresse nella presente relazione provengono dagli autori e non rappresentano necessariamente quelle di MSD Italia S.r.l".*

L'Istituzione e lo Sperimentatore Responsabile dovranno attenersi, nella esecuzione delle Presentazioni Pubbliche, alla legislazione, ai regolamenti e alle linee guida consolidate per i periodici medici accreditati nonché alle linee guida specifiche valide per i periodici e/o i congressi ai quali siano destinate le Presentazioni Pubbliche. L'Istituzione e lo Sperimentatore Responsabile assicureranno che gli autori e co-autori indicati in tutte le dette Presentazioni Pubbliche siano dotati dei requisiti minimi a norma del Comitato Internazionale degli Editori di Pubblicazioni Mediche.

C Registrazione dello Studio
Lo Sperimentatore Responsabile e/o l'Istituzione si impegnano a registrare lo Studio presso il sito www.clinicaltrials.gov prima dell'inizio dello stesso (cioè prima del pagamento iniziale e/o della fornitura iniziale del Medicinale Sperimentale), nonché a pubblicarne i risultati finali al più tardi entro un (1) anno dalla conclusione effettiva del medesimo.

## 10. Forniture

A. MSD renderà disponibili gratuitamente allo Sperimentatore Responsabile, tramite la farmacia ospedaliera sufficienti quantità del Medicinale Sperimentale in conformità al Protocollo, nei lotti ed alle scadenze di consegna concordati con MSD**.** L'Istituzione e lo Sperimentatore Responsabile si impegnano ad adottare un'appropriata gestione del Medicinale Sperimentale (ivi compresi l'eventuale confezionamento/etichettatura necessari per l'impiego interno nello Studio), a norma del Protocollo nonché delle leggi e dei regolamenti applicabili. Il Medicinale Sperimentale non potrà venire utilizzato per scopi diversi da quelli dello Studio e da quanto previsto nel Protocollo, né potrà essere ceduto a terzi in assenza del consenso scritto di MSD, salvi i casi di consegna del Medicinale Sperimentale ai soggetti interessati nello Studio a norma del Protocollo e senza oneri per tali soggetti. Il Medicinale Sperimentale non potrà essere utilizzato nel quadro di attività di ricerca o sperimentazione comportante facoltà di uso o licenza a beneficio di terzi, se non previa approvazione scritta di MSD. L'Istituzione e lo Sperimentatore Responsabile dovranno ottenere la preventiva autorizzazione scritta da parte di MSD a riguardo di necessità particolari di spedizione o di sdoganamento del Medicinale Sperimentale. MSD indicherà all'Istituzione e allo Sperimentatore Responsabile le eventuali necessità relative all'imballaggio, deposito e smaltimento del Medicinale Sperimentale ove richiesto. Se necessario, l'Istituzione e lo Sperimentatore Responsabile si faranno carico di assicurare che contratti o previsioni di controllo qualitativo vengano posti in essere tra l'Istituzione e MSD e/o tra l'Istituzione ed eventuali terzi incaricati del confezionamento.

(i) **Aspetto esteriore del farmaco:** Nel caso in cui il Medicinale Sperimentale fosse previsto come medicinale attivo e come placebo corrispondente, MSD fornirà informazioni circa l'aspetto del Medicinale Sperimentale (forma, colore, eventuali incisioni). Ove quest'ultimo venga fornito in bulk in vista del riconfezionamento ad uso dei singoli pazienti, l'Istituzione e/o lo Sperimentatore Responsabile saranno responsabili di tale riconfezionamento e della distribuzione delle confezioni finali in conformità alla legislazione ed ai regolamenti applicabili. Nel caso in cui vengano fornite confezioni individuali MSD si assicurerà che tutte le approvazioni necessarie siano state ottenute prima che il Medicinale Sperimentale sia spedito all'Istituzione. Quanto sopra comprenderà la certificazione secondo le linee guida di buona pratica di fabbricazione (GMP) relativamente al Medicinale Sperimentale da parte di un Soggetto Qualificato. MSD fornirà i propri dati di formulazione, fabbricazione, controllo (CMC) alle Autorità Regolatorie competenti per il tramite dello Sperimentatore Responsabile, al fine di confermare la regolarità delle richieste dell'Istituzione ove necessarie, nonché di rispondere a tutte le richieste avanzate da parte delle Autorità Regolatorie riguardo ai dati CMC. MSD non procederà alla spedizione del Medicinale Sperimentale (sia attivo che placebo) sino a che MSD non abbia ricevuto conferma dell'approvazione dello Studio da parte delle Autorità Regolatorie ai sensi dell'art. 1 e sempre che le condizioni per il pagamento della prima tranche del contributo in base alla Tabella dei Pagamenti si siano verificate.

(ii) **Medicinale non autorizzato in Italia**: L'Istituzione e lo Sperimentatore Responsabile convengono che ogni e qualsiasi riferimento al Medicinale Sperimentale in sede di discussioni pubbliche, inclusi gli elenchi, dovrà essere limitato alla denominazione MSD "MK-3475". La denominazione o struttura chimica, il nome generico, la formulazione della molecola o qualsiasi altra informazione relativa al composto non dovrà essere menzionata in pubblico. Il riferimento specifico o la menzione di informazioni relative a qualsiasi farmaco di comparazione usato nello Studio dovranno altresì essere evitati. Resta fermo quanto previsto al punto (ii) che precede.

B. Fermi restando gli altri adempimenti previsti nel Contratto e nel Protocollo, nell'eventualità che si rendessero necessarie forniture aggiuntive del Medicinale Sperimentale al fine di continuare nell'espletamento dello Studio, l'Istituzione dovrà informarne MSD con anticipo di almeno 6 (sei) mesi rispetto all'esaurimento del Medicinale Sperimentale: le forniture aggiuntive verranno effettuate a condizione che MSD abbia ricevuto quanto di seguito indicato: (i) documentazione aggiornata per l'approvazione da parte del Comitato Etico; (ii) corrispondenza comprovante l'invio di idonea informativa al Comitato Etico da parte dello Sperimentatore Responsabile in relazione ai rapporti precauzionali sulla sicurezza ed agli aggiornamenti al Dossier dello Sperimentatore, se prescritti; (iii) relazioni periodiche in merito all'arruolamento dei

pazienti, alla sicurezza e ai rendiconti quantitativi riguardo al Medicinale Sperimentale.

## 11. Indennizzi e assicurazione

A. Obbligo di Manleva da parte di MSD per i vizi inerenti il Medicinale Sperimentale
MSD dovrà manlevare l'Istituzione, i suoi rappresentanti o funzionari e lo Sperimentatore Responsabile (i "**Soggetti Garantiti**") da responsabilità, oneri o pretese di terzi o sentenze conseguenti a vizi di fabbricazione del Medicinale Sperimentale fornito a termini del Contratto, ovvero alla sua mancata conformità alle specifiche di fabbricazione applicabili.

Le obbligazioni di garanzia a carico di MSD saranno soggette alle seguenti condizioni:

(i) avviso immediato a MSD ogniqualvolta il Soggetto Garantito venga a conoscenza di circostanze dalle quali si possa desumere il verificarsi di un incidente comportante lesioni personali o morte o danni a cose ed immediata informativa a MSD relativamente a tutti i dati e circostanze di detto incidente;

(ii) adempimento da parte del Soggetto Garantito a tutte le sue obbligazioni relativamente alle procedure informative concernenti eventi pregiudizievoli come previste nel Contratto;

(iii) piena cooperazione ed assistenza da parte dei Soggetti Garantiti quanto alle indagini e alla contestazione delle domande o azioni unitamente alla autorizzazione di MSD ai fini della gestione e contestazione in via autonoma da parte di questa di dette domande o azioni;

(iv) i Soggetti Garantiti non dovranno transigere o conciliare dette domande o azioni in assenza del preventivo consenso scritto di MSD.

B. Obbligo di Manleva da parte dell'Istituzione per responsabilità derivanti dalla conduzione dello Studio
Al di fuori degli specifici obblighi di manleva assunti da MSD in base al paragrafo A che precede, l'Istituzione dovrà manlevare MSD, i suoi rappresentanti o funzionari, dirigenti, incaricati, dipendenti, la sua casa madre e le consociate in genere da responsabilità, oneri o pretese di terzi o sentenze conseguenti alla conduzione dello Studio (ivi compresi, a titolo non limitativo, l'uso e la conservazione del Medicinale Sperimentale) in modo non conforme al Protocollo.

C Obbligazioni ex D.Lgs 81/2008 e Copertura Assicurativa dello Studio
Gli obblighi previsti del D. Lgs. n. 81/2008 in materia di sicurezza sul lavoro gravano esclusivamente sull'Istituzione per quanto riguarda il personale che si trovi presso di essa nell'espletamento delle attività connesse all'attuazione del Contratto.
Lo svolgimento dello Studio è assistito da idonea copertura assicurativa, a carico del Promotore, ai sensi del D.M. 14.07.2009 e delle altre norme di legge e regolamentari applicabili.

## 12. Invenzioni e Brevetti

A. Diritti relativi al Medicinale Sperimentale

L'Istituzione prende atto e riconosce che il Medicinale Sperimentale che viene fornito all'Istituzione al fine di condurre lo Studio è oggetto di diritti di proprietà intellettuale appartenenti a MSD ovvero a questa concessi in licenza. Il Contratto non potrà essere considerato né interpretato nel senso di cedere, trasferire o concedere in licenza alcuno dei suddetti diritti di proprietà intellettuale a favore dell'Istituzione, salvo che per quanto riguarda i limitati diritti che consentano all'Istituzione di condurre lo Studio nel corso della durata del Contratto.

B. Diritti di Proprietà Intellettuale derivanti dalla conduzione dello Studio
La proprietà ed i diritti relativi a qualunque scoperta, tecnologia, know-how o diversa proprietà intellettuale originale, brevettabile o meno, derivante dalla conduzione del Protocollo e dello Studio sarà soggetta alla disciplina che segue: le Invenzioni sviluppate esclusivamente dallo Sperimentatore Responsabile o dai dipendenti dell'Istituzione resteranno di proprietà dell'Istituzione (di seguito le "**Invenzioni dell'Istituzione**"). L'Istituzione informerà senza indugio MSD per iscritto riguardo a dette Invenzioni. A tal fine, l'Istituzione/lo Sperimentatore Responsabile si impegnano a notificare tempestivamente a MSD qualsiasi invenzione o scoperta.

C. Utilizzazione dei Dati e dei Risultati dello Studio a fini commerciali
Qualora, nel corso dello Studio o a Studio concluso il Promotore e il Responsabile dello Studio decidessero di utilizzare in qualsiasi modo i dati ed i risultati dello Studio, incluse le Invenzioni dell'Istituzione, a fini commerciali, inclusi quelli registrativi, si impegna sin da ora l'Istituzione per sé e per lo Sperimentatore Responsabile, (per gli studi multicentrici: nonché per i Centri e il loro personale) a darne pronta comunicazione scritta a MSD. MSD avrà il diritto irrevocabile di acquistare e l'Istituzione, per sé, per lo Sperimentatore Responsabile e per i suoi collaboratori, nonché, ove presenti, per gli altri centri partecipanti, si impegna a cedere a MSD, i dati e i risultati dello Studio e i relativi diritti sugli stessi, inclusi i diritti di proprietà intellettuale e industriale, nel rispetto di quanto previsto dall'art. 3 del DM 30.11.2021 (il "Decreto") e del presente Contratto.
In particolare, qualora MSD intendesse acquistare i dati e i risultati dello Studio dovrà comunicare per iscritto all'Istituzione tale decisione nel termine di 6 (sei) mesi dal ricevimento della comunicazione dell'Istituzione di cui al precedente paragrafo e le Parti procederanno a nominare di comune accordo l'esperto cui sarà deferita la determinazione del corrispettivo della cessione ai sensi dell'art. 3, comma 2, lett. a) del Decreto tra gli esperti di consulenza brevettuale iscritti all'Albo consulenti in proprietà industriale abilitati / o all'Albo degli Avvocati di Milano.
In caso di mancato accordo nell'individuazione dell'esperto o se la stima dovesse essere manifestamente iniqua o erronea la determinazione sarà fatta dal Tribunale di Milano_____ ai sensi dell'art. 1349 c.c.
All'esito della stima MSD rimarrà in ogni caso libera di non procedere all'acquisto dei dati e dei risultati dello Studio e l'Ente, lo Sperimentatore e i co-sperimentatori saranno liberi di stipulare il contratto, alle medesime condizioni, con altro soggetto terzo.
In caso di mancato accordo delle Parti o di rifiuto di MSD, l'Istituzione si impegna a non offrire a terzi per un periodo di un (1) anno, a condizioni migliori di quelle offerte da MSD, i dati e i risultati dello studio, incluse le Invenzioni dell'Istituzione, relative esclusivamente al Medicinale Sperimentale di MSD compresi, senza limitazioni, gli usi terapeutici, gli

indicatori di risposta e i relativi metodi (di seguito "Invenzioni del Farmaco MSD"). L'Istituzione si impegna altresì a comunicare a MSD eventuali nuove offerte di terzi, pari o superiori alle condizioni in precedenza rifiutate da MSD, e in tal caso quest'ultima avrà un periodo di trenta (30) giorni per accettare o rifiutare l'offerta.

D. Invenzioni derivanti dall'indebito utilizzo del Medicinale Sperimentale
Ferme le previsioni che precedono, tutte le invenzioni e scoperte derivanti dall'utilizzazione non autorizzata del Medicinale Sperimentale, brevettabili o meno, sviluppate da parte dello Sperimentatore Responsabile o dei dipendenti dell'Istituzione resteranno di esclusiva proprietà di MSD (di seguito le "**Invenzioni MSD**"). L'Istituzione dovrà informare senza indugio MSD per iscritto riguardo alle Invenzioni MSD. A richiesta di MSD ed a spese di questa l'Istituzione fornirà a MSD l'assistenza necessaria per l'ottenimento dei brevetti concernenti dette Invenzioni MSD, ivi incluso il perfezionamento degli atti di cessione necessari e della documentazione ulteriore.

## 13. Comunicazioni

Ogniqualvolta si rendano necessarie comunicazioni a norma del Contratto, queste dovranno essere date per iscritto a mezzo posta prepagata e certificata o raccomandata (con avviso di ricevimento), corriere espresso (con avviso di ricevimento) o consegna a mano alla Parte interessata all'indirizzo di seguito indicato ovvero nel diverso luogo o località che ciascuna delle Parti avrà facoltà di indicare per iscritto all'altra Parte. Le comunicazioni si avranno per ricevute all'atto della loro ricezione.

Se dirette all'Istituzione:

Comunicazioni relative allo Studio:

Principal Investigator, dr. **Giuseppe Procopio**:
giuseppe.procopio@istitutotumori.mi.it;

Altri contatti:

dr. **Marco Stellato**:
marco.stellato@istitutotumori.mi.it;

Comunicazioni relative al Contratto: Segreteria TTO segreteria.TTO@istitutotumori.mi.it/ trasferimento.tecnologico@pec.istitutotumori.mi.it;

Se dirette a MSD:

**Medical Affairs Director, Oncology**
**Maura Camozzi**
Via Vitorchiano, 151 -00189 Roma
Email: maura.camozzi@msd.com
PEC: msditaliasrl@pec.it

## 14. Cessione o Subappalto

L'Istituzione e lo Sperimentatore Responsabile si obbligano a non cedere né a subappaltare in tutto o in parte i diritti e le obbligazioni scaturenti dal Contratto a terzi senza la preventiva autorizzazione scritta di MSD, restando inteso che in tal caso la cessione e il subappalto non comporta alcuna modificazione agli obblighi e agli oneri dell'Istituzione e dello Sperimentatore Responsabile i quali rimangono i soli responsabili nei confronti di MSD della perfetta esecuzione del Contratto, anche per la parte subappaltata o ceduta. In caso di cessione o subappalto in tutto o in parte dei diritti e delle obbligazioni scaturenti dal Contratto l'Istituzione e lo Sperimentatore Responsabile dovranno garantire che i terzi cessionari o subappaltatori rispetteranno i termini e le condizioni di cui al Contratto. MSD ha la facoltà di cedere il Contratto alle sue consociate senza il preventivo consenso dell'Istituzione e dello Sperimentatore Responsabile. Ciononostante MSD rimarrà responsabile della corretta esecuzione del Contratto.

## 15. Privacy e Protezione dei Dati Personali e Sensibili

**A.** L'Istituzione, e per essa lo Sperimentatore Responsabile, provvederà alla raccolta dei dati personali e particolari dei pazienti, in funzione di quanto previsto dal Protocollo, ed a tal fine si impegna ad ottenere il consenso al trattamento dei dati personali e/o particolari da tutti i partecipanti allo Studio, ed a conservare la relativa documentazione nei propri archivi.

**B.** L'Istituzione, e per essa lo Sperimentatore Responsabile, garantisce che qualsiasi dato raccolto a livello individuale nel corso della Ricerca e che verrà fornito a MSD, lo sarà solo dopo essere stato anonimizzato (dato che a seguito di trattamento, non può essere più associato ad un interessato identificato o identificabile).

**C.** Ai sensi del D.Lgs. 196/2003 e successive modifiche e integrazioni ("**Codice in materia di protezione dei dati personali**") e del "Regolamento Europeo 2016/679 relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali nonché alla libera circolazione di tali dati" ("**Regolamento Europeo**") i dati personali dello Sperimentatore Responsabile e del personale coinvolto nella Sperimentazione (di seguito il "**Personale**"), saranno trattati usando supporti cartacei e/o informatici e/o telematici, direttamente o anche attraverso terzi che gestiscano servizi e/o attività per conto della stessa MSD e/o delle aziende del suo gruppo (società collegate, controllate e/o che ne detengono il controllo, di seguito collettivamente il "**Gruppo**"), esclusivamente in funzione della esecuzione del Contratto e/o a fini di farmacovigilanza ed in osservanza di tutte le leggi applicabili sulla privacy, incluso il Regolamento Europeo.
MSD garantisce che i Dati Personali del Personale saranno mantenuti esatti e aggiornati. Il Personale può richiedere modifiche ai propri Dati personali contattando MSD all'indirizzo e-mail privacy.italy@msd.com.
D. Ai fini del presente Contratto per:

i. "Dati personali" si intende qualsiasi informazione relativa ad una persona identificata o identificabile, inclusi i dati che identificano una persona o che potrebbero essere utilizzati per identificare, localizzare, rintracciare o contattare una persona. I Dati personali comprendono sia elementi identificativi diretti,

come un nome, un numero di identificazione o una qualifica univoca, sia elementi identificativi indiretti, come la data di nascita, un numero di identificazione univoco di un dispositivo mobile o indossabile, le informazioni che potrebbero essere utilizzate per identificare un nucleo familiare, un numero di telefono, i dati codificati con chiavi, gli identificatori online, come gli indirizzi IP o le attività personali, il comportamento o le preferenze; comprendono inoltre tutti i dati che sono "dati personali" ai sensi del GDPR.

ii. "Dati personali del Personale" si intende i Dati personali forniti dall'Istituzione, dal Ricercatore Responsabile e da qualsiasi persona che partecipi o svolga un compito o ricopra un ruolo in relazione allo svolgimento della Ricerca. Questi soggetti sono definiti, per le sole ed esclusive finalità di questa clausola, individualmente e collettivamente "Personale", ma ciascuno di essi può esercitare i propri diritti descritti nel presente articolo singolarmente. I Dati personali trattati da MSD per la gestione del presente Contratto generalmente includono informazioni quali nome, specializzazione e informazioni di contatto.

E. Il Personale può esercitare in qualsiasi momento i seguenti diritti in relazione ai propri Dati personali trattati da MSD:

a. Diritto di accesso e rettifica: il Personale ha diritto di richiedere l'accesso ai propri Dati personali. Ciò include, a titolo esemplificativo e non esaustivo, il diritto di essere informato se vengono trattati i Dati personali, quali Dati personali vengono trattati e le finalità del trattamento. Il Personale ha inoltre il diritto di richiedere la correzione dei Dati personali inesatti o incompleti
b. Diritto di opposizione: il Personale ha il diritto di opporsi a un determinato trattamento dei Dati personali, incluso ad esempio quando MSD basa il trattamento dei Dati personali su un interesse legittimo.
c. Diritto alla cancellazione: il Personale può anche richiedere che i Dati personali vengano cancellati se, a titolo esemplificativo e non esaustivo, tali dati non sono più necessari per le finalità per i quali sono stati raccolti, se il trattamento è illecito o se i Dati Personali devono essere cancellati in conformità ad un obbligo legale.

F. MSD rappresenta che potrebbero esserci situazioni in cui ragioni di riservatezza e altri obblighi ai sensi della normativa applicabile, potrebbero impedire di dare seguito ad una richiesta di esercizio di diritti. Salvo laddove vietato dal Regolamento Europeo o da altra normativa applicabile, MSD potrebbe respingere la richiesta del Personale qualora essa (1) fosse in contrasto con una legge o un obbligo etico, che ad esempio imponga a MSD di comunicare i Dati personali secondo quanto previsto da una legge e a seguito di una richiesta di una autorità pubblica, ad esempio per finalità di sicurezza nazionale o per esplicita richiesta delle forze dell'ordine, (2) impedisca a MSD di analizzare, esercitare o difendere i propri diritti e (3) impedisca a MSD di eseguire contratti, gestire rapporti o svolgere altre attività commerciali legittime che siano coerenti con la trasparenza e i principi di limitazione delle finalità e che sono state intraprese facendo affidamento sui Dati personali. Entro quindici giorni lavorativi da qualsiasi decisione di respingere una

richiesta di esercizio dei diritti ai sensi del presente Articolo, MSD provvederà a documentare e comunicare tale decisione al Personale interessato.
G. Se l'Istituzione o il Personale dovessero presentare dei reclami in relazione al trattamento dei Dati personali o desiderassero ricevere ulteriori informazioni, potranno contattare MSD in qualsiasi momento. Il Personale potrà presentare un reclamo, in merito al trattamento dei Dati personali da parte di MSD, all'autorità garante per la protezione dei dati competente (ovvero l'autorità sita nel luogo dove si trova o lavora il Personale o dove si è verificata una presunta violazione dei dati).
H. MSD potrebbe comunicare i Dati personali del Personale (inclusi i dettagli di eventuali pagamenti effettuati all'Istituto) a terzi se richiesto dalle agenzie regolatorie o altrimenti se espressamente consentito o richiesto dalla normativa applicabile. MSD tratterà i Dati personali del Personale, raccolti nel corso dell'esecuzione del Contratto, solo per le finalità per i quali sono stati raccolti, inoltre i Dati personali saranno trattati solo dai dipendenti autorizzati che ricoprono una posizione che richiede loro di trattare i Dati personali per lo svolgimento del proprio lavoro. I Dati personali del Personale sono trattati per un periodo non superiore a quello necessario per le finalità per cui sono stati raccolti. MSD conserva i Dati personali nei limiti previsti dalla legge ed in osservanza delle sue procedure in materia di tempi di conservazione. MSD ha adottato le misure tecniche e organizzative appropriate per proteggere i Dati personali e delle politiche interne per il trattamento sicuro dei Dati personali.
I. MSD non comunicherà i Dati personali del Personale a terze parti a meno che ciò non ci sia richiesto ai sensi della normativa applicabile o sia necessario per l'esecuzione del Contratto. Tuttavia, i Dati personali del Personale potrebbero essere comunicati a, e trattati da, fornitori terzi che forniscono servizi a MSD ("Responsabili del trattamento") per consentire a tali aziende di fornire i servizi richiesti da MSD. A tali società saranno comunicati solo i Dati personali del Personale necessari al conseguimento delle finalità sopra indicate. Tutti i Responsabili del trattamento sono tenuti ad attenersi alle istruzioni e ai contratti (anche sottoscritti in osservanza dell'art. 28 del GDPR), in essere con MSD e devono attuare misure tecniche e organizzative adeguate per la protezione dei Dati personali.
L.MSD tratta i Dati personali su più server nell'UE. I Dati personali potranno essere trasferiti, raccolti ed utilizzati anche nella sede principale Merck & Co. Inc. (Rahway, NJ, U.S.A.), e/o all'interno del suo Gruppo, in USA, sempre comunque in conformità a quanto previsto dal Regolamento Europeo. A tale riguardo, si rappresenta infatti che il Gruppo MSD ha adottato delle Binding Corporate Rules approvate nell'Unione Europea dalle autorità garanti della Privacy degli Stati Membri e ha in atto ulteriori misure supplementari idonee a garantire un livello adeguato di protezione dei dati trasferiti fuori dalla Unione Europea. In ogni caso il trattamento dei Dati personali e/o professionali sarà improntato ai principi di correttezza, liceità e trasparenza, con modalità idonee a garantirne la sicurezza e la riservatezza.

M. MSD è titolare del trattamento dei Dati personali del Personale per le finalità sopra descritte. In caso di richieste sul trattamento dei Dati personali da parte di MSD, è possibile scrivere alla seguente email: privacy.italy@msd.com.
L'Istituzione, ai fini dell'esecuzione del Contratto, è Titolare del Trattamento dei dati personali, anche dei pazienti. Il Responsabile del Trattamento dei Dati Personali per conto

dell'Istituzione è il Dr. Giuseppe Procopio, Sperimentatore Responsabile, via Venezian, 1 20133 Milano.

## 16. Legge applicabile e foro competente

Il Contratto è retto dalla la legislazione italiana e verrà interpretato alla stregua del diritto italiano. Per ogni controversia relativa all'interpretazione ed esecuzione del Contratto, sarà competente in via esclusiva il Tribunale di Milano.

## 17. Pubblicità

Nessuna delle Parti potrà utilizzare il nome dell'altra Parte (ovvero il nome di qualsiasi divisione o società consociata a MSD) in assenza di preventivo consenso scritto. Nessun comunicato stampa, pubblicità o dichiarazione pubblica, sia orale che scritta, salvo che le Presentazioni Pubbliche di cui all'articolo 9, potranno essere rilasciati da parte dell'Istituzione o dello Sperimentatore Responsabile in relazione al Contratto nonché al Studio in assenza del preventivo consenso scritto da parte di MSD.

## 18. Autonomia

La conclusione del presente Contratto non determinerà, ai fini fiscali o per qualunque altro fine, la creazione di un'Agenzia, di una Partnership, di una Joint Venture o di qualunque altra forma di associazione tra le Parti, le quali rimarranno indipendenti l'una dall'altra.
Resta convenuto tra le Parti che l'Istituzione e lo Sperimentatore Responsabile agiranno in autonomia e non quali dipendenti, rappresentanti o associati di MSD. L'Istituzione e lo Sperimentatore Responsabile non avranno alcun potere di rappresentanza di MSD né capacità di impegnarsi o agire in sua vece.

## 19. Modifiche al Contratto

Il Contratto non potrà essere modificato salvo che mediante atto scritto sottoscritto da entrambe le Parti.

## 20. Autonomia delle previsioni

Nel caso in cui alcuno dei termini o delle condizioni di cui al Contratto dovesse risultare contrario alla legge, non valido o non eseguibile, e la sua eliminazione comportare pregiudizio agli interessi di una delle Parti, i restanti termini e condizioni del Contratto non ne saranno pregiudicati e detti termini e condizioni conserveranno la loro validità ed efficacia nei limiti massimi consentiti dalla legge.

## 21. Rinunzie

Il mancato esercizio o godimento di un diritto spettante ad alcuna delle Parti da parte di essa non comporterà rinuncia a tale diritto né costituirà motivo di decadenza al fine dell'esercizio o godimento dello stesso in qualsiasi momento o occasione successivi.

## 22. Disciplina sull'Anticorruzione

Ciascuna Parte si impegna a rispettare la normativa anticorruzione applicabile in Italia.
Ciascuna Parte dichiara di aver adottato misure di vigilanza e controllo ai fini del rispetto e dell'attuazione delle previsioni del D. Lgs. 8 giugno 2001 n. 231 e successive modifiche e integrazioni, per quanto ad esse applicabili, nonché, in quanto applicabile, del Foreign Corrupt Practices Act degli Stati Uniti, e loro successive modifiche ed integrazioni. L'Istituzione si impegna a collaborare in buona fede con il personale di MSD al fine di facilitare la piena e corretta attuazione degli obblighi che ne derivano e l'attuazione delle procedure operative a tal fine messe a punto da MSD.
Ai sensi e per gli effetti della L. n. 190 del 06 novembre 2012 ("Legge Anticorruzione") e sue successive modificazioni, L'Istituzione dichiara di avere adottato il Piano Triennale per la prevenzione della corruzione.
Ciascuna Parte s'impegna a informare immediatamente le altre Parti circa ogni eventuale violazione del presente articolo di cui venga a conoscenza e a rendere disponibili tutti i dati informativi e la documentazione per ogni opportuna verifica.
L'Istituzione può divulgare per qualsiasi scopo legittimo, nei limiti della normativa sul trattamento dei dati, i termini del presente Contratto o di qualsiasi suo emendamento.
La violazione di quanto previsto da questo articolo costituisce grave inadempimento del presente Contratto ai sensi e per gli effetti di cui all'art. 1456 del Codice Civile, risultando pregiudicato il rapporto di fiducia tra le Parti.

L'Istituzione e lo Sperimentatore Responsabile si obbligano a non corrispondere, direttamente o indirettamente, denaro ovvero altra utilità (di seguito "**Pagamenti**") a favore di Funzionari Governativi (definiti come appresso) ove tali Pagamenti abbiano lo scopo di influenzare le decisioni o i comportamenti concernenti l'oggetto del Contratto ovvero altri aspetti delle attività di MSD. Il termine "**Funzionario Governativo**" indicherà (i) qualsiasi funzionario o dipendente dello Stato o di organizzazione pubblica internazionale, (ii) qualsiasi persona che agisca ufficialmente per conto di uno Stato o di una organizzazione pubblica internazionale e (iii) qualsiasi funzionario di un partito politico o candidato a carica pubblica. L'Istituzione dovrà riferire a MSD di qualunque violazione alle prescrizioni di cui al presente paragrafo con impegno a rendere disponibili per MSD o per i suoi rappresentanti tutte le relative attestazioni e la restante documentazione a fini di disamina.

## 23. Forza maggiore

L'inadempimento di una delle Parti alle obbligazioni di cui al Contratto dovuto a forza maggiore (intendendosi per tali leggi o regolamenti di qualunque governo, guerra, insurrezione, distruzione di unità produttive, incendio, inondazione, terremoto o tempesta, interferenze con il lavoro, carenza di materie prime, interruzioni di pubblici servizi o di trasporti pubblici inaspettati) ovvero a qualsiasi altra causa al di fuori del ragionevole controllo della Parte interessata non costituirà violazione del Contratto e detta Parte sarà esentata dall'adempimento della obbligazione relativa per la durata della impossibilità a provvedervi, a condizione che detta impossibilità venga resa nota all'altra Parte per iscritto e che venga impiegata la massima diligenza al fine di far cessare l'evento di forza maggiore, porvi rimedio o altrimenti porvi fine.

## 24. Totalità degli accordi

Il Contratto, ivi inclusi i relativi allegati e tabelle, costituisce la totalità degli accordi esistenti tra le Parti in relazione al contenuto dello stesso. Esso supera ed annulla tutti i precedenti accordi tra le Parti, sia orali che per iscritto, in relazione al contenuto dello stesso. Nel caso di qualsiasi discrepanza tra il Contratto e l'allegato Protocollo (Allegato A) il testo del Contratto avrà prevalenza.

Il presente atto è soggetto a registrazione solo in caso d'uso, ai sensi dell'art. 5, 2° comma, D.P.R. 131/86. Le spese di registrazione sono a carico di chi la richiede.
Le Parti si danno reciproco atto di avere negoziato adeguatamente il contenuto della presente Convenzione e di ritenere pertanto inapplicabile ad essa l'art. 1341 cod. civ.

In fede di quanto precede le Parti hanno stipulato, in persona dei loro rappresentanti debitamente autorizzati, il Contratto.

| **Fondazione IRCCS Istituto Nazionale dei Tumori** | **MSD Italia Srl** |
|---|---|
| NOME Dr Maria Teresa Montella<br>QUALIFICA Direttore Generale | NOME Dr Giorgio Ursillo<br>QUALIFICA Medical Operations Director |
| FIRMA _____ | FIRMA GIORGIO URSILLO 07.03.2025 17:26:10 UTC |
| DATA _____ | DATA _____ |

Dichiaro di aver letto e di accettare i termini del Contratto che mi riguardano e che intendo svolgere e compiere le attività a me affidate per lo Studio in conformità allo stesso ed al Protocollo. Dichiaro altresì di consentire al trattamento, comunicazione e esportazione dei miei dati personali per gli usi e le comunicazioni necessarie ai fini della esecuzione del Contratto e delle richieste ed esame da parte di qualsiasi autorità sanitaria o di controllo.

….., lì _____

GIUSEPPE PROCOPIO

Firmato digitalmente da GIUSEPPE PROCOPIO
ND: dnQualifier=20235040578, c=IT, serialNumber=TINIT-PRCGPP68C12D086G, [illegible], givenName=GIUSEPPE, cn=GIUSEPPE PROCOPIO, [illegible]

_____
Dr Giuseppe Procopio
Sperimentatore Responsabile

ALLEGATO A
(Protocollo)

ALLEGATO B
(Tabella dei Pagamenti)

ALLEGATO C
(Formulario di aggiornamento periodico)

ALLEGATO D
(Global Safety Intake Form)

ALLEGATO E
(Safety Fax Form)

**SPONSOR: Fondazione IRCCS Istituto Nazionale dei Tumori di Milano**

**TITLE: Activity of Pembrolizumab plus Enfortumab Vedotin in Collecting Duct and Renal Medullary Carcinoma (REPRINT trial)**

**EudraCT NUMBER:** 2024-511587-93-00

**Principal Investigator**: Dr. Giuseppe Procopio
Genitourinary Medical Oncology, Director
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano
Via G. Venezian 1, 20133 Milan, Italy
email: giuseppe.procopio@istitutotumori.mi.it

## Documentation History Page

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## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | Pembrolizumab plus Enfortumab Vedotin for Collecting Duct Carcinoma |
| Trial Phase | II |
| Clinical Indication | Collecting Duct Carcinoma and Medullary Renal cell Carcinoma |
| Trial Type | interventional |
| Type of control | none |
| Route of administration | IV |
| Treatment Groups | 1 |
| Number of trial participants | 23 |
| Estimated enrollment period | 24 months |
| Estimated duration of trial | 5 years |
| Duration of Participation | |
| Estimated average length of treatment per patient | 6 months |

## 2.0 TRIAL DESIGN

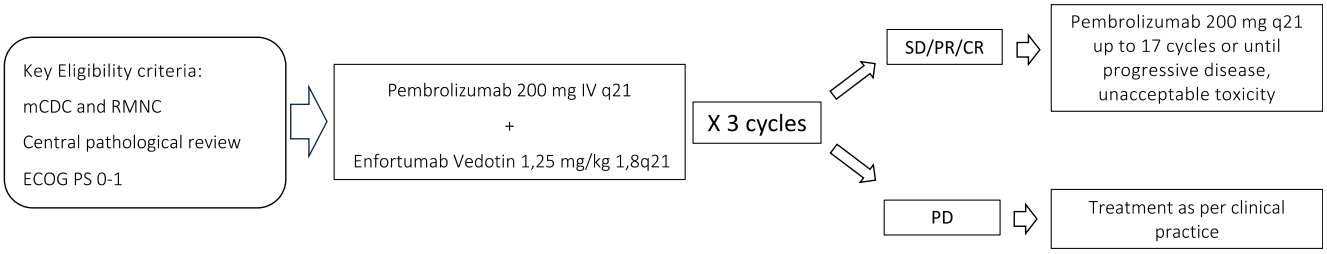
This is, single-arm, monocentric, phase II trial, enrolling patients with histological diagnosis of collecting duct carcinoma and renal medullary carcinoma with locally advanced or metastatic disease who will be treated with Pembrolizumab plus Enfortumab Vedotin.

23 patients will be enrolled. At screening, pre-existing archival primary and metastatic FFPE tumor specimen will be collected and submitted for central pathology review and translational analysis. All participants will undergo baseline screening imaging for clinical staging. Patients will be treated with Pembrolizumab q21 plus Enfortumab Vedotin 1,8q21 for 3 cycles (3 infusion of Pembrolizumab and 6 infusions of Enfortumab Vedotin) then radiological imaging will be repeated and patients with SD, PR or CR will continue pembrolizumab until disease progression, unacceptable toxicities or completion of treatment (35 cycles). Patients with progressive disease after 3 cycles of study intervention will be treated as per clinical practice.

Patients who will experience progressive disease during pembrolizumab monotherapy treatment could restart Enfortumab Vedotin.

The study will also involve collection of a blood sample taken at the commencement of treatment, at the first cycle, after cycle 3 and at the end of treatment or progression of disease, to be used for research purposes as described below.

## 2.1 TRIAL SCHEMA




N of Patients = 23

Simon's two stage optimal design
I stage ≥ 2/9 responses required
II stage ≥ 6/14 responses required

## 2.2 SCHEDULE OF ACTIVITIES

### Table 1 Study Schedule of Activities

| Study Period: | Screening | Intervention | | | | | | | Follow-up (30 days post last dose, +/- days) | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number/Title: | 1 Screening | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 Discontinuation | |
| Scheduled Hour, Day, Week, etc., and Window: | | C1 D1 | C1 D8 | C2 D1 | C2 D8 | C3 D1 | C3 D8 | C4-35 | | |
| Administrative Procedures | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | If the investigator plans to treat beyond disease progression, additional consent is required. |
| Inclusion/Exclusion Criteria | X | | | | | | | | | |
| Participant Identification Card | X | | | | | | | | | Add the allocation number at the time of allocation |
| Medical History (includes substance usage and Family history of premature CV disease) | X | | | | | | | | | Substances: Drugs, Alcohol, tobacco and caffeine |
| Prior/Concomitant Medication Review | X | X | X | X | X | X | X | X | | |
| Intervention [Allocation] | X | | | | | | | | | |
| Pembrolizumab or EV Administration/Dispensing | | X | X | X | X | X | X | X | | |
| Efficacy Procedures | | | | | | | | | | |

| Study Period: | Screening | Intervention | | | | | | | Follow-up (30 days post last dose, +/- days) | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number/Title: | 1 Screening | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 Discontinuation | |
| Scheduled Hour, Day, Week, etc., and Window: | | C1 D1 | C1 D8 | C2 D1 | C2 D8 | C3 D1 | C3 D8 | C4-35 | | |
| CT scan | | | | | | | X | | X | Imaging will be performed as described in section 8.1.4 |
| Safety Procedures | | | | | | | | | | |
| Full physical examination including height and weight | X | X | X | X | X | X | X | X | X | |
| Height | X | | | | | | | | | |
| Weight | X | X | X | X | X | X | X | X | X | If ≥10% change in body weight occurs, weight-based therapy should be re-adjusted. |
| Directed Physical Examination | X | X | | X | | X | | X | X | |
| Vital Signs (heart rate, blood pressure) | X | X | X | X | X | X | X | X | | Heart Rate, Respiratory Rate, temperature, blood pressure, pulse oximetry will be obtained prior to study intervention administration) to be collected] |
| 12-lead ECG | X | | | X | | | | X | | |
| [HIV, hepatitis B and C screen (per site SOP)] | X | | | | | | | | | |
| Hematology | | X | X | X | X | X | X | X | X | |

| Study Period: | Screening | Intervention | | | | | | | Follow-up (30 days post last dose, +/- days) | Notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number/Title: | 1 Screening | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 10 Discontinuation | |
| Scheduled Hour, Day, Week, etc., and Window: | | C1 D1 | C1 D8 | C2 D1 | C2 D8 | C3 D1 | C3 D8 | C4-35 | | |
| Urinalysis | | X | | X | | X | | | X | |
| Chemistry | | X | X | X | X | X | X | X | X | |
| Thyroid Function Tests (TSH, T3, free T4; periodically) | X | X | | X | | X | | X | X | |
| PT and aPTT (baseline only) | X | | | | | | | | | |
| Blood Collection for translational analysis | | X | | | | X | | | X | |
| AE/SAE review | | X | ←==========→ | | | | | | X | |

## Table 2 Study Schedule of Activities: Survival Status

| Study Period | Screening Phase | Treatment Cycles (3-Week Cycles) | | | | | | EOT | Post Treatment Visits | | | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle | Screening (Visit 1) | 1 | 2 | 3 | 4 | 5 | 6 to 35 | DC | Safety Follow-up | Efficacy Follow-up | Survival Follow-up | |
| Scheduling Window (Days): | -42 to -1 | +3 | ±3 | ±3 | ±3 | ±3 | ±3 | Time of DC | 30 Days from the last dose (+7 days) | Every 9 or 12 Weeks (±7 days) | Every 12 Weeks (±7 days) | |
| Administrative Procedures | | | | | | | | | | | | |
| Subsequent Anti-neoplastic Therapy Status | | | | | | | | X | X | X | X | |
| Survival Status | | <----------> | | | | | | X | | | | After investigator determined disease progression or start of new anticancer treatment. |

## Table 3 Study Schedule of Activities: Tumor Imaging

| Study Period: | Screening Phase | Treatment Cycles (3-Week Cycles) | | | | | End of Treatment | Post-Treatment | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Screening (Visit 1) | 1 | 2 | 3 | Week 10 | To be repeated every 12 weeks | Discontinuation | Safety Follow-Up | Follow-Up Visits | Survival Follow-Up |
| Scheduling Window (Days): | -28 to -1 | +3 | ±3 | ±3 | ±7 | ±7 | At time of discontinuation | 30 days post discontinuation | Every 6 weeks post discontinuation | Every 12 weeks |
| Tumor imaging (chest, abdomen, and pelvis) | X | | | | X | X | | | | X |

# 3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

## 3.1 PRIMARY OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

**Objective:** To evaluate activity of the combination Enfortumab Vedotin plus Pembrolizumab in terms of ORR.

**Hypothesis:** Pembrolizumab + Enfortumab improves Objective Response Rate (ORR) in metastatic Collecting Duct and Medullary Renal Cell Carcinoma patients

**Primary Endpoint:** ORR according to RECIST v1.1

## 3.2 SECONDARY OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

- (1) **Objective**: to evaluate progression-free survival (PFS) and overall-survival (OS)

  **Hypothesis**: Pembrolizumab + Enfortumab improves median Progression Free Survival (PFS) and Overall Survival (OS) in metastatic Collecting Duct and Medullary Renal Cell Carcinoma patients

  **Secondary Endpoint**: PFS and OS

- (2) **Objective**: to evaluate tolerability

  **Hypothesis**: Pembrolizumab + Enfortumab Vedotin is safe for treatment of metastatic Collecting Duct and Medullary Renal Cell Carcinoma patients

  **Secondary Endpoint**: Participants experiencing adverse events (AEs) and participants discontinuing study drug due to AEs according to CTCAE v.5

## 3.3 EXPLORATORY OBJECTIVE(S)

1. To identify the somatic mutation profiles in CDC and RMNC on disease associated targets by NGS;
2. to identify transcript fusions of selected genes by performing a RNA sequencing;
3. to assess the association between tumour defined genomic and transcription signatures and response to treatment;
4. to correlate these findings with previous described in BONSAI (NCT03354884) and CICERONE trials (NCT05372302).

# 4.0 BACKGROUND & RATIONALE

## 4.1 BACKGROUND

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical

development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

Enfortumab Vedotin (EV) is an ADC comprised of a fully human anti-Nectin-4 IgG1 kappa mAb conjugated to the small molecule microtubule disrupting agent, MMAE, via a protease cleavable maleimidocaproyl vc linker. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug to antibody ratio of approximately 3:8.

EV binds to the V domain of Nectin-4 protein [Challita-Eid, P. M., et al 2016]. In the presumed mechanism of action, the drug binds to the Nectin-4 protein on the cell surface and is internalized, causing proteolytic cleavage of the vc linker and intracellular release of MMAE. Free MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest.

Information about mode of action, chemical structure, and pharmacokinetics of EV are provided in the EV IB.

### 4.1.1 Pharmaceutical and Therapeutic Background

**Pembrolizumab**

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based

inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in Collecting Duct Carcinoma and Renal Medullary Carcinoma.

**Enfortumab Vedotin**

Nectin-4 is a 66 kDa type I transmembrane protein that belongs to the Nectin family of adhesion molecules. It is composed of an ECD containing 3 Ig-like subdomains, a transmembrane helix, and an intracellular region [Takai, Y., et al 2008]. Nectins are thought to mediate Ca2+-independent cell-cell adhesion via both homophilic and heterophilic trans- interactions at adherens junctions where they can recruit cadherins and modulate cytoskeletal rearrangements [Rikitake, Y. 2008]. Sequence identity of Nectin-4 to other Nectin family members is low and ranges from 25% to 30% in the ECD [Reymond, N., et al 2001].

The 3 Ig-like subdomains in the ECD of Nectin-4 are designated V, C1, and C2. The C1 domain is responsible for cisplatin-interaction (homodimerization), while V domains of most Nectin molecules contribute to trans-interaction and cell-cell adhesion [Mandai, K., et al 2015] [Takai, Y., et al 2008].

Nectin-4 was originally identified by bioinformatics and cloned from human trachea [Reymond, N., et al 2001]. In humans, Nectin-4 is normally expressed in keratinocytes of the skin, sweat glands, hair follicles, transitional epithelium of the bladder, salivary gland ducts, esophagus, breast, and stomach [Challita-Eid, P. M., et al 2016]. Nectin-4 was identified as markedly upregulated in urothelial carcinoma using suppression subtractive hybridization on a pool of urothelial carcinoma specimens. Immunohistochemical characterization of expression in multiple tumor specimens demonstrated high levels of Nectin-4 in bladder, breast, pancreatic, lung, ovarian and other cancers [Challita-Eid, P. M., et al 2016] [Fabre- Lafay, S., et al 2007].

**Enfortumab Vedotin in Combination with Pembrolizumab**

Combining PD-1/PD-L1 inhibitors with a novel therapy, such as EV, may improve patient outcomes. Data from preclinical studies of brentuximab vedotin (a CD30-directed ADC comprising the same linker and MMAE payload as EV), shows potential to induce ICD, antigen presentation, and tumor immune infiltration [Gardai, S. J., et al 2015]. These results suggest that the effects are due to MMAE. Treatment with brentuximab vedotin in vitro and in preclinical models has been shown to induce hallmarks of ICD. ICD is characterized by induction of the endoplasmic reticulum stress response and subsequent surface

presentation of DAMPs immune stimulatory molecules. These DAMPs induce innate immune migration and activation into the tumor microenvironment [Cao, A. T., et al 2017] [Cao, A. T., et al 2018].

Based on the potential enhancement of immune response, it is hypothesized that combining EV with pembrolizumab will result in improved response leading to prolonged PFS and OS in patients with Collecting Duct Carcinoma and Renal Medullary Carcinoma with minimal overlapping toxicities between the 2 agents.

### 4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

## 4.2 RATIONALE

### 4.2.1 Rationale for the Trial and Selected Population

Non-clear cell renal cell carcinomas (nccRCC) comprise several rare and poorly described diseases. Among them, Renal medullary carcinoma (RMNC) represents less than 0,5% and Collecting Duct Carcinoma (CDC) represents 1% of all renal cell carcinomas [Pagani et al 2019]. Both are characterized by an aggressive clinical behaviour and a particular poor prognosis. Both tumors are under-represented in prospective randomized trials predominantly including clear-cell histotype. Thus, a standard of treatment for these rare and aggressive histologies has not been defined yet. Based on the data of a small phase II study with responses of 23%, the more used first line therapy in both cases is a platinum-based cytotoxic chemotherapy that has the ability to control the disease but only for a limited time [Oudard S et al 2007]. More recently, the prospective BONSAI trial met its primary endpoint showing encouraging efficacy of cabozantinib in first line with an objective response (ORR) of 35% in 25 patients with metastatic CDC (mCDC) [Procopio G et al 2022]. Immune-checkpoint inhibitors (ICI) such as Pembrolizumab in combination with Tyrosine Kinase Inhibitors are now recommended as standard-of-care options for clear-cell renal cell carcinoma due to the relevant results in term of antitumor activity and Overall Survival (OS). Cases of excellent response to ICI are reported in literature also in previously treated mCDC patients. Enfortumab Vedotin showed encouraging activity in different tumour types and when combined with pembrolizumab showed relevant results in term of ORR and PFS. More recently, the combination of EV and pembrolizumab in the EV-103/KEYNOTE-869 (NCT03288545) study has demonstrated dramatic improvement in ORR in cisplatin- ineligible patients with locally advanced and metastatic urothelial carcinoma, with a preliminary ORR of 73% (95% CI: 58, 85) regardless of PD-L1 expression level [Rosenberg, J., et al 2020].

Due to the mechanism of action of Enfortumab Vedotin, the expression of NECTIN-4 in CDC is under analysis in the CICERONE trial (NCT05372302). Unpublished results from this trial, state that NECTIN-4 is expressed in 30% of CDC tissue. Furthermore, biology of CDC and of Urothelial

Carcinoma is similar, and this support the expression of NECTIN-4 in this orphan disease and the activity of EV.

Based on the encouraging data regarding the use of ICI in clear cell renal cell carcinoma, we hypothesize that in these histotypes it may be useful to evaluate in more depth the action of drugs that act on the immune system in combination with Antibody-Drug Conjugate (ADC).

Regarding the treatment schedule, intermittent versus continuous treatment can be an effective strategy in certain types of cancer, such as colorectal carcinoma. Intratumoral cell-cell competition between sensitive and resistant cells drives the development of chemotherapy resistance. Therefore, it has been proposed that adaptive chemotherapy dosing regimens, whereby a drug is given intermittently at a fixed dose, may provide clinical benefits to patients compared to traditional dosing. This is supported by mathematical models using modified Lotka-Volterra systems to study dose timing, which show that rapid competitive release of the resistant population and tumor outgrowth occur when cytotoxic chemotherapy is maximally dosed (Cordelia McGehee et al., npj Systems Biology and Applications, 10:140, 2024).

Dose modification and scheduling of Enfortumab Vedotin do not significantly impact its efficacy in patients with urothelial carcinoma (Nobuki Furubayashi et al., In Vivo, 2025). Furthermore, we considered that a “stop-and-go” strategy is effective in some types of cancer, such as colorectal carcinoma.

Based on these considerations, the reintroduction of EV therapy in patients who progressed on pembrolizumab monotherapy after three cycles of EV + P induction could benefit patients by exerting a cytotoxic effect on cancer cell clones sensitive to EV.

### 4.2.2 Justification for Dose

**Pembrolizumab**

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range.
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

**Enfortumab Vedotin (EV)**

EV will be administered at a dose of 1.25 mg/kg (up to a maximum dose of 125 mg) as an IV infusion over approximately 30 minutes on Days 1 and 8 of each 3-week cycle.

In the monotherapy setting, EV is administered on Days 1, 8, and 15 of each Q4W cycle. Based on PK data from previous studies, the half-life of EV is approximately 3 to 4 days. No notable intra-cycle accumulation (<30%) of ADC was observed with this monotherapy dosing regimen at any dose level. Minimal intra-cycle accumulation (<50%) of MMAE was observed.

When comparing the same dose level, the average weekly total exposure of EV following administration on Days 1 and 8 of each Q3W is predicted to be similar to that observed for dosing on Days 1, 8, and 15 of a Q4W. Thus, it is anticipated that the dosing schedule in the current combination study will achieve ADC exposures over each 3-week cycle that may lead to a favorable balance of antitumor activity and safety similar to that observed in the Phase 2 Study EV-201.

The safety and antitumor activity of EV 1.25 mg/kg administered on Days 1 and 8 (dosed 7 days apart) of each Q3W cycle in combination with pembrolizumab is currently being evaluated in the ongoing EV-103/KEYNOTE-869 study. Early safety data from the combination of EV and pembrolizumab shows the combination to be tolerable. The evaluation of the maximum duration of EV therapy has been determined to be a total of 9 cycles. Pembrolizumab will be used for a total of 35 cycles and will be used in combination with 3 cycles of EV.

### 4.2.3 Rationale for Endpoints

#### *4.2.3.1 Efficacy Endpoints*

The primary Efficacy Endpoint is Objective Response Rate (ORR)

**ORR** is defined as the proportion of patients who have complete responses (CR) or partial responses (PR) according to RECIST v1.1 criteria.

ORR are acceptable measures of clinical benefit for a late-stage study that demonstrates efficacy of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

The secondary endpoints of this study are progression-free survival (PFS), overall-survival (OS) and tolerability.

**OS** is defined as the time from assignment to study intervention to death due to any cause.

The use of OS as the primary endpoint in this study would considerably lengthen the study interval, and possibly delay access to improved therapeutic options for this participant population; thus, OS is being evaluated as a key secondary endpoint and is included in the multiplicity analysis.

PFS is defined **as** the time from assignment to study intervention to disease progression or death from any cause.

PFS is a common surrogate endpoint for OS that is used to evaluate the efficacy of cancer therapies. PFS is a widely accepted endpoint in oncology clinical studies since prolonged PFS constitutes clinically meaningful benefit for patients.

**Safety endpoints**

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version [5.0].

#### *4.2.3.2 Planned Exploratory Biomarker Research*

Analysis on biomarkers is exploratory by nature and will be performed retrospectively after the main study analysis is completed. Tissue assessments will include the identification of somatic mutations in CDC and the assessment of the mutational load by focused exome analysis, as well as the identification of transcript fusions by RNA sequencing.

Plasma and viable peripheral blood mononuclear cell (PBMC) will be isolated and stored frozen for subsequent analysis. PBMC will be studied for immune cell profile by multicolor cytofluorimetry (including frequency and activation state of antitumor and immunosuppressive cell subsets of both innate and adaptive immunity), associated with gene-expression profiling and Cibersort analysis for assessing the activation state of the immune cell subsets.

Results will be crossed with clinical data in terms of response rate (RR), to detect any predictive value of blood immune cell profiling during treatment, with the aim of identifying early biomarkers of response, or immune cell profiles in CDC.

## 5.0 METHODOLOGY

### 5.1 STUDY POPULATION

#### 5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of metastatic or advanced Collecting Duct Carcinoma or Medullary Renal Cell Carcinoma will be enrolled in this study.
2. Incapacitated participants are eligible to participate in the study when informed consent of their legally designated representative has been obtained. All conditions set in Article 31 of Reg (EU) 536/2014 are met.
3. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
4. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
5. Have confirmed histology diagnosis of Collecting Duct Carcinoma or Medullary Renal Cell Carcinoma by central pathology review.
6. Archival tumor tissue sample or newly obtained [core, incisional or excisional] biopsy of a tumor lesion not previously irradiated has been provided. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
8. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study intervention.
9. Participants who are HBsAg positive are eligible if they have received HBV anti-viral therapy for at least 4 weeks and have undetectable HBV viral load prior to treatment allocation.

   Note: Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

   Hepatitis B screening tests are not required unless:

   - Known history of HBV infection
   - As mandated by local health authority

10. Participants with a history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative anti-viral therapy at least 4 weeks prior to treatment allocation.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

11. HIV-infected participants must have well-controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/$mm^3$ at the time of screening.
    b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening.
    c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months.
    d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study.
    e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

**Table 4 Adequate Organ Function Laboratory Values**

| System | Laboratory Value |
|---|---|
| Hematological | |
| Absolute neutrophil count (ANC) | ≥1500/μL |
| Platelets | ≥100 000/μL |
| Hemoglobin | ≥9.0 g/dL or ≥5.6 mmol/L[a] |
| Renal | |
| Creatinine OR<br>Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl) | ≤1.5 × ULN OR<br>≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN |
| Hepatic | |
| Total bilirubin | ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN (≤5 × ULN for participants with liver metastases) |
| Coagulation | |
| International normalized ratio (INR) OR prothrombin time (PT)<br>Activated partial thromboplastin time (aPTT) | ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants |

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

### 5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
2. Has received prior systemic anti-cancer therapy, including investigational agents, within 2 weeks prior to treatment allocation.

3. Has received prior radiotherapy within 2 weeks of start of study intervention or radiation-related toxicities requiring corticosteroids. Note: Two weeks or fewer of palliative radiotherapy for non-CNS diseases permitted. The last radiotherapy treatment must have been performed at least 7 days before the first dose of study intervention.
4. Has received a live vaccine or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
5. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
7. Known additional malignancy that is progressing or has required active treatment within the past 2 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.
8. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.
9. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
10. Has active autoimmune disease that has required systemic treatment in the past 2 years except replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid)
11. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has an active infection requiring systemic therapy.
13. Has not adequately recovered from major surgery or has ongoing surgical complications.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality or other circumstance that might confound the results of the study, interfere with the participant's participation for the full duration of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

16. Females who are pregnant, breastfeeding, or planning to conceive a child during the study duration (from screening through 12 months after the last dose of trial treatment) are excluded. Additionally, male participants who plan to father a child during treatment or within 9 months after the last dose of trial treatment are also excluded.
17. Has had an allogenic tissue/solid organ transplant.
18. Has a history of hypersensitivity reaction to Enfortumab Vedotin active substance and/or to any of the excipients.

### 5.1.3 Lifestyle Considerations

#### *5.1.3.1 Meals and Dietary Restrictions*

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

#### *5.1.3.2 Contraception*

Male Participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

- Enfortumab Vedotin: 9 months
- Pembrolizumab: 0 Days (no requirement)

Refrain from donating sperm

PLUS either:

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the

local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Note: Prior to treatment, male participants should be advised to seek information on fertility preservation and sperm cryoconservation.

Female Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

Is not a WOCBP OR

Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

- Enfortumab Vedotin: 12 months
- Pembrolizumab: 4 months

  NOTE: Female participants who are WOCBP and who do not choose to remain abstinent from heterosexual intercourse that will receive Enfortumab Vedotin + pembrolizumab must use an acceptable form of contraception (as described in Appendix 5) plus male partner's use of a condom. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours (serum) or 24 hours (urine) before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.1.3.2
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to
- decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.
- Note: Prior to treatment, WOCBP should be advised to seek information on fertility preservation.

#### *5.1.3.3 Pregnancy*

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or pembrolizumab plus EV, the participant will be immediately discontinued from study intervention(s). The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

## 5.2 TRIAL INTERVENTION(S)

The intervention(s) to be used in this trial is outlined below in **Table 5**

**Table 5 Trial Intervention(s)**

| Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period | Use |
|---|---|---|---|---|---|
| Pembrolizumab | 200 mg | Q3W | IV infusion | Day 1 of each 3-week cycle | Experimental |
| Enfortumab Vedotin | 1,25 mg/kg | 1,8q21 for 3 cycles | IV infusion | Day 1 and Day 8 each 3 week for 3 cycles | Experimental |

Trial intervention(s) should begin on the day of random assignment or as close as possible to the date on which intervention is allocated/assigned.

### 5.2.1 Treatment

- Pembrolizumab will be given for a maximum of 2 years i.e. a total of 35 cycles of pembrolizumab with the q3 week dosing. Participants who complete study intervention after 2 years of pembrolizumab are eligible for up to 1 year of additional pembrolizumab (second course) upon experiencing disease progression.
- Enfortumab Vedotin will be given for a maximum of 3 cycles on day 1 and day 8 each 3 weeks. EV treatment could be re-started in case of Progressive Disease RECIST v1.1 during pembrolizumab monotherapy treatment.

### 5.2.2 Second Course

All participants who have completed the first course [or stopped for confirmed CR] may be eligible for up to an additional 35 cycles of pembrolizumab if there is investigator-determined progressive disease [by RECIST 1.1, Lugano, etc.] after initial treatment. This retreatment is the Second Course of this study.

Participants may enter the Second Course if all the following criteria are met:

1. The participant received pembrolizumab.
2. No new anticancer treatment was administered after the last dose of study intervention.
3. The participant meets all of the inclusion criteria and none of the exclusion criteria.
4. The study is ongoing

### 5.2.3 Timing of Dose Administration

For the first 3 cycles, trial interventions should be administered on Day 1 and Day 8 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 2.2. Trial interventions may be administered up to 3 days before or after the scheduled Day 1 and Day 8 of each cycle due to administrative reasons. After the third cycle, trial intervention will be administered on Day 1 and will consist in pembrolizumab monotherapy.

All trial interventions will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Enfortumab Vedotin will be administered at a dose of 1.25 mg/kg (up to a maximum dose of 125 mg) as an IV infusion over approximately 30 minutes on Days 1 and 8 of each 3-week cycle, for the first 3 cycles.

When pembrolizumab and Enfortumab Vedotin will be given the same day, Enfortumab Vedotin will be administered first.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab and Enfortumab Vedotin infusion fluid and administration of infusion solution.

### 5.2.4 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously.

Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 6.

**Attribution of Immune-Related Toxicity:**

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to pembrolizumab or to EV, all drugs must be held according to the criteria in Table 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

**Holding Study IO Interventions:**

When study interventions are administered in combination, if the AE is considered immune-related, all IO interventions should be held according to recommended dose modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must discontinue all IO therapy.

**Restarting Study Interventions:**

Participants may restart pembrolizumab and/or EV as described below.

- If the toxicities do resolve and conditions are aligned with what is defined in Table 6, the study interventions may be restarted at the discretion of the investigator.

## Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab and IO combination partners

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. All IO treatments must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If IO treatments have been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab + all IO Drugs | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper<br>• Add prophylactic antibiotics for opportunistic infections | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment |
| | Recurrent Grade 2, Grade 3 or 4 | Permanently discontinue | | |
| Diarrhea/Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab + all IO Drugs | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | and of bowel perforation (ie, peritoneal signs and ileus)<br>• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion |
| AST or ALT Elevation or Increased Bilirubin | Grade 2 [a] | Withhold | • Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable) |
| | Grade 3 [b] or 4 [c] | Permanently discontinue | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | |
| T1DM or Hyperglycemia | New onset T1DM or Grade 3 or 4 hyperglycemia | Withhold [d] | • Initiate insulin replacement therapy for participants with T1DM | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab + all IO Drugs | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| | associated with evidence of β-cell failure | | • Administer antihyperglycemic in participants with hyperglycemia | |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hypothyroidism | Grade 2 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold until clinically stable or permanently discontinue [d] | | |
| Nephritis: grading according to increased creatinine or acute kidney injury | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab + all IO Drugs | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Neurological Toxicities | Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1) | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 2, 3 or 4 | Permanently discontinue | | |
| Exfoliative Dermatologic Conditions | Suspected SJS, TEN, or DRESS | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue | | |
| All Other irAEs | Persistent Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the event [e] | | |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab + all IO Drugs | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

**Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.**

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab or its IO combination partner is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab or its IO combination partner may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

## Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab or other drugs in combination may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7. For other drugs, refer to specific infusion treatment guidelines in Table 10.

### Table 7 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines | No subsequent dosing |

| | | |
|---|---|---|
| interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Participant is permanently discontinued from further study drug intervention.** | |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov | | |

**Other allowed dose interruption for pembrolizumab**

Pembrolizumab monotherapy or in combination may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

## 6.0 DOSE MODIFICATION RECOMMENDATIONS FOR EV-ASSOCIATED TOXICITY

Dose modification recommendation for EV-associated toxicities is presented in table 8.

Dose reduction or delay for other EV-associated toxicity is permitted at the discretion of the site investigator. Dose reduction from 1.25 mg/kg to 1 mg/kg or to 0.75 mg/kg will be allowed depending on the type and severity of toxicity. Participants requiring a dose reduction may be re-escalated by 1 dose level (ie, participants reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study intervention discontinuation and has returned to baseline or ≤Grade 1. If the toxicity recurs, re-escalation will not be permitted. Participants with ≥Grade 2 corneal AEs will not be permitted to dose re-escalate.

If a dose interruption is required, an interruption of all Day 1 doses (EV and pembrolizumab) must be considered at investigator discretion. The Day 1 and Day 8 doses of EV must be given 7 days apart. The Day 8 dose of EV must be given within 3 days of the planned dose (Day 8 + 3 days). If toxicities warranting a dose delay occur after Day 1 dosing and are not resolved prior to Day 8 dosing (up to Day 11), Day 8 EV administration must be skipped rather than delayed. A dose interruption may last up to 6 weeks (2 cycles). Dose interruption for participants who are deriving clinical benefit from treatment may be extended beyond 6 weeks, if the participant’s toxicity does not otherwise require permanent discontinuation. If there is a dose interruption, the schedule for response assessments will not be adjusted.

EV may be delayed for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should resume study intervention as soon as clinically safe as assessed by the investigator. For delays longer than 6 weeks, the medical monitor should be consulted before resuming study intervention. The reason for delay should be documented in the participant's CRF.

**Table 8 Enfortumab Vedotin Dose Reductions**

| Dose Level | Enfortumab Vedotin |
|---|---|
| 0 | 1.25 mg/kg |
| 1 | 1.0 mg/kg |
| 2 | 0.75 mg/kg |

**Table 9 Recommended Dose Modification for Enfortumab Vedotin-associated Hematologic Toxicity**

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| Continue at same dose level. | Continue at same dose level.<br><br>For Grade 2 thrombocytopenia, withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then resume treatment at the same dose level. | Withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.<br><br>Transfusions or growth factors may be used as indicated per institutional guidelines. | Withhold dose until toxicity is ≤Grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines.<br><br>For anemia, treatment discontinuation should be strongly considered. |

Note: Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia, and febrile neutropenia.

## Table 10 Recommended Dose Modification for Enfortumab Vedotin-associated Nonhematological toxicites

| **Toxicities** | **Grade** | | | |
|---|---|---|---|---|
| | Any Grade | | | |
| | For suspected Stevens-Johnson Syndrome (SJS) or suspected toxic epidermal necrolysis (TEN) or bullous lesions, immediately withhold EV and refer the participant to a dermatologist/specialist for diagnosis and specialized care. For confirmed SJS or TEN permanently discontinue treatment. If SJS or TEN is ruled out, see recommendations provided below for skin reactions, including for dose modifications. | | | |
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Skin reaction | For Grade 1 rash or skin reactions, may continue at same dose level. See also Section 6.2 for recommended management of rash. | Continue at same dose level.<br><br>For worsening rash or skin reactions or skin reactions with concomitant fever, withhold EV until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the participant to a dermatologist/ specialist for diagnosis and specialized care. See also Section 6.2 for recommended management of rash. | For Grade 3 rash or skin reactions, withhold EV until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the participant to a dermatologist/specialist for diagnosis and specialized care. See also Section 6.2 for recommended management of rash.<br><br>Participants who have confirmed SJS or recurrent Grade 3 rash events should have therapy permanently discontinued. | For confirmed SJS or TEN, or Grade 4 rash, permanently discontinue treatment. |
| Ocular | For Grade 1 Continue at same dose level.<br><br>If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist. | For Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 corneal AEs, withhold dose until toxicity is ≤ Grade 1, then reduce the dose by 1 dose level and resume treatment.<br><br>If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist. | For Grade 3 corneal AEs, discontinue treatment at the discretion of the investigator.<br><br>If ocular symptoms and/or changes in vision are identified, the participant should be evaluated by an optometrist or ophthalmologist. | For Grade 4 AEs, discontinue treatment. |

| | | | | |
|---|---|---|---|---|
| Neuropathy | Continue at same dose level | For Grade 2 neuropathy AEs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. For the second occurrence of Grade 2 neuropathy AEs, withhold dose until toxicity is<br><br>≤ Grade 1, then reduce the dose by 1 dose level and resume treatment. | For Grade 3 neuropathy AEs, discontinue treatment at the discretion of the investigator. | For Grade 4 AEs, discontinue treatment. |
| Gastrointestinal | Continue at same dose level | Continue at same dose level | Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by<br><br>1 dose level. | For Grade 4 AEs, discontinue treatment.<br><br>Grade 4 vomiting and/or diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management does not require discontinuation. |
| Hyperglycemia | Continue at same dose level | Continue at same dose level | For Grade 3 hyperglycemia or blood glucose >250 mg/dL, withhold EV treatment. Resume treatment once hyperglycemia/ elevated blood glucose is<br><br>≤250 mg/dL and participant is clinically and metabolically stable. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 8 and Management of Hyperglycemia section below. | For Grade 4 hyperglycemia or elevated blood glucose<br><br>>500 mg/dL withhold EV treatment and undertake a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once blood glucose is ≤250 mg/d and the participant is clinically and metabolically stable, dosing may resume with close consultation with the medical monitor. See also pembrolizumab dose modification recommendations for hyperglycemia in Table 8 and Management of Hyperglycemia section below. |
| Pneumonitis/ ILD | Continue at same dose level. | Withhold dose until ≤Grade 1, then resume at the same dose level or consider dose reduction by 1 dose level. | Permanently discontinue treatment. | Permanently discontinue treatment. |

| | | | | |
|---|---|---|---|---|
| All Other (not previously mentioned) | Continue at same dose level. | Continue at same dose level. | Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level | For Grade 4 AEs, discontinue treatment[a] |

AEs=adverse events; EV=Enfortumab enfortumab vedotin; ILD = interstitial lung disease; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis
Grade 3/4 electrolyte imbalances/laboratory abnormalities, except hyperglycemia, that are not associated with clinical sequelae or are corrected with supplementation/appropriate management within 72 h of their onset do not require discontinuation (eg, Grade 4 hypouricemia). Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay.

## 6.1 MANAGEMENT OF HYPERGLYCEMIA

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, participants should be treated according to local standard of care and referral to endocrinology may be considered.

Participants, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

Participants who enter the study with an elevated HbA1c (≥6.5%) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked on the day of EV dosing prior to study intervention administration as per the SoA (Section 2.2) and dose should be withheld for blood glucose level >250 mg/dL. EV dosing may continue once the participant's blood glucose has improved to ≤250 mg/dL and participant is clinically and metabolically stable. The use of insulin is permitted as part of standard of care. Blood glucose >500 mg/dL considered related to EV requires drug interruption and a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once hyperglycemia/elevated blood glucose has improved to ≤250 mg/dL and the participant is clinically and metabolically stable, dosing may resume with close monitoring after consultation with the Sponsor.

## 6.2 MANAGEMENT OF RASH RELATED TO ENFORTUMAB VEDOTIN

Enfortumab Vedotin is a Nectin-4 directed ADC. Nectin-4 is a cell adhesion molecule that is highly expressed in urothelial carcinoma. Low to moderate levels of Nectin-4 are also expressed on normal tissues, including skin keratinocytes, sweat glands and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are AEs of interest in all clinical studies with Enfortumab Vedotin.

A cumulative review of post-marketing safety data from 18-DEC-2019 (the approval date of Enfortumab Vedotin in the US) through 22-OCT-2020 identified reports of severe cutaneous adverse reactions in 15

patients receiving Enfortumab Vedotin, some of whom had fatal outcomes. These reactions occurred predominantly during the first cycle of treatment. AEs reported in these cases included SJS (5 cases), blister (3 cases), dermatitis bullous (3 cases), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE; 2 cases), and 1 case each of dermatitis exfoliative, exfoliative rash, epidermal necrosis, oropharyngeal blistering, stomatitis, and TEN.

In Enfortumab Vedotin monotherapy studies of urothelial carcinoma, SAEs of severe cutaneous adverse reactions were reported in 11 of 749 subjects (1.5%) and included dermatitis bullous (0.4%), drug eruption (0.4%), blister (0.1%), conjunctivitis (0.1%), SJS (0.1%), stomatitis (0.1%), and toxic skin eruption (0.1%).

Participants should be informed that rashes and severe skin reactions have occurred after administration of Enfortumab Vedotin, and to contact the investigator immediately if they have signs and symptoms of skin reactions, oral mucosal, and ocular abnormalities including mucositis or conjunctivitis. Starting in the first cycle and throughout treatment, closely monitor subjects for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions, refer to Table 10.

For the EV and pembrolizumab study treatment arm, if the rash or skin reaction is determined by the investigator to be related to study treatment, initial management actions (i.e., to withhold or discontinue study treatment) should apply to both study treatments and the investigator should follow the most conservative dose modification recommendations described in Sections 6.0 (Table 8, 9, 10). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the participant's ADLs, continued dosing of EV may be considered following consultation with the Sponsor. Neither EV nor pembrolizumab should be administered in the setting of a Grade ≥ 3 skin reaction.

### 6.3 MANAGEMENT OF INFUSION REACTIONS

An IRR may occur during the infusion of study intervention with EV. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for IRRs.

Premedications for IRRs may include pain medication (eg, acetaminophen or equivalent), an antihistamine (eg, diphenhydramine hydrochloride), and a corticosteroid administered approximately 30–60 minutes prior to each EV infusion and after the pembrolizumab infusion. Should a participant experience IRRs in the setting of premedication, continued treatment must be discussed with the Sponsor prior to the next planned dose. Prophylactic premedication prior to combination treatment on Cycle 1 Day 1 for prevention of IRRs may not be administered.

If anaphylaxis occurs, study intervention administration should be immediately and permanently discontinued.

### 6.4 MANAGEMENT OF PNEUMONITIS/INTERSTITIAL LUNG DISEASE RELATED TO ENFORTUMAB VEDOTIN

Severe, life-threatening, or fatal pneumonitis/interstitial lung disease have occurred in patients receiving enfortumab vedotin. Monitor participants for signs and symptoms indicative of pneumonitis/interstitial lung disease such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. For recommendations regarding dose modifications for pneumonitis/interstitial lung disease due to enfortumab vedotin, refer to Section 6.0 Table 10.

### 6.5 OVERLAPPING ADVERSE REACTIONS

The IBs for EV and pembrolizumab individually describe AEs commonly observed relative to those agents. Some AEs, including rash or skin reactions or pneumonitis/interstitial lung disease, may represent overlapping toxicities for EV and pembrolizumab, and attribution to an individual study treatment may be difficult. For overlapping AEs of skin reaction or pneumonitis/interstitial lung disease the management actions (ie, to withhold or discontinue study treatment) should apply to both EV and pembrolizumab and the investigator should follow the most conservative dose modification guidelines as described in Section 6.0 (Table 8, 9, 10). However, for Grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the participant's ADLs, continued dosing of EV may be considered following consultation with the Sponsor.

## 7.0 TREATMENT ALLOCATION

This is a phase II non-randomized trial so all patients included will receive pembrolizumab and Enfortumab Vedotin.

### 7.1 STRATIFICATION

No stratification will be done

### 7.2 CONCOMITANT THERAPY

The following medications and vaccinations are prohibited during the study:

- Live or attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
- Systemic glucocorticoids except when used for the following purposes:

- To modulate symptoms of an AE that is suspected to have an immunologic etiology
- For the prevention of emesis
- To premedicate for IV contrast allergies
- To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study intervention period, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy or biological therapy not specified in this protocol.
- Investigational agents other than those specified in the protocol.
- Radiation therapy. Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Investigational vaccines (ie. those not licensed or approved for Emergency Use) are not allowed.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered 30 days after the last dose of trial intervention are to be recorded as defined in Section 9.0.

### 7.2.1 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.4, [Table 6].

## 7.3 PARTICIPANT DISCONTINUATION CRITERIA

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.2 unless the participant has withdrawn from the study (Section 7.4).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in section 8.1.4.5 and 8.1.4.6 and in Appendix 3.
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.4.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

### 7.4 PARTICIPANT WITHDRAWAL FROM STUDY

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

### 7.5 PARTICIPANT REPLACEMENT STRATEGY

A participant who discontinues from study intervention will not be replaced.

### 7.6 CLINICAL CRITERIA FOR EARLY TRIAL TERMINATION

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug

In the event of MSD decision to no longer supply study drug, adequate notification will be provided so that appropriate adjustments to participant treatment can be made.

### 7.7 BEGINNING AND END-OF-STUDY DEFINITION

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last. As the study is conducted in a country in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR)

## 8.0 TRIAL ASSESSMENTS AND PROCEDURES

### 8.1 TRIAL PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities, Section 2.2.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- Additional evaluations/testing may be deemed necessary by the investigator, the Sponsor and/or MSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 8.1.1 Administrative and General Procedures

#### *8.1.1.1 Informed Consent*

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in this clinical trial. If there are changes to a participant's status during the study (e.g., health requirements) the investigator must ensure appropriate documented informed consent is in place.

#### *8.1.1.2 General Informed Consent*

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information

will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or his/her legally acceptable representative will be asked to sign consent.

#### *8.1.1.3 Inclusion/Exclusion Criteria*

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

#### *8.1.1.4 Medical History*

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically important by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in).

#### *8.1.1.5 Prior and Concomitant Medications Review*

##### *8.1.1.5.1 Prior Medications*

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

##### *8.1.1.5.2 Concomitant Medications*

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. In addition, new medication started during the Second Course should be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 9.0.

#### *8.1.1.6 Disease Details and Treatments*

##### *8.1.1.6.1 Disease Details*

The investigator or qualified designee will obtain prior and current details regarding disease status.

##### *8.1.1.6.2 Prior Treatment Details*

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

##### *8.1.1.6.3 Subsequent Anti-Cancer Therapy Status*

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up.

#### *8.1.1.7 Assignment of Screening Number*

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

#### *8.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)*

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record. Refer to Section 6.0 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab, and for dose modifications for EV.

There are no meal or dietary restrictions. Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

### 8.1.2 Clinical Procedures/Assessments

#### *8.1.2.1 Adverse Event (AE) Monitoring*

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 4). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 9.0 for detailed information regarding the assessment and recording of AEs.

#### *8.1.2.2 Physical Exam*

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### *8.1.2.3 Full Physical Exam*

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2.2. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### *8.1.2.4 Directed Physical Exam*

For cycles that do not require a full physical exam per the Section 2.2, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

#### *8.1.2.5 Vital Signs*

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Schedule of Activities (Section 2.2). Vital signs should include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.

#### *8.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale*

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Activities (Section 2.2).

#### *8.1.2.7 Electrocardiograms*

12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (see Section 2.2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and [QTc] intervals.

*Elevated Transaminases With Treated HBV or HCV*

Participants who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

If baseline AST/ALT <2×ULN and an increase of AST/ALT ⩾5×ULN

If baseline AST/ALT ⩾2×ULN and an increase of AST/ALT >3 × baseline level

AST/ALT ≥2×ULN and an increase of AST/ALT >3 × baseline level

Viral load testing and additional hepatitis serologies should be included as required.

### 8.1.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 21 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Study Schedule of Activities (Section 2.2) for the timing of laboratory assessments.

#### *8.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)*

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

#### *8.1.3.2 Pregnancy Testing*

Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.

Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study interventions. The length of time required to continue pregnancy testing for each study intervention is as follows:

- Enfortumab Vedotin [12 months]
- Pembrolizumab [4 months]

### 8.1.4 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Expedited confirmation of measurable disease based on RECIST v.1.1 at Screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST v.1.1 is highly recommended prior to participation.

#### *8.1.4.1 Initial Tumor Imaging*

Initial tumor imaging at Screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the central imaging vendor.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

#### *8.1.4.2 Tumor Imaging During the Study*

The first on-study imaging assessment should be performed at 10 weeks (70 days ±7 days]) from the date of allocation. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should

not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 12 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 8.1.4.6), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided, they have met the conditions detailed in Section 8.1.4.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 8.1.4.6.

#### *8.1.4.3 End of Treatment and Follow-up Tumor Imaging*

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 12 weeks in Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

#### *8.1.4.4 Second Course (Retreatment) Tumor Imaging*

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 12 weeks (79 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (79 days ±7 days) or more frequently, if clinically indicated.

Per RECIST 1.1 (Section 8.1.4.5), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression with the option of continuing treatment while awaiting radiological confirmation of progression in clinically stable patients. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed 4 to 8 weeks after the first tumor imaging indicating PD, by the investigator using iRECIST, in clinically stable participants.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (79 days ±7 days) until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the mstudy, whichever occurs first.

#### *8.1.4.5 RECIST 1.1 Assessment of Disease*

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

#### *8.1.4.6 iRECIST Assessment of Disease*

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 3. This allowance to continue treatment despite initial radiologic disease progression takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of disease progression and is not required to have repeat tumor imaging for confirmation of disease progression by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm disease progression by iRECIST, per investigator assessment. Images should continue to be sent in to the iCRO for potential retrospective BICR.

If repeat imaging does not confirm disease progression per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If disease progression is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 3, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6 and submitted to the iCRO.

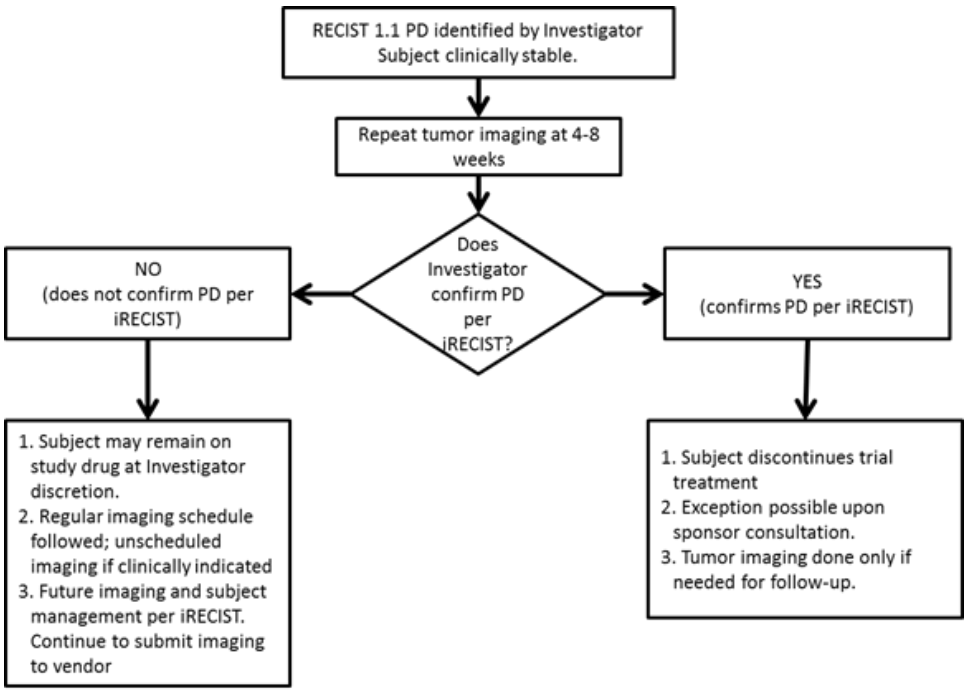
A description of the adaptations and iRECIST process is provided in Appendix 3. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 11 and illustrated as a flowchart in Figures 1.

**Table 11 Imaging and Treatment After First Radiologic Evidence of Progressive Disease**

| | **Clinically Stable** | | **Clinically Unstable** | |
|---|---|---|---|---|
| | **Imaging** | **Treatment** | **Imaging** | **Treatment** |
| First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment | Repeat imaging at 4 to 8 weeks to confirm disease progression | May continue study treatment at the assessment of the investigator and after the participant's consent | Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only. | Discontinue treatment |
| First radiologic evidence of disease progression by RECIST 1.1 | Repeat imaging at 4 to 8 weeks to confirm disease progression. | May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST. | Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only. | Discontinue treatment |
| Repeat tumor imaging confirms disease progression (iCPD) by iRECIST per investigator assessment. | No additional imaging required. | Discontinue treatment (exception is possible upon consultation with Sponsor). | No additional imaging required. | Not applicable |
| Repeat tumor imaging shows iUPD by iRECIST per investigator assessment. | Repeat imaging at 4 to 8 weeks to confirm disease progression. May occur at next regularly scheduled imaging visit. | Continue study intervention at the investigator's discretion. | Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only. | Discontinue treatment |
| Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per | Continue regularly scheduled imaging assessments. | Continue study intervention at the investigator's discretion. | Continue regularly scheduled imaging assessments. | May restart study intervention if condition has improved and/or clinically stable per |

| | **Clinically Stable** | | **Clinically Unstable** | |
|---|---|---|---|---|
| | **Imaging** | **Treatment** | **Imaging** | **Treatment** |
| First radiologic evidence of disease progression by RECIST 1.1 per investigator assessment | Repeat imaging at 4 to 8 weeks to confirm disease progression | May continue study treatment at the assessment of the investigator and after the participant's consent | Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only. | Discontinue treatment |
| investigator assessment. | | | | investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule. |
| iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression | | | | |

**Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator**



### 8.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

Biopsy from kidney or newly obtained core or excisional biopsy of renal tumor lesion (not previously irradiated) must be provided for testing and be deemed adequate for evaluation and central histology revision, prior to treatment allocation. Newly obtained biopsies are preferred to archived tissue. FFPE tissue blocks are preferred to slides. If submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory. If the sample is determined to be non-evaluable prior to testing by the central laboratory, a new sample should be submitted, if available. The tissue analysis will include PD-L1 expression (Dako PD-L1 IHC 22C3 pharmDx kit) and other biomarkers aligned with the objectives of the protocol. The tissue samples will be stored at the Pathology Department of the Fondazione IRCCS Istituto Nazionale dei Tumori.

Blood samples will be collected for exploratory research. In particular, 30 ml of research blood sample (EDTA or equivalent tube) will be collected at baseline, after cycle 3 and at the end of treatment or progression of disease. If the patients go off the study for unacceptable toxicity or treatment refusal, blood sample can still be collected until PD in consenting patients.

Samples will be sent to the Laboratory of Clinical Pharmacology of the Sponsor (Fondazione IRCCS Istituto Nazionale dei Tumori) for collection.

Plasma and viable peripheral blood mononuclear cell (PBMC) will be isolated and stored frozen for subsequent analysis. PBMC will be studied for immune cell profile by multicolor cytofluorimetry (including frequency and activation state of antitumor and immunosuppressive cell subsets of both innate and adaptive immunity), associated with gene-expression profiling and Cibersort analysis for assessing the activation state of the immune cell subsets.

Results will be crossed with clinical data in terms of response rate (RR), to detect any predictive value of blood immune cell profiling during treatment, with the aim of identifying early biomarkers of response, or immune cell profiles in CDC.

These analysis will be conducted at the Experimental Oncology and Molecular Medicine Department, Unit of Immunotherapy of Human Tumors of the Fondazione IRCCS Istituto Nazionale dei Tumori, under the responsibility of Dr.ssa Rivoltini.

#### *8.1.5.1 **Collection, storage and future use of biological samples***

For the storage of biological samples, specific means will be taken to ensure the subject's right to privacy and the pertinent guidance documents and regulations will be considered. Subjects may withdraw their consent to store the biological samples. If a subject requests destruction of their tissue and blood samples, the Sponsor will make every attempt to destroy the samples. The Sponsor will notify the Investigator in writing that samples have been destroyed if requested by the subject. Samples that are not depleted or destroyed may be retained according to the site's policies to complete study defined analyses and respond to inquiries from regulatory agencies.

Samples will be collected and sent to the laboratories designated for the trial where they will be processed (see Section 8.1.5).

Samples will be labeled with a code number and kept in secured storage. Only limited site staff will know the research subject identity and will be able to link research samples with the research subject identity.

After study completion, samples will be destroyed.

### 8.1.6 Other Procedures

#### *8.1.6.1 Discontinuation and withdrawal*

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA (Section 2.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.0.

#### *8.1.6.2 Blinding/Unblinding*

This is not applicable as this is an open-label study.

### 8.1.7 Visit Requirements

Visit requirements are outlined in Section 2.2 – Schedule of Activities. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

#### *8.1.7.1 Screening*

Documented consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing documented consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within approximately 42 days prior to the first dose of study intervention except as described below.

- Disease assessments or imaging scans performed as part of routine clinical management are acceptable for use as the screening imaging scan if they are of diagnostic quality and performed within the imaging window of ≤28 days prior to treatment allocation.
- Most laboratory tests are to be performed within 14 days prior to treatment allocation . Hepatitis/HIV testing may be done up to 28 days, and ACTH and cortisol testing may be done up to 42 days prior to treatment allocation.
- Imaging studies are to be performed within 28 days prior to treatment allocation.

- Evaluation of ECOG is to be performed within 14 days prior to treatment allocation.
- WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
- Ophthalmologic assessment for all participants is required at screening. Prior ophthalmologic exam done within 3 months of enrollment is acceptable provided there are no new symptoms since the exam.

  Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

*8.1.7.1.1 Screening Period*

Pre-treatment evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or trial-related procedures will be initiated before the signed consent has been obtained. Imaging may be done before obtaining informed consent if done routinely. Subjects will not be required to undergo additional scanning if suitable images taken within 4 weeks of treatment period are available. Pre-treatment evaluations will be performed according to the eligibility criteria. If the subject is eligible for the study, the parameters at the screening visit showing subject health status, including blood values, will be recorded in the eCRF.

### *8.1.7.2 Treatment Period*

The treatment period extends from the day of first treatment with pembrolizumab + Enfortumab Vedotin to 4 weeks. The time between patient consent signed and first administration should be as brief as possible in accordance with the country- specific drug order lead time.

### *8.1.7.3 Post-Treatment Visits*

The End of Treatment Visit should occur at the time study intervention is discontinued for any reason. If the End of Treatment assessments cannot be completed at time of treatment discontinuation, the End of Treatment assessments may be combined with the safety follow-up visit. If the Discontinuation Visit occurs ≥30 days after the last dose of study intervention, the Safety Follow-up Visit is not required.

*8.1.7.3.1 Safety Follow-Up Visit*

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. Participants who are eligible for retreatment with pembrolizumab (as described in Section

5.2.2) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

*8.1.7.3.2 Efficacy Follow-up Visits*

Participants who complete the protocol-required cycles of study intervention of who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.2 will move from the Efficacy Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA for retreatment with pembrolizumab.

*8.1.7.3.3 Survival Follow-up Contacts*

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).
- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

*8.1.7.3.4 Post Study*

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less then 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine of any AEs have occurred since the poststudy clinic visit.

# 9.0 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES), AND OTHER REPORTABLE SAFETY EVENTS

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 4.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

## 9.1 TIME PERIOD AND FREQUENCY FOR COLLECTING AE, SAE, AND OTHER REPORTABLE SAFETY EVENT INFORMATION

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Section 5.1.3.2, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator. Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered drug related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor within the time frames as indicated in Table 12.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

**Table 12 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events**

| **Type of Event** | **Reporting Time Period: Consent to Allocation** | **Reporting Time Period: Allocation through Protocol-specified Follow-up Period** | **Reporting Time Period: After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to the Sponsor** |
|---|---|---|---|---|
| | | | | |
| Serious Adverse Event (SAE) | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>- drug/vaccine related. (Follow ongoing to outcome) | Within 2 business days but no longer than 3 calendar days of receipt of information |
| Pregnancy/Lactation Exposure | Report if:<br><br>- participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)<br>Exception: A positive pregnancy test | Report all | Previously reported – Follow to completion/termination; report outcome | Within 2 business days but no longer than 3 calendar days of receipt of information |

| **Type of Event** | **<u>Reporting Time Period:</u> Consent to Allocation** | **<u>Reporting Time Period:</u> Allocation through Protocol-specified Follow-up Period** | **<u>Reporting Time Period:</u> After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to the Sponsor** |
|---|---|---|---|---|
| | at the time of initial screening is not a reportable event. | | | |
| Event of Clinical Interest (require regulatory reporting) | Report if:<br>- due to intervention<br>- causes exclusion | Report<br>- potential drug-induced liver injury (DILI)<br>- require regulatory reporting | Not required | Within 2 business days but no longer than 3 calendar days of receipt of information |
| Cancer | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Not required | Within 2 business days but no longer than 3 calendar days of receipt of information |
| Overdose | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in | Report all | Not required | Within 2 business days but no longer than 3 calendar days of receipt of information |

| **Type of Event** | **Reporting Time Period: Consent to Allocation** | **Reporting Time Period: Allocation through Protocol-specified Follow-up Period** | **Reporting Time Period: After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to the Sponsor** |
|---|---|---|---|---|
| | or other run-in treatment | | | |

### 9.1.1 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 9.1.2 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up. In addition, the investigator will make every attempt to follow all nonserious AEs that occur in allocated participants for outcome. Further information on follow-up procedures is given in Appendix 4.

### 9.1.3 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

### 9.1.4 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

### 9.1.5 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Potential DILI events defined as: an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

## 10.0 STATISTICAL ANALYSIS PLAN

### 10.1 STATISTICAL ANALYSIS PLAN SUMMARY

This is a single-arm phase II trial enrolling patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease. The sample size is 23 and the primary endpoint is ORR.

### 10.2 STATISTICAL ANALYSIS PLAN

This is a single-arm phase II trial enrolling patients with histological diagnosis of CDC with untreated locally advanced or metastatic disease.

Demographic characteristics and baseline disease characteristics will be summarized for the ITT population. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized by frequencies and percentages.

Univariable and multivariable logistic and Cox proportional hazard regression models will be generated.

The primary endpoint is ORR, defined as the proportion of subjects who have best overall response of CR or PR as determined by central radiological review using RECIST v1.1 criteria.

The Simon’s two-stage optimal design will be applied. In order to reject an ORR equal to 15% with a one-sided alpha error of 10% and to detect an ORR equal to 35% with a power of 80% 9 patients will be enrolled in the first stage. If at least 2 responses will be observed in the first stage other 14 patients will be enrolled in the second stage. If at least 6 responses will be collected after the second stage, the interesting activity of Pembrolizumab plus Enfortumab Vedotin will be proved.

Secondary endpoints are PFS, defined as the time from treatment allocation to disease progression per RECIST v1.1 or death from any cause (whichever occur first), and OS, defined as the time from treatment allocation to the date of death from any cause. Subject who are lost to follow up and those who are alive at the date of data cut-off will be censored at the date the subject was last known to be alive or date of data cut-off, whichever occur first.

The population will be analyzed according to Intention-To-Treat (ITT) and per protocol principle.

The total number of patients enrolled will be 23.

Trial expected duration (comprehensive of accrual, treatment and follow-up): 24 months (stage 1 + stage 2). This should be added to a planned duration of follow up of 6 months since the enrollment of the last patient (resulting in a maximum of 30 months).

In the ITT principle, all patients included in the trial by signing the informed consent and assigned a study patient number will be considered for the analysis.

Using per protocol principle, patients who did not receive treatment for any causes, severely violated protocol inclusion/exclusion criteria or withdrawal informed consent will be excluded for the analysis. Patients not evaluable for response will be considered as non responders

Statistical analyses will be carried out using SAS® (SAS Institute Inc.), R software (http://www.r-project.org/, last access March 31st, 2017). The results will be considered statistically significant whenever a two-sided *p* value below 0.05 will be achieved.

## 11.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 11.1 INVESTIGATIONAL PRODUCT

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by MSD as summarized in Table 13.

Enfortumab Vedontin wil be provided by Fondazione IRCCS Istituto Nazionale dei Tumori as summarized in Table 13.

**Table 13 Product Descriptions**

| Product Name & Potency | Dosage Form |
|---|---|
| Pembrolizumab 100 mg/ 4mL | Solution for Injection |
| Enfortumab Vedotin 20 mg/10 mL | Solution for Injection |
| Enfortumab Vedotin 30 mg/10 mL | Solution for Injection |

### 11.2 PACKAGING AND LABELING INFORMATION

Supplies will be labeled in accordance with regulatory requirements.

### 11.3 CLINICAL SUPPLIES DISCLOSURE

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drugs identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

### 11.4 STORAGE AND HANDLING REQUIREMENTS

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Clinical supplies may not be used for any purpose other than that stated in the protocol.

### 11.5 RETURNS AND RECONCILIATION

The investigator is responsible for keeping accurate records of the clinical supplies received from MSD or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.
Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 12.0 ADMINISTRATIVE AND REGULATORY DETAILS

### 12.1 GOOD CLINICAL PRACTICE

The study will be conducted in compliance with Regulation 536/2014, in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

### 12.2 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and

well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator.

### 12.3 PATIENT INFORMATION AND INFORMED CONSENT

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

### 12.4 PREMATURE CLOSURE OF THE STUDY

This study may be prematurely terminated, if in the opinion of the investigator, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

should the study be closed prematurely, all study materials will be stored for 15 years at Fondazione IRCCS Istituto Nazionale dei Tumori of Milan.

### 12.5 RECORD RETENTION

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

## 12.6 SITE MONITORING/SCIENTIFIC INTEGRITY

Investigative trial site is monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). Clinical data are reviewed for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per Sponsor policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

## 12.7 DATA PROTECTION

The Sponsor will conduct this study in compliance with all applicable data protection regulations.
Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

## 12.8 CONFIDENTIALITY OF DATA

The Sponsor guarantees that information will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication .

## 12.9 CONFIDENTIALITY OF PARTICIPANT RECORDS

The Sponsor, IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process.
The Sponsor will treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

## 12.10 COMPLIANCE WITH STUDY REGISTRATION AND RESULTS POSTING REQUIREMENTS

Under the terms of the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, https://euclinicaltrials.eu/ or other local registries. The Sponsor will submit the information necessary to fulfill these requirements.
Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

## 12.11 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

The investigator and the Sponsor will conduct the study in an efficient and diligent manner and in conformance with this protocol, in compliance with generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), with Regulation 536/2014, and all applicable state and local laws, rules and regulations relating to the conduct of the clinical study.
The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.
The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study. The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.
Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened. The investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

## 12.12 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic CRF. The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Study documentation will be promptly and fully disclosed upon request and also shall be made available upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator and the Sponsor agrees to promptly take any reasonable steps that are requested by any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs. The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

## 12.13 BENEFIT/RISK ASSESSMENT

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. In this study, participants will receive EV with pembrolizumab for metastatic

or locally advanced Collecting Duct Carcinoma for 3 cycles. After this initial treatment, patients with SD/PR/CR will receive pembrolizumab up to 35 cycles.

Pembrolizumab + EV has demonstrated clinical activity in 1L metastatic urothelial carcinoma with impressive results in term of OS, PFS and ORR. EV monotherapy is approved in the 3L setting for the treatment of patients with locally advanced/metastatic urothelial carcinoma who previously received a PD-1/PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Due to the similarities of mCDC and Urothelial Carcinoma and the expression of NECTIN-4 in mCDC, it is expected that the efficacy of EV and pembrolizumab observed in mUC will be reproduced in mDCD and RMNC. Given the high aggressivity and mortality for mCDC and RMC patients, there remains a high unmet need in this population.

EV combined with pembrolizumab has the potential to offer significant benefits without compromising the safety of patients. Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

Potential risks of these novel combination interventions may be increased toxicity, intolerability, or unanticipated adverse drug reactions. Some of these expected AEs as skin reaction or hepatotoxicity.

Finally, the investigational combination might not be active in the selected population but this risk is minimized by the fact that there is no SoC for these patients and NECTIN-4 is expressed in mCDC.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

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## 14.0 APPENDICES

## APPENDIX 1: ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

## APPENDIX 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

**Table 12 Protocol-required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit | RBC Indices:<br>MCV<br>MCH<br>%Reticulocytes | WBC count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Chemistry | BUN | Potassium | AST/SGOT | Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN) |
| | Albumin | Bicarbonate | Chloride | Phosphorous |
| | Creatinine | Sodium | ALT/SGPT | Total Protein |
| | Glucose [Indicate if fasting, or nonfasting] | Calcium | Alkaline phosphatase | |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Pregnancy Testing | • [Highly sensitive serum or urine] hCG pregnancy test (as needed for POCBP) | | | |
| Other Screening Tests | • FSH (as needed in WONCBP only)<br>• [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable]<br>• [Serology [(HIV antibody, HBsAg, and hepatitis C virus antibody)] [or specify other tests] [if applicable] | | | |

| | |
|---|---|
| | |
| | |
| ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential | |
| | |

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

## APPENDIX 3: Description of the iRECIST Process for Assessment of Disease Progression

*Assessment at Screening and Prior to RECIST 1.1 Progression*

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

*Assessment and Decision at RECIST 1.1 Progression*

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 8 and Figures 1 and 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG Performance Status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be

calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

*Assessment at the Confirmatory Imaging*

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

*Confirmation of Progression*

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

*Persistent iUPD*

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

*Resolution of iUPD*

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

*Management Following the Confirmatory Imaging*

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 8.

*Detection of Progression at Visits After Pseudo-progression Resolves*

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased

from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al, 2017].

# APPENDIX 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## 14.1 DEFINITIONS OF MEDICATION ERROR, MISUSE, AND ABUSE

**Medication error**
This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

**Misuse**
This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

**Abuse**
This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

## 14.2 DEFINITION OF AE

### AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by MSD for human use in this study.

### Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

**Events NOT meeting the AE definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

## 14.3 DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

**a. Results in death**

**b. Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study intervention and is documented in the participant's medical history.

**d. Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

**f. Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

## 14.4 ADDITIONAL EVENTS TO BE REPORTED

### Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose of pembrolizumab
    - For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

## 14.5 RECORDING AE AND SAE

### AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity/toxicity**

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.

Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

**Assessment of causality**

1. Did study intervention cause the AE?
2. The determination of the likelihood that study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
3. The following components are to be used to assess the relationship between the study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely study intervention caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was study intervention discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
  - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.
  - (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
- **Rechallenge:** Was the participant re-exposed to study intervention in this study?
  - If yes, did the AE recur or worsen?
  - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study intervention (s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY STUDY INTERVENTION, OR IF RE-EXPOSURE TO STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding study intervention or drug class pharmacology or toxicology?
5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of study intervention relationship).

- Yes, there is a reasonable possibility of study intervention relationship:
- There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of study intervention is reasonable. The AE is more likely explained by study intervention than by another cause.
- No, there is not a reasonable possibility of study intervention relationship:
- Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 2 business days but no longer than 3 calendar days of receipt of the information.

## 14.6 REPORTING OF AEs, SAEs, AND OTHER REPORTABLE SAFETY EVENTS TO THE SPONSOR

Information about all SAEs will be transmitted by the Principal Investigator via paper-form to the Contract Research Organization (CRO) OPIS, in charge of SAE collection for this trial, via email at all_phv@opisresearch.com or by fax using the following number: Fax: +39 0362 633622.

Any SAE collected by OPIS will be promptly forwarded to Sponsor. The Sponsor or designee will comply with regulatory requirements relating to safety reporting to the regulatory authorities, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigator as required by laws."

# APPENDIX 5

## 14.7 DEFINITIONS

**Women of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 14.7.1 Contraception Requirements

**Table15**

| **Contraceptives allowed during the study include[a]:** |
|---|
| **Highly Effective Contraceptive Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Progestogen-only subdermal contraceptive implantb<br>• IUS |

| |
|---|
| • Non-hormonal IUD<br>• Bilateral tubal occlusion |
| • Azoospermic partner (vasectomized or secondary to medical cause)<br>This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.<br>Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. |
| **Sexual Abstinence**<br>• Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |
| *a* Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br>*b* If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation.<br>Note: The following are not acceptable methods of contraception:<br>- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.<br>- Male condom with cap, diaphragm, or sponge with spermicide.<br>- Male and female condom should not be used together (due to risk of failure with friction). |

**ALLEGATO B**
(Contributo)

| | |
|---|---|
| **Contributo totale (in valuta locale - EURO)** | **Euro 144.705,00 + IVA** |
| **Totale n° di pazienti arruolabili** | **23** |

Il suddetto contributo è assoggettato ad IVA ai sensi del DPR n. 633/72.

Il Contributo di cui sopra, sarà erogato in valuta locale (Euro) per l'IIS #101404 con le seguenti modalità, con emissione di regolari ricevute:

1° pagamento: € 36.176,25 + IVA (pari al 25% del Contributo) alla stipula del presente contratto e all'ottenimento del parere favorevole da parte del Comitato Etico, dell'autorità competente e della conferma della registrazione su www.clinicaltrial.gov.

2° pagamento: € 21.705,75 + IVA (pari al 15 % del Contributo) alla ricezione dello Status Update trimestrale indicante l'arruolamento del primo soggetto valutabile.

3° pagamento: € 28.941,00 + IVA (pari al 20% del Contributo) alla ricezione dello Status Update trimestrale indicante l'attuale arruolamento da 2 a 9 soggetti valutabili in conformità all'endpoint previsto dal Protocollo.

4° pagamento: € 28.941,00 + IVA (pari al 20% del Contributo) alla ricezione dello Status Update trimestrale riportante il raggiungimento del disegno statistico (Simon's two-stage optimal design) e corrispondente all'attuale arruolamento da 14 a 23 soggetti valutabili.

5° pagamento: € 14.470,50 + IVA (pari al 10% del Contributo) alla ricezione della relazione clinica finale a MSD. (MSD rivedrà la relazione prima di procedere con il rilascio del pagamento).

Pagamento finale: € 14.470,50 + IVA (pari al 10% del Contributo) a fronte della ricevuta di Protocol Registration and Result System (PRS) in clinicaltrials.gov attestante che l'Istituzione ha sottomesso i risultati finali dello studio e che gli stessi saranno pubblicati sul sito www.clinicaltrial.gov.

Nel caso in cui le attività sopra meglio definite non vengano svolte e/o vengano svolte solo in parte e non in toto i pagamenti di cui sopra verranno ridefiniti in proporzione alle attività effettivamente svolte.

| Global Clinical Development Standards – Execution Resource |
|---|
| **Document Number: 1301.ER10**<br>**Title: IIS/CSP & OTSP Status Update Reports** |

# Investigator Initiated Studies (IIS)
# Clinical Status Update Report (SUR)

| | | | |
|---|---|---|---|
| **Person Completing this Form:** | | **Date:** | |
| **Phone No:** | | **Email:** | |
| **Primary Investigator:** | Giuseppe Procopio | **IIS Tracking #:** | 101404 |
| **Study Title:** | Activity of Pembrolizumab plus Enfortumab Vedotin in Collecting Duct and Renal Medullary Carcinoma | | |

| **Milestone (All fields are required)** | **Response** |
|---|---|
| Target Enrollment: | 23 |
| Number of Evaluable Subjects Enrolled:<br>• Not including screen failures<br>• Evaluable is defined as all subjects who data can be used in the final analysis data set | |
| Number of Active Subjects on Treatment (if applicable): | |
| **Milestone (All fields are required)** | **Date (Actual/Planned)** |
| Date First Patient is Enrolled: | |
| Date 50% Enrollment is Complete: | |
| Date Enrollment is Complete: | |
| Date all Patient Visits are Complete: | |
| Date Final Deliverable to be Submitted: | |
| **Serious Adverse Event (SAE) Information (All fields are required)** | **Response** |
| Have any Serious Adverse Events (SAEs) occurred since your last update? | ☐ Yes<br>☐ No |

| Global Clinical Development Standards – Execution Resource |
|---|
| **Document Number: 1301.ER10**<br>**Title: IIS/CSP & OTSP Status Update Reports** |

| | |
|---|---|
| If Yes, I confirm the SAE has been reported to the company | ☐ Yes<br>☐ No |
| **Publication Information (All fields are required)** | **Response** |
| Are you planning to present at a scientific meeting? | |
| Target Congress/Meeting: | |
| Target Congress/Meeting Date: | |
| Target date for manuscript submission to MSD: | |
| Target Journal: | |
| **Additional Information (optional)** | **Response** |
| Summary of Study Progress: | |

# 601.3 GLOBAL SAFETY INTAKE FORM

| Local Reference ID No.: | Global Safety ID No.: | | Other ID No.: | Date Learned: / / | Central Receipt Date: / / |
|---|---|---|---|---|---|

**Complete this Section According to Local Privacy Laws**

**Patient Demographics:** Gender: ☐ Male ☐ Female Age: **Date of Birth: / /** **(Collected as MM/YYYY for Clinical trial subjects greater than 2 years of age)**

| **Reporter Details:** | | | | | |
|---|---|---|---|---|---|
| | Name: | | | Telephone: | |
| | Address: | | | Fax number: | |
| | Anonymized: | | | E-mail address: | |
| | Reporter type (Physician, Pharmacist, Consumer etc) : | | | | |

**Study Information:** Patient ID.: Randomization No. Protocol: Site: MK No.

**Study Title:**

**Report Type:**

☐ Study ☐ Spontaneous

☐ Initial Report ☐ Follow-up Report

**Classification (Not Applicable for trials using InForm):**

☐ Mkt Research ☐ PAS ☐ Pre Clinical Toxicity ☐ Local Clinical Evaluation
☐ Social Media ☐ PSP ☐ Post Marketing Active Surveillance
☐ EPPV ☐ Non Interventional

**Country of Occurrence:**
**Country of Patient:**
**Country of Reporter:**

| **ADVERSE EVENT(S)** (including any reportable pregnancy related terms) | **ONSET DATE** | **CAUSALITY Y or N if Yes specify drug(s)** | **RELATED to Study Procedure? Y/N If Yes, specify procedure(s)** | **Death** | **Life Threatening** | **Hospitalization** | **Prolongation of Hospitalization** | **Disability** | **Other medically significant event** | **Congenital Anomaly** | **Cancer** | **Overdose** | **ECI** | **OUTCOME[1]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |

| **SUSPECT DRUG(S) (complete a separate row for each Study Medication administered to the patient and any concomitant medication considered suspect drug)** | **BLINDED Y OR N** | **START DATE** | **STOP DATE** | **LOT # / BATCH #** | **INDICATION** | **FORMU-LATION** | **ROUTE OF ADMINIS-TRATION** | **STRENGTH (specify units)** | **FREQUENCY** | **TOTAL DAILY DOSE (specify units)** | **ACTION TAKEN[2]** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
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| | | | | | | | | | | | |

# 601.3 GLOBAL SAFETY INTAKE FORM

| Local Reference ID No.: | Global Safety ID No.: | | Other ID No.: | Date Learned: / / | Central Receipt Date: / / |
|---|---|---|---|---|---|
| | | | | | |

| CONCOMITANT THERAPY | START DATE | STOP DATE | INDICATION | FORMULATION | ROUTE OF ADMINIS-TRATION | STRENGTH (specify units) | FREQUENCY | TOTAL DAILY DOSE (specify units) | ACTION TAKEN[2] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

| | |
|---|---|
| **Did Adverse Event (AE) diminish after stopping suspect drug?**<br>☐ **Yes** ☐ **No** ☐ **Not Applicable** (Suspect drug not stopped)<br>**Did AE reappear after restarting drug?**<br>☐ **Yes** ☐ **No** ☐ **Not Applicable** (Suspect drug not stopped) | **If 'YES' specify AE(s)**<br><br>**If 'YES' specify AE(s)** |

| | CONCURRENT CONDITIONS | MEDICAL HISTORY |
|---|---|---|
| | | |
| | | |
| | | |
| | | |

| | LABORATORY RESULTS / DIAGNOSTIC TESTS (RELEVANT TO AE) | DATE | VALUE/RESULTS | UNITS | COMMENTS |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

| | |
|---|---|
| | **NARRATIVE SUMMARY:** |
| | **Schedule Follow-up** ☐ **No follow-up required/available** ☐ |

| Form completed by: | | Date: | QC check completed by, if applicable | Date: |
|---|---|---|---|---|
| | | | | |

# 601.3 GLOBAL SAFETY INTAKE FORM

**[1]Outcome:**

1 = fatal
2 = not recovered/not resolved
3 = recovered/resolved
4= recovered/resolved with sequelae
5 = recovering/resolving
6 = unknown

**[2]Action Taken:**

1 = dose decreased
2 = dose increased
3 = dose interrupted
4 = dose not changed
5 = not applicable
6 = unknown 7 = withdrawn

# Investigator Initiated Studies Program

# FAX

**Date:**

**Number of pages including cover sheet:**

| | |
|---|---|
| **To:** | MSD Italy Pharmacovigilance dept |
| **Fax No.:** | 06/3339327 |

| | |
|---|---|
| **From:** | |
| **Phone No.:** | |
| **Fax No.:** | |
| **Email:** | |

# SERIOUS ADVERSE EVENT REPORT COVER PAGE

**Protocol Title:**

| | | | |
|---|---|---|---|
| **Study Drug:** | Pembrolizumab | **MSD Protocol Number or MISP 6 digit identifier:** | 101404 |
| **Principal Investigator:** | Giuseppe Procopio | **Site Investigator:** | |
| **Serious Event:** | | **Patient (Screening/ Randomization No.):** | |
| **Country of Incidence** | | **Type of Report:** | ☐ **Initial**<br>☐ **Follow-up** |

**PLEASE ATTACH YOUR COMPLETED ADVERSE EVENT REPORTING FORM (MEDWATCH FORM 3500 or EQUIVALENT)**