IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

DELIBERAZIONE N. **1016** DEL **07/11/2025**

OGGETTO: PRESA D'ATTO DI AVVENUTA STIPULA DEL RESEARCH COLLABORATION AGREEMENT (RCA) TRA ASTRAZENECA UK LIMITED e IFO-IRE ED ACCETTAZIONE DEL FINANZIAMENTO DI € 39.000,00 (INCLUSA IVA) PER LO SVOLGIMENTO DEL PROGETTO DI RICERCA DAL TITOLO: "CIRCULATING MICRORNAS AS BIOMARKERS FOR MONITORING MUCOSITIS INSURGENCE AND PROGRESSION UPON DATOPOTAMAB DERUXTECAN (DATO-DXD)", DI CUI P.I. DOTT. GIOVANNI BLANDINO.

Esercizi/o e conto 2025 Centri/o di costo 110005 **- Importo presente Atto: € € 39.000,00** **- Importo esercizio corrente: € € 39.000,00** Budget **- Assegnato: € .** **- Utilizzato: € .** **- Residuo: € .** **Autorizzazione n°: .** Servizio Risorse Economiche: **Giovanna Evangelista**	STRUTTURA PROPONENTE **UOSD Servizio Amministrativo Ricerca** Il Dirigente Responsabile **Giovanna Evangelista** Responsabile del Procedimento **Emanuela Miceli** L'Estensore **Emanuela Miceli** Proposta n° DL-837-2025
PARERE DEL DIRETTORE SANITARIO Positivo Data 06/11/2025 IL DIRETTORE SANITARIO f.f. **Costanza Cavuto**	**PARERE DEL DIRETTORE AMMINISTRATIVO** Positivo Data 05/11/2025 IL DIRETTORE AMMINISTRATIVO **Massimo Armitari**

Parere del Direttore Scientifico IRE f.f. **Giovanni Blandino** data 30/10/2025 Positivo

Parere del Direttore Scientifico ISG **Maria Concetta Fargnoli** data 04/11/2025 Positivo

La presente deliberazione si compone di n° 9 pagine e dei seguenti allegati che ne formano parte integrante e sostanziale:
Research Collaboration Agreement AZ - IRE

Il Dirigente della UOSD Servizio Amministrativo Ricerca

Visto il decreto legislativo 30 dicembre 1992 n. 502 e successive modificazioni ed integrazioni;

Visto il decreto legislativo 16 ottobre 2003 n. 288 e il decreto legislativo 23 dicembre 2022 n. 200 di riordino della disciplina degli Istituti di Ricovero e Cura a Carattere Scientifico;

Vista la legge regionale 23 gennaio 2006, n. 2;

Vista la deliberazione n. 814 del 03.09.2025 recante "*Presa d'atto della deliberazione della Regione Lazio 7 agosto 2025 n.697 avente ad oggetto: Approvazione del Regolamento di Organizzazione e Funzionamento dell'IRCCS Istituti Fisioterapici Ospitalieri. Adozione del Regolamento di Organizzazione e Funzionamento degli IFO.*";

Visto il Decreto del Presidente della Regione Lazio n. T00015 del 12 febbraio 2025 avente ad oggetto "Nomina del Direttore Generale dell'IRCCS Istituti Fisioterapici Ospitalieri (Art. 8, comma 7 bis, della legge regionale 16 giugno 1994, n. 18 e s.m.i.)";

Vista la deliberazione n. 160 del 18.02.2025 di presa d'atto dell'insediamento del Direttore Generale dell'IRCCS Istituti Fisioterapici Ospitalieri Dott. Livio De Angelis;

Vista la deliberazione n.293 del 31.03.2025 con la quale il Dott. Massimo Armitari è stato nominato Direttore Amministrativo degli Istituti Fisioterapici Ospitalieri (IFO);

Vista la deliberazione n.367 del 23 aprile 2024 con la quale la Dott.ssa Costanza Cavuto è stata nominata Direttore Sanitario f.f. degli Istituti Fisioterapici Ospitalieri;

Visto il D.M. del Ministero della Salute del 20 giugno 2024 di conferma del riconoscimento del carattere scientifico dell'IRCCS di diritto pubblico agli Istituti Fisioterapici Ospitalieri (IFO) relativamente alla disciplina di "oncologia" per l'Istituto

Nazionale Tumori Regina Elena (IRE) e alla disciplina di "dermatologia" per l'Istituto Santa Maria e San Gallicano (ISG);

Vista la deliberazione n.877 del 29.10.2024 avente ad oggetto: *"Nomina della Prof.ssa Maria Concetta Fargnoli quale Direttore Scientifico dell'Istituto Santa Maria e San Gallicano (ISG)"*;

Vista la liberazione n.171 del 28.02.2025 avente ad oggetto: *"Nomina del Prof. Giovanni Blandino, Direttore della UOC Ricerca Traslazionale Oncologica, quale Direttore Scientifico IRE facente funzioni, a decorrere dal 01.03.2025.";*

Visto il decreto legislativo 10 febbraio 2005, n.30 recante il "Codice di Proprietà Industriale";

Vista la legge n. 102 del 24 luglio 2023 recante modifiche al "Codice della Proprietà Industriale";

Visti gli artt. 8 e 9 del decreto legislativo 16 ottobre 2003 n. 288, come da ultimo modificati dal D.lgs. 23 dicembre 2022, n. 200, che prevedono la possibilità per gli IRCCS di stipulare accordi e convenzioni, costituire e/o partecipare a consorzi e attuare misure di collegamento e sinergia con altre strutture di ricerca e assistenza sanitaria, pubbliche e private, nonché con le Università, per la realizzazione di comuni progetti di ricerca, in conformità all'art. 15 L. n. 241/1990;

Visti gli artt. 7 e 10 del suddetto decreto, che contemplano le diverse tipologie di ricavi degli IRCCS;

Visto l'art. 1, punto b) del D.lgs 288/2003 ai sensi del quale gli IRCCS sono tenuti a promuovere l'innovazione e il trasferimento tecnologico;

Vista la legge delega del 3 Agosto 2022, n.129, di riordino della disciplina degli IRCCS, che ha introdotto principi per favorire il trasferimento tecnologico, riconoscendo gli IRCCS come luoghi vocati alla ricerca traslazionale ed introducendo l'obbligo per queste strutture di dotarsi di Uffici di Trasferimento Tecnologico (UTT) per la valorizzazione dei risultati della ricerca e la collaborazione con le imprese al fine di facilitare il trasferimento tecnologico e l'innovazione, promuovendo le collaborazioni tra gli IRCCS e il settore industriale, nonché trasformare la ricerca scientifica in prodotti, servizi e tecnologie innovative;

Visto l'art. 8, comma 3 bis, del decreto legislativo 16 ottobre 2003 n. 288 ai sensi del quale le reti di ricerca degli IRCCS sono reti di eccellenza che perseguono finalità di ricerca prevalentemente traslazione, promuovendo il progresso delle conoscenze, sperimentando modelli di innovazione nei diversi settori dell'area tematica e che tali reti sono aperte alla collaborazione non solo con altri enti pubblici ma anche con partner scientifici e industriali nazionali e internazionali di natura privata;

Visto l'articolo 8 comma 5 sexies del decreto legislativo del 23 dicembre 2022, n. 200, ai sensi del quale gli IRCCS di diritto pubblico individuano il partner industriale in possesso di adeguate competenze tecnologiche e di ricerca per il trasferimento dei risultati della ricerca in ambito industriale anche mediante contratti di collaborazione industriale, di licenza, nonché attraverso la creazione di spin-off e start up e che a tal fine istituiscono e gestiscono l'albo dei partner industriali;

Premesso che l'IRCCS Istituto Nazionale Tumori Regina Elena (IRE), nello svolgimento delle proprie attività istituzionali, promuove azioni finalizzate alla valorizzazione dei risultati della ricerca scientifica attraverso collaborazioni con il settore industriale al fine di traslare la ricerca scientifica in nuovi trovati brevettabili, nonché in prodotti, servizi e tecnologie innovative;

Premesso che gli IFO adottano misure volte al trasferimento tecnologico, nonché a tutelare la Proprietà Intellettuale e Industriale delle proprie idee brevettuali, know-how, segreti commerciali, invenzioni industriali, modelli di utilità, topografie dei prodotti a semiconduttori, segreti commerciali e nuove varietà vegetali;

Premesso che, in virtù di quanto sopra, l'IRCCS IFO - IRE conduce diverse attività di ricerca nel campo della generazione di signature di miRNA, al fine di studiare attraverso i livelli di espressione di biomarcatori, meccanismi di analisi predittive a ed approcci diagnostici e terapeutici in grado durante la progressione del cancro o di altre patologie oncologiche, di orientare la terapia e la gestione sanitaria del paziente sottoposto a trattamenti chemioterapici o radioterapici ad alte dosi;

Premesso che in questo settore l'IRCCS "IFO-IRE" ha realizzato numerosi progetti di ricerca e studi di fattibilità all'interno del laboratorio di Translational Oncology Research, debitamente approvati dalle autorità competenti e dai Comitati Etici, che

hanno condotto alla generazione di signature di microRNA (miRNA), successivamente brevettate presso la struttura;

Premesso che per gli scopi di cui sopra l'IRCCS "IFO-IRE" si avvale di numerose attività di collaborazione con partner industriali di comprovata esperienza e competenza tecnologica e di ricerca, tra i quali figura anche AstraZeneca UK limited;

Premesso che AstraZeneca UK Limited operando nel settore della Ricerca e Sviluppo (R&S) nel campo farmaceutico, attraverso un accesso rapido ed equo ai medicinali più efficaci e a cure di alta qualità, con un focus sull'identificazione precoce e la prevenzione ha richiesto, sulla base delle collaborazioni già in essere, la disponibilità della UOC Ricerca Traslazionale Oncologica ad analizzare gli effetti citotossici di Dato-DxD su linee cellulari mucosali normali primarie, trattate con il farmaco "Datopotamab-DxD", misurandone l'espressione in una signature di sei microRNA (miRNA) disponibile presso la struttura;

Considerato che l'attività di cui sopra è di grande interesse scientifico per gli scopi di ricerca istituzionali di IRCCS IFO-IRE e compatibile con le linee di ricerca degli Istituti;

Preso atto della nota dell'11 Aprile 2024, mediante la quale la UOC Ricerca Traslazionale Oncologica, ha confermato la disponibilità a fornire le prestazioni richieste;

Dato atto che per gestire le attività richieste, ossia indagare gli effetti citotossici di Dato-DxD" su linee cellulari mucosali normali primarie trattate con il farmaco "Datopotamab-DxD", come indicato all'interno del piano di Ricerca (Research Plan) che, allegato al presente atto, ne costituisce parte integrante e sostanziale (All. RCA), nelle more dell'adozione dell'albo dei partner industriali, è stato necessario stipulare, in data 5 Giugno 2024, un *Research Collaboration Agreement (RCA)* tra AstraZeneca UK Limited e IRCCS "IFO-IRE" dal titolo: "*Circulating microRNAs as biomarkers for monitoring mucositis insurgence and progression upon Datopotamab Deruxtecan (Dato-Dx) treatment"*;

Dato atto che le attività contemplate nel predetto RCA saranno svolte presso la UOC Ricerca Traslazionale Oncologica dell'IRCCS "IFO-IRE" sotto la responsabilità scientifica del Direttore della struttura;

Dato atto altresì che l'avvio degli esperimenti è avvenuto a decorrere dal mese di luglio 2025, in ragione della necessità di completare attività propedeutiche di carattere tecnico-scientifico, quali l'ottimizzazione dei protocolli sperimentali, la verifica della qualità e della stabilità delle linee cellulari mucosali primarie da impiegare nello studio, nonché la messa a punto delle piattaforme analitiche per la misurazione dell'espressione dei microRNA selezionati, al fine di garantire la robustezza, la riproducibilità e l'affidabilità dei risultati di ricerca;

Dato atto che il predetto RCA per lo svolgimento delle attività previste all'interno del piano di Ricerca (Allegato: *"Schedule 1 - Research Plan*) prevede un compenso omnicomprensivo in favore dell'IRCCS IFO – IRE pari ad € 39.000,00 (euro trentanovemila/00) comprensivo di IVA, nelle seguenti modalità;

- € 19.500,00 (euro diciannovemilacinquecento/00) comprensivo di IVA di legge, al momento della sottoscrizione del contratto;
- € 19.500,00 (euro diciannovemilacinquecento/00/) comprensivo di IVA di legge, al completamento di tutti i risultati ed all'elaborazione di un Report finale.

Preso atto della deliberazione del Commissario Straordinario n. 801 del 26 ottobre 2015 con la quale è stato disposto di accantonare, dai finanziamenti acquisiti per la ricerca finalizzata provenienti da Enti erogatori pubblici e privati, una quota pari al 10% da suddividere come di seguito specificato:

5,75% Direzione Scientifica IRE;
4,25% Ente;

Acquisito il parere favorevole del Direttore Scientifico IRE con comunicazione a mezzo e-mail del 27/05/2024;

Ritenuto opportuno prendere atto dell'avvenuta stipula, in data 5 Giugno 2024, del *Research Collaboration Agreement (RCA)* tra AstraZeneca UK Limited e IRCCS "IFO-IRE" dal titolo *"Circulating microRNAs as biomarkers for monitoring mucositis insurgence and progression upon Datopotamab Deruxtecan (Dato-DxD) treatment"*;

Ritenuto opportuno accettare il finanziamento erogato da AstraZeneca UK Limited in favore di IRCCS "IFO-IRE" per l'attività di ricerca commissionata, pari a € 39.000,00 (euro trentanovemila/00) comprensivo di IVA di legge, nelle seguenti modalità:

- € 19.500,00 (euro diciannovemilacinquecento/00) comprensivo di IVA di legge, al momento della sottoscrizione del contratto;

- € 19.500,00 (euro diciannovemilacinquecento/00) comprensivo di IVA di legge, al completamento di tutti i risultati di progetto ed all'elaborazione di un Report finale;

Attestato che il presente provvedimento, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art. 1 della legge 20/94 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, primo comma, della legge 241/90, come modificata dalla legge 15/2005.

Propone

Per i motivi di cui in narrativa che si intendono integralmente confermati di:

- prendere atto dell'avvenuta stipula, in data 5 Giugno 2024, del *Research Collaboration Agreement* (*RCA*) tra AstraZeneca e IRCCS "IFO-IRE" dal titolo*: "Circulating microRNAs as biomarkers for monitoring mucositis insurgence and progression upon Datopotamab Deruxtecan (Dato-DxD) treatment",* al fine di indagare gli effetti citotossici di Dato-DxD su linee cellulari mucosali normali primarie, trattate con il farmaco "Datopotamab-DxD", come indicato all'interno del piano di Ricerca (Research Plan) che, allegato al presente atto, ne costituisce parte integrante e sostanziale (All. RCA);

- accettare il finanziamento erogato da AstraZeneca UK Limited in favore di IRCCS "IFO-IRE" per le attività di indagine svolte pari a € 39.000,00 (euro trentanovemila/00) comprensivo di IVA di legge, nelle seguenti modalità:

- - € 19.500,00 (euro diciannovemilacinquecento/00) comprensivo di IVA di legge, al momento della sottoscrizione del contratto;

- - 19.500,00 (euro diciannovemilacinquecento/00) comprensivo di IVA di legge, al completamento di tutti i risultati ed all'elaborazione di un Report finale;
- dare esecuzione alla deliberazione del Commissario Straordinario n. 801 del 26 ottobre 2015, accantonare dal finanziamento la quota di 10% e redistribuirla come di seguito specificato:

- 5,75% Direzione Scientifica IRE;
- 4.25% Ente;

- dare mandato alla UOC Risorse economiche di iscrivere al piano dei conti n. 401030401 e al centro di costo n. 110005 l'importo di € 39.000,00 (Comprensivo di IVA di legge);
- Disporre che il Technology Transfer Office (TTO) ed il Servizio Amministrativo per la Ricerca (SAR), curerà tutti gli adempimenti per l'esecuzione della presente deliberazione.

Il Dirigente della UOSD Servizio Amministrativo Ricerca

Giovanna Evangelista

Il Direttore Generale

Visto	il decreto legislativo 30 dicembre 1992, n. 502 e s.m.i.;
Vista	la legge regionale 23 gennaio 2006 n. 2;
Visto	il decreto legislativo 16 ottobre 2003 n. 288 e il decreto legislativo 23 dicembre 2022 n. 200 "Riordino della disciplina degli Istituti di ricovero e cura a carattere scientifico";
Vista	la deliberazione n. 814 del 03.09.2025 recante *"Presa d'atto della deliberazione della Regione Lazio 7 agosto 2025 n.697 avente ad oggetto: Approvazione del Regolamento di Organizzazione e Funzionamento dell'IRCCS Istituti Fisioterapici Ospitalieri. Adozione del Regolamento di Organizzazione e Funzionamento degli IFO.";*
Visto	l'art. 3 comma 6 del D.lgs. 502/92 e successive modificazioni ed integrazioni, nonché l'art. 8 comma 7 della L.R. del Lazio n. 18/94.
In virtù	dei poteri di cui alla delibera IFO n. 160 del 18 febbraio 2025 inerente l'insediamento del Direttore Generale Dott. Livio De Angelis;
Preso atto	che il Dirigente proponente il presente provvedimento, sottoscrivendolo, attesta che lo stesso a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art. 1 della legge 20/94 e s.m.i., nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, primo comma, della legge 241/90, come modificata dalla legge 15/2005.
Visto	il parere favorevole del Direttore Amministrativo e del Direttore Sanitario Aziendale;

ritenuto di dover procedere;

Delibera

di approvare la proposta così formulata concernente *"PRESA D'ATTO DI AVVENUTA STIPULA DEL RESEARCH COLLABORATION AGREEMENT (RCA) TRA ASTRAZENECA UK LIMITED e IFO-IRE ED ACCETTAZIONE DEL FINANZIAMENTO DI € 39.000,00 (INCLUSA IVA) PER LO SVOLGIMENTO DEL PROGETTO DI RICERCA DAL TITOLO: "CIRCULATING MICRORNAS AS BIOMARKERS FOR MONITORING MUCOSITIS INSURGENCE AND PROGRESSION UPON DATOPOTAMAB DERUXTECAN (DATO-DXD)", DI CUI P.I. DOTT. GIOVANNI BLANDINO."* e di renderla disposta.

Il Direttore Generale

Dott. Livio De Angelis

Documento firmato digitalmente ai sensi del D.Lgs 82/2005 s.m.i. e norme collegate

RESEARCH COLLABORATION AGREEMENT

Between

ASTRAZENECA UK LIMITED

And

ISTITUTO REGINA ELENA-CENTRO RICERCHE SPERIMENTALI

Dated as of 29th May 2024

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RESEARCH COLLABORATION AGREEMENT

This Research Collaboration Agreement (this "**Agreement**"), is effective as of 29th May 2024 (the "**Effective Date**"), by and between:

(1) **AstraZeneca UK Limited,** a company incorporated in England under no. 03674842 whose registered office is at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, England CB2 0AA ("**AZ**");

and

(2) **IRCCS Istituti Fisioterapici Ospitalieri - Istituto Nazionale Tumori Regina Elena (IFO- IRE)**, with offices located at Via Elio Chianesi 53 -00144 Roma Tax Code 02153140583 and VAT no. 01033011006, represented by the Extraordinary Commissioner Dr. Livio De Angelis, domiciled for the purpose at the IRCCS, as well as proper delegation to the Scientific Director Prof. Gennaro Ciliberto ("**Institution**").

BACKGROUND

AZ and Institution wish to collaborate on scientific research related to circulating microRNAs as biomarkers for monitoring mucositis insurgence and progression upon Datopotamab Deruxtecan treatment, on and subject to the terms of this Agreement.

AGREEMENT

The Parties agree as follows:

1. DEFINITIONS

In this Agreement, the following terms shall have the following meanings:

1.1. "**Affiliate**" means, in relation to a Party, any person that Controls, is Controlled by or is under common Control with that Party. "Control" shall mean direct or indirect: (a) to possession of the power to direct the management and policies of an entity or (b) ownership of more than fifty percent (50%) of the outstanding voting securities or other ownership interest of such Party.

1.2. "**Applicable Laws**" means all applicable laws and regulations, including any guidelines or other requirements of regulatory authorities that may be in effect from time to time. For clarity, Applicable Laws include GLP.

1.3. "**Authors**" has the meaning set out in Section 13.2.

1.4. "**AZ Materials**" means those materials to be provided by or on behalf of AZ to Institution as set out in the Research Plan and: (a) any substance or structure that is a derivative, analogue, modification, replication, complex, or subunit of such materials; and (b) any other compositions made using such materials.

1.5. "**AZ Results**" means all Results that are: (a) related to the AZ Materials, their biomarkers, or their uses or indications, whether as a single agent or in combination with other agents; or (b) created, generated or developed solely by or on behalf of AZ or any of its Affiliates.

1.6. "**Background Intellectual Property**" has the meaning set out in Section 11.1.

1.7. "**Collaboration Compound**" means the AZ Material DS-1062.

1.8. "**Collaboration Partner**" means any person or entity with whom, as of the Effective Date, AZ has entered into an agreement for the development and/or commercialization of the Collaboration Compound or Product relating to the Research Activities, including the Affiliates of such person or entity.

1.9. "**Confidential Information**" means all information or material that, at any time before, on or after the Effective Date, has been or is provided or communicated to a Party or any of its Affiliates by or on behalf of the other Party or any of its Affiliates under or in connection with this Agreement or any related discussions or negotiations including any data, ideas, concepts or techniques embodied or contained in such information or materials. Confidential Information may be disclosed orally, visually, in writing, by delivery of materials containing Confidential Information or in any other form now known or hereafter invented. Notwithstanding the foregoing: (a) all AZ Results shall be the Confidential Information of AZ, and AZ shall be deemed to be the Disclosing Party and Institution shall be deemed to be the Receiving Party with respect thereto; (b) all Institution Results shall be the Confidential Information of Institution, and Institution shall be deemed to be the Disclosing Party and AZ shall be deemed to be the Receiving Party with respect thereto; and (c) the terms of this Agreement shall be deemed to be the Confidential Information of both Parties and both Parties shall be deemed to be the Receiving Party and the Disclosing Party with respect thereto.

1.10. "**Data**" means any data or know-how to be shared by or on behalf of either Party with the other Party for use in the Research Activities, as described in the Research Plan.

1.11. "**Disclosing Party**" means, subject to the last sentence of the definition of Confidential Information, the Party disclosing, or whose Affiliates are disclosing, Confidential Information.

1.12. "**Final Report**" has the meaning set out in Section 5.2.2.

1.13. "**GLP**" means all then-current applicable laws, regulations and guidance of relevant regulatory authorities that constitute good laboratory practices.

1.14. "**HCO**" has the meaning set out in Section 10.3.1.

1.15. "**HCP**" has the meaning set out in Section 10.3.1.

1.16. "**Human Biological Samples**" or "**HBS**" means human biological samples being biological materials acquired or derived from living or deceased human beings which consist of or include human cells, and any derivatives or components thereof.

1.17. "**Institution Results**" means all Results, other than the AZ Results.

1.18. "**Negotiation Period**" has the meaning set out in Section 11.5.2.

1.19. "**Option**" has the meaning set out in Section 11.5.1.

1.20. "**Option Notice**" has the meaning set out in Section 11.5.2.

1.21. "**Option Period**" has the meaning set out in Section 11.5.2.

1.22. "**Parties**" means AZ and Institution, and "**Party**" means either of AZ or Institution.

1.23. "**Payment or Transfer of Value**" has the meaning set out in Section 10.3.2.

1.24. "**Principal Investigator**" means a senior scientist of Institution appointed to supervise the Research Activities and identified in the Research Plan.

1.25. "**Product**" means any pharmaceutical product containing a Collaboration Compound, in any and all forms, presentations, doses and formulation.

1.26. "**Publication**" means the publication of an abstract, article or paper in a journal or an electronic repository, or an oral presentation at a conference or seminar, or other form of public disclosure in whatever form or medium, regarding any of the Research Activities carried out or Results generated under this Agreement.

1.27. "**Receiving Party**" means, subject to the last sentence of the definition of Confidential Information, the Party receiving (or whose Affiliates are receiving) Confidential Information.

1.28. "**Research Activities**" means all those tests, studies and other activities performed pursuant to the Research Plan or required to obtain the information set out in Research Plan.

1.29. "**Research Budget**" has the meaning set out in Section 4.1.

1.30. "**Research Documentation**" means all documents, records, accounts, books, notes, reports and other data relating to the Research Activities, in any form, created by or on behalf of Institution.

1.31. "**Researchers**" has the meaning set out in Section 3.1.

1.32. "**Research Plan**" means a description of the research to be carried out by the Parties as set out in Schedule 1 (Research Plan), as amended from time to time by the Parties in writing.

1.33. "**Results**" means any ideas, inventions, discoveries, know-how, data (including raw data, biomarker data), documentation (including the Research Documentation), reports, materials, writings, designs, computer software, algorithms, predictive models, AI tools, processes, principles, methods, techniques and other information, recorded in any form, that are developed, discovered, conceived, reduced to practice or otherwise generated as a result of or in connection with the Research Activities, and any patent, trade secret, copyright, rights in know how or other intellectual property rights pertaining to any of the foregoing and the right to apply for any of such patent or other intellectual property rights. Results shall exclude the AZ Materials, HBS, Data and any other Background Intellectual Property.

1.34. "**Term**" has the meaning set out in Section 18.1.

2. RESEARCH PROGRAM

2.1. **Research Activities and Research Plan**. Each Party shall carry out the Research Activities allocated to it in the Research Plan:

2.1.1. with all due skill, care and diligence, allocating sufficient time, effort, equipment and suitably skilled personnel;

2.1.2. in a good scientific manner, and in compliance with Applicable Laws; and

2.1.3. in accordance with the Research Plan (including any timescales set out in it).

3. MANAGEMENT OF THE RESEARCH ACTIVITIES

3.1. **Principal Investigator**. Institution shall ensure that the Principal Investigator is responsible for the Research Activities and supervises and directs the work of all students, employees or agents of Institution involved in the Research Activities ("**Researchers**"). The Principal Investigator shall serve as the primary contact for AZ on all matters related to the Research Activities. Institution shall not substitute or remove the Principal Investigator without the prior written approval of AZ. If the Principal Investigator ceases to be associated with Institution, becomes incapacitated or is otherwise unable to perform under this Agreement, Institution shall promptly notify AZ, shall use diligent efforts promptly to secure a substitute Principal Investigator acceptable to AZ and, in any event, shall ensure that the Research Activities are adequately supervised at all times.

3.2. **Updates on the Research Activities**. During the Term, the Principal Investigator and representatives of AZ shall meet at regular intervals (in person, by teleconference or by videoconference) as agreed by the Parties to discuss the progress of the Research Activities and the Results. Unless Institution is otherwise notified by AZ in writing, the contact person at AZ will be as specified in the Research Plan.

4. RESEARCH FUNDING

4.1. **Research Budget**. In return for Institution's performance of the Research Activities, AZ shall pay Institution the amounts specified in the research budget set out in Schedule 2 (the "**Research Budget**") in accordance payment schedule set out in Schedule 2 (Research Budget). The aggregate amount specified in the Research Budget is the maximum amount payable by AZ under this Agreement for all Research Activities to be performed, expenses incurred, and rights granted, by Institution under this Agreement. The Parties acknowledge that the amounts to be paid by AZ in accordance with the Research Budget are reasonable compensation, representing the fair market value for the work performed by Institution, and rights granted by Institution to AZ under this Agreement, and that Institution has not received any other compensation or inducement in connection with this Agreement or its participation in the Research Activities.

4.2. **Payments**. AZ shall pay all invoices within sixty (60) days from receipt of a valid and undisputed invoice. All amounts payable by AZ under this Agreement are stated exclusive of any sales tax which Institution may be obliged to charge. If withholding tax applies, AZ shall be entitled to make deductions or withholdings as required by Applicable Laws.

4.3. **Invoices**. No payment will be made by AZ unless a purchase order is issued by AZ. Purchase orders and invoices shall be issued in accordance with Schedule 3 (Invoice Requirements), which may be updated from time to time upon written notice by AZ.

4.4. **Interest on Late Payments.** If either Party fails to pay any undisputed amount due under this Agreement within fourteen (14) days after payment is due, then the other Party may charge simple interest on the overdue amount on a daily basis at a rate equal to the lesser of: (a) the European Central Bank main refinancing rate plus two percent (2%); or (b) the maximum rate permitted under Applicable Laws.

4.5. **Books and Records**. Institution shall maintain complete and accurate books, records and accounts that, in reasonable detail, fairly reflect the use of the financial support provided by AZ under this Agreement. AZ may review and audit such books, records and accounts.

5. RECORDS, REPORTING AND INFORMATION EXCHANGE

5.1. **Record keeping**. Institution shall prepare and maintain complete, current, accurate, organised and legible records of all Research Documentation. Institution shall keep the Research Documentation secure and separate from other records and to a standard suitable for patent and regulatory purposes. Institution shall retain all Research Documentation until the third (3rd) anniversary of the end of the Term (or longer if so required by Applicable Laws). Then (or earlier if so agreed by the Parties), Institution shall transfer the Research Documentation to AZ (or destroy it) at AZ's request and expense.

5.2. **Reporting**.

5.2.1. **Periodic Reports**. Institution shall submit written progress reports to AZ as and when specified in the Research Plan. Each such report shall include a detailed summary of all work done and all Results, including samples of any materials generated and all raw data and other information obtained, for the relevant period.

5.2.2. **Final Report**. Institution shall submit a final written report to AZ within thirty (30) days after completion of the Research Activities (or, if earlier, the end of the Term). Such final report shall include a comprehensive summary of the Research Activities carried out and the Results (the "**Final Report**").

5.2.3. **Sharing with Collaboration Partner**. AZ may share Confidential Information and Results and reports received from Institution with its Collaboration Partner. Any such disclosures between AZ and its Collaboration Partner made pursuant to this Section shall be made in confidence, in accordance with existing confidentiality obligations between AZ and its Collaboration Partner.

5.3. **Information Exchange**. Each Party shall provide Data, Research Documentation, Results and reports on the Research Activities to the other Party in a safe and secure manner, in the formats and in accordance with the methods for transferring such information (or otherwise making it accessible) to the other Party set out in the Research Plan or as otherwise agreed between the Parties. The provisions of this Section 5.3 are without prejudice to any other term of this Agreement (including those in relation to data privacy and cyber security), and in the event of any conflict, the most stringent measures for the exchange of information will prevail.

6. AUDIT AND INSPECTION

6.1. **Audits**. AZ or its representatives shall have the right, during regular working hours, to:

6.1.1. monitor the conduct of the Research Activities and inspect Institution's premises where the Research Activities are, or will be, carried out;

6.1.2. review and audit or inspect all Research Documentation, AZ Materials and HBS during the Term and during the period thereafter in which Institution is required to retain the same pursuant to the terms of this Agreement (or, if earlier, or if no such retention period is specified herein, until such time as the same have been transferred to AZ or destroyed in accordance with this Agreement); and

6.1.3. interview the Principal Investigator and the Researchers;

in each case to verify Institution's compliance with its obligations under this Agreement. Institution shall and shall cause the Principal Investigator, the Researchers and other Institution personnel to cooperate with any such activities.

6.2. **Regulatory Inspections**. Institution shall promptly inform AZ if any governmental or regulatory authority carries out (or states that it intends to carry out) an audit, inspection or other action connected with or potentially affecting the Research Activities or Research Documentation. Institution shall keep AZ reasonably updated on such action (including material correspondence related to it, and the findings and consequences of it).

7. SUPPLY OF AZ MATERIALS

7.1. **AZ Materials**. AZ shall supply to Institution the quantities of AZ Materials (at such times) that are specified in the Research Plan. As between the Parties, AZ owns and shall keep ownership of the AZ Materials. Institution shall keep the AZ Materials under its control and store them securely. Institution understands and acknowledges that the Research Activities relate to one or more Collaboration Compounds or Products and agrees that, with regard to the Research Activities, the rights and obligations regarding confidentiality and ownership of Results and AZ Materials shall apply to both AZ and its Collaboration Partner for the particular Collaboration Compound or Product

7.2. **Use and Handling of the AZ Materials**. Institution acknowledges and agrees that the AZ Materials are experimental in nature. Institution shall use the AZ Materials only in connection with the performance of the Research Activities, and for no other purpose. In the event Institution uses the AZ Materials outside the scope of the Research Activities, any results arising from such a breach of the Agreement and related to the Materials or their uses shall be deemed to be AZ Results and shall be treated accordingly. Institution shall use, store and handle the AZ Materials in accordance with any instruction provided by AZ and Applicable Laws.

7.3. **Restrictions**. Institution shall not use the AZ Materials: (a) for the benefit of any third party, or transfer them to any person, without the prior written consent of AZ except for transfers to the Principal Investigator and the Researchers; (b) in research or testing involving human subjects; (c) for any commercial purpose, or (d) in combination with any other pharmaceutically active agent except as explicitly set out in the Research Plan.

7.4. **Prohibition on Structure Determination**. Institution shall not (and shall ensure that the Principal Investigator and the Researchers shall not) (and shall not attempt to) determine the structure of

the AZ Materials (e.g., chemical structure, amino acid sequence or nucleotide sequence) or otherwise characterise the AZ Materials without the prior written consent of AZ, except as contemplated by the Research Plan.

7.5. **Return or Destruction of AZ Materials**. Institution, at its cost and expense, either return to AZ, or at AZ's option destroy, all AZ Materials within forty-five (45) days following the end of the Term or AZ's earlier request, unless the Parties agree otherwise in writing.

7.6. **Disclaimer**. AZ Materials are provided "AS IS" and to the maximum extent permitted by Applicable Law, AZ hereby disclaims and excludes all representations, warranties, conditions or other terms, whether written or oral, expressed or implied, with respect to the AZ Materials, including any representation or warranty of quality, performance, merchantability or fitness for a particular use or purpose, or that the use of the AZ Materials does not infringe any intellectual property rights or other proprietary rights of a third party.

7.7. **No Liability**. To the fullest extent permitted by Applicable Laws, AZ shall not be liable to Institution, its subcontractors, or any of its employees or agents (including the Principal Investigator and the Researchers) whether for breach of contract, negligence or otherwise, with regard to the supply of the AZ Materials to, or the use or possession thereof by, Institution, its subcontractors or any of its employees or agents (including the Principal Investigator and the Researchers).

8. HBS

8.1. With respect to any and all Human Biological Samples to be used by or on behalf of the Institution in the Research Activities, Institution shall ensure that all HBS are and have been sourced, stored, handled, retained, used, transferred, transported, packaged, labelled and disposed of in accordance with Applicable Laws. Without prejudice to the foregoing, Institution represents, warrants and undertakes that:

8.1.1. it will conduct the Research Activities in accordance with the applicable sections of AZ's then-current Global Standard on Bioethics, which can be found on AZ's website and as at the Effective Date is available at:

https://www.astrazeneca.com/content/dam/az/Sustainability/Bioethics_Policy.pdf

8.1.2. it has adequate facilities to collect and store the HBS for research purposes;

8.1.3. it has relevant licences, permissions and ethical approvals for: (a) the collection of the HBS; and (b) the storage and use of the HBS for research purposes (including DNA or RNA analysis, if any);

8.1.4. to the extent required by Applicable Law, it has obtained, or will obtain, explicit informed consent to use such HBS for research purposes (including DNA or RNA analysis, if any) from (or on behalf of) donors from whom the HBS were obtained or (subject to explicitly informing AZ that this is the case) it has obtained authorised research ethics committee approval for such research purposes; and

8.1.5. the proposed storage and use of the HBS in the Research Activities (in collaboration with AZ) falls within the scope of such consent or research ethics committee approval (as applicable).

8.2. If Institution obtains HBS from a third party, Institution shall ensure that such third party: (a) grants Institution the right to freely use such HBS in carrying out the Research Activities; and (b) satisfies the requirements set out in Section 8.1 in respect of such HBS (including in respect of having obtained informed consents or research ethics committee approvals for the storage and use of the HBS, as applicable).

8.3. Institution shall provide AZ with a copy of the pro-forma consent form used for obtaining consent for the HBS and any associated data or (where applicable) a complete and accurate copy of the

research ethics committee approval for the use of the HBS and any associated data (including any associated restrictions), prior to commencing the Research Activities.

8.4. Institution shall retain all HBS used or collected in the performance of the Research Activities for the Term and thereafter until: (a) the 3rd anniversary of the Effective Date; or (b) such later date as may be required by Applicable Laws; (the "**HBS Retention Period**"). Subject to Applicable Laws and the relevant informed consents or research ethics committee approvals (as applicable), during the HBS Retention Period, Institution shall make all such HBS available upon request for inspection, analysis and use by or on behalf of AZ.

8.5. To the extent any HBS and any Data relating to any donor of HBS are delivered to AZ pursuant to this Agreement shall be delivered in such a format so that AZ does not know the identity of the donor. AZ acknowledges the importance of data privacy of donors and it commits not to: (a) attempt to locate or re-identify any donor: (b) combine such Data with other sources of data that could lead to the identification of any donor or other individual; or (c) reverse engineer, reverse assemble or decompile such Data. Despite the fact such Data is not to include any information from which the donor's identity could be known by AZ, to the extent such Data constitutes Personal Data, Section 9 shall apply.

8.6. Institution shall, in the event that a donor withdraws their consent to the use of their HBS or if the terms of the research ethics committee approval require that use or storage of the HBS must cease, notify AZ, and the Parties shall cooperate and provide reasonable assistance as is necessary to each other to enable them to comply with such request or requirement in accordance with Applicable Laws.

9. DATA AND PERSONAL DATA

9.1. Each Party shall provide to the other Party the Data that are specified in the Research Plan (at such times as are specified in the Research Plan), in accordance with Section 5.3. For clarity, the other Party's use of such Data shall be subject to the terms of this Agreement, including those set out in Section 11 and Section 12.

9.2. For the purpose of carrying out the Research Plan, Personal Data will be collectedwhich will always be treated in a strictly confidential manner, in such a way as to guarantee its confidentiality, protection and security, in compliance with Applicable Laws.

9.3. The Parties to this Agreement guarantee the implementation of the principle of minimization in the use of Personal Data, i.e. that only data that is adequate, relevant and limited to what is necessary to achieve the purposes of this Agreement will be processed.

9.4. The Parties undertake to adopt all appropriate technical and organizational security measures required by Applicable Laws both during the collection of Personal Data and use and transmission phases of the same.

9.5. The Parties shall comply with Applicable Laws in relation to the transfer, acquisition or other processing of Personal Data. Each Party shall ensure that any Personal Data shared with the other Party in connection with the Research Activities is delivered in such a format so that AZ does not know the identity of the donor, patient or other individual to whom the Data relates.

9.6. For the purpose of this Section 9, "**Personal Data**" means any information relating to an identified or identifiable natural person who can be identified directly or indirectly and in particular includes but is not limited to the following information about a living individual: first and last name, age, date of birth, gender, address, contact information, government-issued identifiers (such as passport and social security numbers), location data, an online identifier or any specific physical, health related, physiological, genetic, mental, economic, cultural or social information about that natural person.

10. TRANSPARENCY REQUIREMENTS

10.1. Institution recognises AZ's commitment to compliance with Applicable Laws and transparency principles and shall cooperate with AZ to meet such commitments. To that end, and to the extent required by Applicable Law or any applicable industry code of practice, AZ may disclose on websites controlled by AZ or any of its Affiliates (or on websites controlled by relevant industry bodies) and report to government entities and other third parties, the payments made to Institution by or on behalf of AZ pursuant to this Agreement, or (where applicable) any payments made by Institution to an external HCP or HCO with AZ's written approval.

10.2. Institution shall not contract with or make any Payment or Transfer of Value to an HCP or HCO in connection with the Research Activities or this Agreement or on behalf of AZ without AZ's prior written approval. Any payments to an HCP or HCO will be made according to rates agreed with AZ. Such rates must be based on relevant local fair market value rates (rates may differ between countries). Institution acknowledges and agrees that any request for payment of, or reimbursement for, a Payment or Transfer of Value to an HCP or HCO will require that Institution provide AZ with detailed expenditure information either through a template and/or system access, or as a file extract out of Institution's own system including all the required data fields as outlined by AZ. If applicable, AZ and Institution will annually discuss the data collection process to confirm Institution's understanding of AZ's requirements. Institution shall provide such expenditure reporting to AZ by the end of the month after the month in which such Payment or Transfer of Value to an HCP or HCO is made. Documentation concerning Payments or Transfers of Value to an HCP or HCO must be maintained by Institution for five (5) years.

10.3. In this Section 10:

10.3.1. A healthcare professional ("**HCP**") includes a member of the medical, dental, pharmacy, and nursing professions, related administrative staff, and governmental officials who may prescribe, purchase, recommend, supply or administer medicines. A healthcare organisation ("**HCO**") includes any legal entity that is a healthcare, medical or scientific association, organisation or learned society; or through which one or more HCPs provide services. AZ's Global Payment Transparency Team will determine if payments/transfers of value provided to recipients meet the individual country HCP/HCO transparency obligations for disclosure (per the definition of an HCP or HCO and applicable reporting requirements).

10.3.2. A "**Payment or Transfer of Value**" is any payment or transfer of value from AZ, or from Institution at the direction or request of AZ, to an HCP or HCO, and may include: compensation, matters or products that are provided free of charge or on a subsidised basis (such as free medicines or equipment), reimbursement for expenses, meals, travel, medical journal reprints, study supplies and medical writing and publications assistance.

11. INTELLECTUAL PROPERTY

11.1. **Background Intellectual Property**. All intellectual property, data and know-how owned or controlled by a Party or any of its Affiliates which is: (a) existing as of the Effective Date, or (b) developed, acquired or generated outside the scope of this Agreement ("**Background Intellectual Property**") shall remain the property of the owning or controlling Party. Nothing in this Agreement shall transfer any rights in such Background Intellectual Property to the other Party.

11.1.1. Each Party (and in the case of AZ, its Affiliates) and their respective permitted subcontractors shall be permitted to use the Data (and, if applicable, other Background Property) of the other Party solely if and to the extent necessary to perform the Research Activities; and

11.1.2. If a licence to certain Background Intellectual Property owned or controlled by Institution is necessary for AZ to develop or exploit commercially any Results, and if Institution is able to grant AZ rights in such Background Intellectual Property, then, on AZ's request,

Institution shall use reasonable efforts to grant to AZ a licence, on commercially reasonable terms, to such Background Intellectual Property.

11.2 Ownership of Results; Cooperation

11.2.1 **AZ Results.** AZ shall own all right, title and interest in and to all AZ Results. Institution hereby assigns to AZ, without additional consideration, all right, title and interest throughout the world in and to all AZ Results generated by or on behalf of Institution.

11.2.2 **Institution Results.** Institution shall own all right, title and interest in and to all Institution Results. AZ hereby assigns to Institution, without additional consideration, all right, title and interest throughout the world in and to all Institution Results generated by or on behalf of AZ.

11.2.3 **Cooperation**. At the request and expense of AZ, Institution shall, and shall cause the Principal Investigator and the Researchers to, execute and deliver any and all documents or instruments and perform all such acts as AZ may reasonably require to give effect to this Section 11 and to enable AZ (or its designee) to apply for, procure, maintain and enforce intellectual property rights in AZ Results anywhere in the world as AZ (or its designee) may in its sole discretion determine. In no event shall Institution file any patent relating to the AZ Results.

11.2.4. **Costs.** Each Party shall be responsible for all costs associated with applying for, prosecuting, maintaining and enforcing intellectual property rights in Results owned by such Party pursuant to Section 11.2.1 or Section 11.2.2.

11.3 **Consultation on Patent Filings**. For patent applications covering Institution Results that AZ has exclusively licensed under Section 11.5, Institution shall consult with and cooperate with AZ prior to and during the preparation, filing, prosecution and maintenance of such patent applications (and resulting patents) and take AZ's reasonable comments into account.

11.4 **Licence to Institution Results**. Institution hereby grants to AZ and its Affiliates a perpetual, non-exclusive, royalty-free, fully paid-up, irrevocable, world-wide licence, with the right to sublicense through multiple tiers, to make, have made, use, have used, sell, have sold, offer for sale, import, export and otherwise use and exploit the Institution Results for all purposes.

11.5 **Option to an Exclusive Licence to inventions within Institution Results**

11.5.1 Institution hereby grants to AZ an exclusive option (the "Option") to take an exclusive, worldwide, perpetual licence on commercially reasonable terms (the "Licence") to any inventions within the Institution Results. The Licence will allow Institution to use any such Institution Results for the sole purpose of academic research and teaching purposes, other than activities for or on behalf of, or funded by, or with, any third party other than a non-profit or governmental organisation.

11.5.2 AZ may exercise the Option at any time until the date twelve (12) months after the date of provision of the Final Report (the "Option Period") by giving Institution written notice ("Option Notice"). Following Institution's receipt of an Option Notice, Institution shall enter into and diligently pursue exclusive good faith negotiations for a period for up to twelve (12) months (the "Negotiation Period") with AZ or its designated Affiliate with the aim of granting AZ or such Affiliate the Licence.

11.5.4 If AZ does not give Institution an Option Notice during the Option Period, or if Institution and AZ or its Affiliate fail to reach agreement on the terms of a licence agreement within the Negotiation Period, then Institution shall be free to negotiate with third parties with respect to the Institution Results and commercialise or license out the Institution Results (subject to AZ's non-exclusive licence rights under Section 11.4).

11.5.5 Institution shall obtain from the Principal Investigator and the Researchers rights to all Results generated by or on behalf of the Institution, such that AZ or its designee shall receive from

Institution, and Institution shall be in a position to grant, without payments beyond those required by Section 4, the assignments, licences and other rights granted hereunder to AZ or its designee.

12. CONFIDENTIALITY

12.1. **Property of the Disclosing Party**. Except as otherwise provided in this Agreement, any Confidential Information disclosed by or on behalf of one Party or any of its Affiliates to the other Party or any of its Affiliates in connection with this Agreement shall remain the property of the Disclosing Party.

12.2. **Confidentiality Obligations**. During the Term and for five (5) years after the expiration or termination of this Agreement, the Receiving Party undertakes and shall cause, its officers, directors and other employees and agents (including the Principal Investigator and the Researchers if Institution is the Receiving Party) to keep confidential and not publish or otherwise disclose and not use, directly or indirectly, for any purpose, any Confidential Information of the Disclosing Party, except to the extent such disclosure or use is expressly permitted by the terms of this Agreement.

12.3. **Exceptions**. The provisions of Section 12.2 shall not apply to any Confidential Information which the Receiving Party can demonstrate to the reasonable satisfaction of the Disclosing Party:

12.3.1. was already in the possession of the Receiving Party and at the Receiving Party's free use and disposal or in the public domain prior to its disclosure by the Disclosing Party under this Agreement;

12.3.2. was, prior to disclosure to it pursuant to this Agreement, legally acquired by the Receiving Party from a third party having good title thereto and the right to disclose the same;

12.3.3. comes into the public domain, otherwise than through the fault of, or breach of this Agreement, by the Receiving Party or any of its Affiliates; or

12.3.4. is independently generated by the Receiving Party or any of its Affiliates without any recourse or reference to the Confidential Information disclosed by the Disclosing Party.

12.3.5. Permitted Disclosure for Granted Rights. Notwithstanding Section 12.2, AZ may disclose Confidential Information of Institution to any third party and allow such third party, subject to confidentiality and use obligations no less onerous than as set out herein, to use such Confidential Information to the extent required for the purposes of exploiting the AZ Results and the Institution Results in accordance with the licences and rights granted under this Agreement.

12.4. **Disclosures Required by Law**. Nothing in Section 12.2 shall preclude disclosure of any Confidential Information required by any governmental, quasi-governmental or regulatory agency or authority or court entitled by law to receive the Confidential Information, or which is required by law to be disclosed (including freedom of information requests), provided that the Receiving Party, subject to Applicable Laws, promptly notifies the Disclosing Party when such requirement to disclose has arisen, to enable the Disclosing Party to seek an appropriate protective order, to inform the relevant agency, authority or court the proprietary nature of the Confidential Information, and to make any applicable claim of confidentiality. The Receiving Party agrees to co-operate in any appropriate action that the Disclosing Party may decide to take. If the Receiving Party is advised to make a disclosure in accordance with this section, it shall only make a disclosure to the extent to which it is obliged.

12.5. **Press Releases and Use of Name**. Except as expressly permitted by this Agreement, neither Party shall make any press release or other public announcement relating to this Agreement or otherwise use the name, insignia, symbol, trademark, trade name or logotype of the other Party or its Affiliates in any publication, press release, promotional material or other form of publicity without the prior written approval of the other Party. The restrictions imposed by this Section 12.6 shall not prohibit either Party from making any disclosure that is required by Applicable Laws.

13. PUBLICATION OF RESULTS

13.1. Each Party recognises that collaborating with respect to Publications may be beneficial to both Parties. The intention of the Parties is jointly to make such Publications, where reasonably possible.

13.2. **Rights and Procedures**. Subject to this Section 13, Institution, the Principal Investigator, Researchers and any additional authors authorised in writing by AZ (collectively "**Authors**"), shall have the right to publish the Results in scientific or other journals or to present the Results at professional conferences or other meetings consistent with academic standards, provided that any such Publication, whether joint with AZ or independent, shall be reviewed in accordance with this Section 13.2. At least forty-five (45) days prior to submission of any material for inclusion in a Publication (including presentations for educational purposes), Institution shall provide AZ with such material for review by AZ and its Collaboration Partners. AZ shall have forty-five (45) days to respond with any comments. Upon AZ's written request, Institution shall and shall ensure that the Authors shall: (a) withhold material from submission for publication or presentation for an additional ninety (90) days from the date of AZ's request to allow for the filing of a patent application or the taking of other measures as AZ deems appropriate to establish and preserve its or its Collaboration Partner's proprietary rights in the information in the material; (b) give reasonable consideration to any request by AZ to modify the publication; and (c) remove any information determined at AZ's sole discretion to be AZ's or its Collaboration Partner's Confidential Information.

13.3. **Timing of Publications**. Institution recognises that scientific lead-time is a key element of the value of the Research Activities and agrees that premature publication of any Results before all Research Activities are completed and the data is pooled and analysed could be misleading. Therefore, Institution shall ensure that Authors agree not to publish or present the outcome of the Research Activities or any Results until the completion of all Research Activities, and, if such Research Activities are part of broader research effort conducted at multiple study sites, until all data is compiled from all study sites.

13.4. **AZ Rights**. AZ and its Affiliates shall also have the right to publish or present independently the Results provided that due acknowledgement is made for the intellectual contribution made by Institution in accordance with standard scientific practice. However, AZ shall obtain the prior written consent of Institution to publish or present independently the Results before the earlier of: (a) the first joint publication, or publication or presentation by the Principal Investigator, of any Results; and (b) twelve (12) months after completion of the Research Activities.

13.5. **Responsibilities of Authors**. Institution shall ensure that Authors comply with the International Committee of Medical Journal Editors criteria regarding authorship and recommendations regarding disclosure of potential conflicts of interest, as well as all requirements with respect to disclosure required by any medical or scientific institution, medical committee or other medical or scientific organisation with which they are affiliated.

14. EXPECTATIONS OF THIRD PARTIES AND ANTI-BRIBERY

14.1. **Institution Expectations**. Institution recognises AZ's commitment to work only with partners who embrace the standards of ethical behaviour consistent with AZ's Expectations of Third Parties Handbook, a copy of which can be found on www.astrazeneca.com or by clicking the "Resources" tab on https://www.astrazeneca.com/sustainability.html, as amended from time to time, and without prejudice to the generality of the foregoing those principles in the Section entitled "Anti-Bribery and Anti-Corruption" as amended from time to time (collectively, "**Institution Expectations**").

14.2. **Compliance with Law and Code of Ethics.** Institution represents and will ensure that it: (a) will perform this Agreement and operate its business in compliance with all Applicable Law; (b) has received and read AZ's Code of Ethics, which can be found on www.astrazeneca.com or by clicking the "Resources" tab on https://www.astrazeneca.com/sustainability.html ("**Code of Ethics**"); (c) will perform this Agreement and operate its business to ethical standards consistent with those set out in the Institution Expectations and the Code of Ethics; (d) will not take any

action that will cause AZ or any AZ Affiliate to be in breach of any Applicable Law for the prevention of fraud, bribery and corruption, racketeering, money laundering, terrorism, product security or product safety, including the US Foreign Corrupt Practices Act and the UK Bribery Act; and (e) will use its reasonable endeavours to cause its affiliated companies, suppliers and subcontractors performing any Research Activities (where applicable) to operate their business in compliance with all Applicable Law and in a manner consistent with the Institution Expectations.

14.3. The Institution declares that it is aware of the current legislation on the administrative liability of companies (Legislative Decree no. 231/2001) and that it has adopted its own suitable Organisation, Management and Control Model, Code of Ethics and a Scientific Research Integrity Code pursuant to Legislative Decree no. 231/2001, published on the institutional website (link: (https://www.ifo.it/amministrazione-trasparente/) to know its contents, and to undertake to base their behavior on the principles of transparency and correctness contained therein.

14.4. **Anti-bribery.** Institution shall not and shall ensure that Principal Investigator and the Researchers shall not offer, pay, request or accept any bribe, inducement, kickback or facilitation payment, and will not make or cause another to make any offer or payment to any individual or entity for the purposes of influencing a decision for the benefit of AZ or any of its Affiliates (and Institution represents and warrants that it has not and Principal Investigator has not done any of the foregoing as at the Effective Date).

15. CYBER SECURITY REQUIREMENTS

15.1. **Cyber Security Measures.** In performing its obligations and exercising its rights under this Agreement, Institution warrants and represents that it will maintain adequate administrative, technical, and physical measures, controls, tools, systems, policies and procedures in accordance with good cyber security industry practice.

15.2. **Security Incidents.** Institution will notify AZ, in writing, about any security incident affecting or which may affect any IT infrastructure or data or facilities owned, leased or used by and/or provided for use by Institution, which may affect the fulfilment of Institution's obligations under this Agreement, without undue delay and in any event within twenty four (24) hours after Institution becomes aware of or suspects that a security incident has occurred. Such notification will be, in the first instance, sent by e-mail to the following e-mail address: SOCITSecurity@astrazeneca.com and immediately followed up by telephone to 0044 1625 513080.

16. LIABILITY AND INSURANCE

16.1. **Responsibilities.** Each Party shall be solely responsible and liable for: (a) its use or other exploitation of the Results; and (b) the collection, storage, use, handling, processing and disposal of any AZ Materials, HBS, and Data pursuant to this Agreement by it or on its behalf. The other Party accepts no liability or responsibility for, or in connection, with any of the foregoing except to the extent that such liability arises out of a breach of an express obligation, or such responsibility has been expressly assumed, by such other Party as set out in this Agreement.

16.2. **Limitation of Liability**. Subject to Section 16.3, neither Party shall be liable to the other Party for any lost profits, damages for lost opportunities or for any special, indirect, incidental punitive or consequential damages, whether in contract, warranty, negligence, tort, strict liability or otherwise, arising out of or in connection with this Agreement.

16.3. **Exceptions to Limits.** Nothing in this Agreement shall limit or exclude either Party's liability arising out of or in connection with this Agreement for: (a) death or personal injury caused by negligence; (b) fraud or fraudulent misrepresentation; (c) wilful misconduct; (d) breach of any of such Party's confidentiality or nondisclosure obligations or use restrictions in relation to Confidential Information, or any of its obligations under Section 8 (HBS), Section 9 (Personal Data) or Section 15 (Cyber Security Requirements); (e) its liability under Section 16.1; or (f) any acts or omissions in respect of which the governing law of this Agreement prohibits the exclusion or limitation of liability.

16.4. **Indemnification of Collaboration Partner**. Institution agrees to defend, indemnify and hold harmless the Collaboration Partner, its affiliates, and their respective officers and employees from and against any and all liabilities, claims, actions, suits, settlements, judgments and expenses, including reasonable attorney's fees, arising out of the use of the Collaboration Compound or Product or their modifications.

16.5. **Insurance**. Each Party will maintain adequate and appropriate insurance or self-insurance with respect to its activities in connection with the conduct of Research Activities. Each Party may request copies of documentation evidencing the existence of such insurance. Such insurance or self-insurance will be in such amounts and subject to such deductions as are required under Applicable Laws and internal risk management practice of a similar nature engaging in similar activities in the applicable jurisdictions.

17. REPRESENTATIONS, WARRANTIES AND COVENANTS

17.1. Each Party represents, warrants and covenants to the other Party that:

17.1.1. it has the full power and authority under its constitution, and has taken all necessary actions, to execute and perform its obligations under this Agreement;

17.1.2. entering into this Agreement, performing its obligations hereunder and granting rights to the other Party as set out in this Agreement does not conflict with any other agreement to which it is a party; and

17.1.3. it has the title and authority to and is entitled to assign to the other Party, the AZ Results (in case of Institution) and the Institution Results (in case of AZ), to grant the Licence and to grant all other rights and licences granted to AZ in accordance with the terms of this Agreement.

17.2. Institution, on behalf of itself and the Principal Investigator (as applicable), represents, warrants and undertakes to AZ as follows:

17.2.1. all necessary consents, approvals and authorisations of all regulatory authorities and other persons required to be obtained by it in connection with this Agreement have been obtained;

17.2.2. none of Institution, the Principal Investigator or Researchers have, or will during the Term have: (a) any financial or other conflict of interest in the outcome of the Research Activities; or (b) entered into any contract that creates a conflict of interest;

17.2.3. entering into this Agreement and performing the Research Activities does not cause Institution, the Principal Investigator or any Researcher to be non-compliant with any policy or procedure of any institution or entity that it or they are affiliated with;

17.2.4. the Principal Investigator is permitted to perform and agree to be bound by the relevant terms of this Agreement and that this Agreement is consistent with the Principal Investigator's obligations to Institution;

17.2.5. shall not (and shall ensure that the Principal Investigator shall not) use any funding provided by any governmental authority to conduct any of the Research Activities if such funding would impair the ability of Institution or the Principal Investigator to perform any of the Research Activities or to own, assign and license any intellectual property rights consistent with the terms of this Agreement;

17.2.6. use in the Research Activities any Person who: (a) is excluded, debarred, suspended or otherwise ineligible to participate in U.S. federal health care, procurement, or non-procurement programs, or any similar programs in any other jurisdiction; (b) has been convicted of a criminal offence that requires exclusion from a U.S. federal health care program or any similar program in any other jurisdiction; or (c) is otherwise disqualified or suspended from performing scientific or clinical investigations or subject to any

restrictions or sanctions by the U.S. Food and Drug Administration or any other governmental or regulatory authority or professional body with respect to the performance of the Research Activities;

17.2.7. during the Term and within two (2) years of the termination of this Agreement ensure that: (a) if Principal Investigator is a member of a committee that sets formularies or develops clinical guidelines, the Principal Investigator will disclose to such committee the existence and nature of this Agreement and will follow the procedures required by the committee; and (b) if the Principal Investigator writes or speaks in public about a matter that is the subject of this Agreement or any other matter relating to AZ, they declare the fact that they are working in collaboration with AZ. Institution further agrees to ensure that the Principal Investigator fully complies with all applicable disclosure obligations relating to Principal Investigator's relationship with AZ that may be externally imposed on Principal Investigator based on the requirements of any institution, medical committee or other medical or scientific organisation with which Principal Investigator is affiliated.

17.3. **Warranty Disclaimer Regarding Results. All Results provided to a Party are provided "AS IS" and to the maximum extent permitted by Applicable Laws and, save as expressly set out in this Agreement, each Party hereby disclaims and excludes all representations, warranties, conditions or other terms, whether written or oral, expressed or implied, with respect to the Results, including any representation or warranty of quality, performance, merchantability or fitness for a particular use or purpose, that the Results do not infringe the intellectual property rights or other proprietary rights of a third party.**

18. TERM AND TERMINATION

18.1. **Term**. This Agreement shall commence on the Effective Date and continue until the later to occur of: (a) one (1) year after the Effective Date; or (b) the completion of the Research Activities and AZ's receipt of the Final Report, unless this Agreement is earlier terminated in accordance with this Section 18 (the "**Term**").

18.2. **Termination for Material Breach by Either Party**. If a Party is in material breach of this Agreement, and such breach remains uncured for thirty (30) days after receipt of a notice of such breach from the other Party, then the other Party shall have the right to immediately terminate this Agreement by giving written notice of termination to the breaching Party.

18.3. **Termination by AZ**. AZ has the right in its sole discretion to terminate this Agreement for any reason or no reason by giving thirty (30) days' written notice to Institution.

18.4. **Termination in absence of Principal Investigator**. If Institution is unable to secure a substitute Principal Investigator reasonably acceptable to AZ in accordance with Section 3.1 within ninety (90) days of notifying AZ that the Principal Investigator has become unavailable, then either Party shall have the right to terminate this Agreement by giving thirty (30) days' written notice to the other Party.

18.5. **Consequences of Expiry or Termination**. Upon expiration or earlier termination of this Agreement:

18.5.1. each Party shall, subject to Section 5.1 return to the other Party or at the other Party's option, destroy all Confidential Information of the other Party (except for one copy of such Confidential Information may be retained for archival purposes, and further provided that such Party shall be permitted to retain such Confidential Information: (a) to the extent necessary to comply with Applicable Laws; or (b) for the purposes of exercising any ongoing licence or rights pursuant to this Agreement);

18.5.2. Institution shall deliver to AZ the Final Report;

18.5.3. Institution shall, in addition to any other remedy that may be available to AZ, promptly reimburse AZ for any excess amounts or unused funding paid to Institution pursuant to Section 4;

18.5.4. in cases of termination of this Agreement by Institution pursuant to Section 18.2 or by AZ pursuant to Section 18.3 or by either Party pursuant to Section 18.4, AZ shall reimburse Institution for all documented non-cancellable costs reasonably committed before receipt of the notice of termination, provided that Institution provides AZ with satisfactory proof that such expenses cannot be cancelled or recovered and in no event shall such expense exceed the aggregate amount budgeted in the Research Budget; and

18.5.5. at AZ's option, Institution shall either destroy or return to AZ all of the AZ Materials, provided that in the case of the destruction of such AZ Materials, Institution shall certify in writing to AZ that such AZ Materials have been destroyed.

18.6. **Survival**. Termination or expiry of this Agreement shall not affect any rights and obligations of the Parties that accrued prior to termination or expiry. All provisions of this Agreement which, in accordance with their terms, are intended to have effect after termination or expiration of this Agreement shall survive indefinitely the termination or expiration of this Agreement.

19. MISCELLANEOUS

19.1. **Force Majeure**. Neither Party shall be held liable to the other Party or be deemed to have breached this Agreement for failure or delay in performing any term of this Agreement when such failure or delay is caused by or results from events beyond the reasonable control of the non-performing Party, including fires, floods, earthquakes, hurricanes, embargoes, shortages, epidemics, pandemics, quarantines, war, acts of war (whether war be declared or not), terrorist acts, insurrections, riots, civil commotion, strikes, lockouts or other labour disturbances (whether involving the workforce of the non-performing Party or of any other Person), acts of God or acts, omissions or delays in acting by any governmental authority (except to the extent such delay results from the breach by the non-performing Party or any of its Affiliates of any term of this Agreement). The non-performing Party shall notify the other Party of such force majeure within thirty (30) days after such occurrence by giving written notice to the other Party stating the nature of the event, its anticipated duration and any action being taken to avoid or minimise its effect. The suspension of performance shall be of no greater scope and no longer duration than is necessary and the non-performing Party shall use commercially reasonable efforts to remedy its inability to perform.

19.2. **Assignment**. This Agreement may not be assigned by either Party in whole or in part without the prior written consent of the other Party, except that AZ without such consent may assign this Agreement and its rights and obligations hereunder to any of its Affiliates or any successor in interest to all or substantially all of the business to which this Agreement relates. AZ shall always have the right to perform any or all of its obligations and exercise any or all of its rights under this Agreement through any of its Affiliates. Each Party will remain fully liable for any acts or omissions of any of its Affiliates in breach of this Agreement as if they were its own.

19.3. **Subcontractors**. Institution shall not engage or make use of subcontractors for the purpose of performing the Research Activities or any other obligations under this Agreement except as expressly authorised by AZ in writing. Any such permitted subcontract shall be subject to the applicable terms and conditions of this Agreement, prior to disclosing to such subcontractor any AZ Confidential Information. No such subcontract shall release Institution from any of its obligations under this Agreement except to the extent such obligations are satisfactorily performed by such subcontractor in accordance with this Agreement.

19.4. Governing Law

The interpretation and construction of this Agreement shall be governed by the laws of England excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Agreement to the substantive law of another jurisdiction.

19.5. Escalation and Jurisdiction

If a dispute arises between the Parties in connection with or relating to this Agreement, then either Party shall have the right to refer such dispute to officers within each of their respective

organisations with the authority to make decisions for attempted resolution by good faith negotiations during a period of thirty (30) business days. If the Parties are unable to resolve any such dispute within such thirty (30) business day period, either Party shall be free to institute litigation in accordance with this Section. The Parties hereby consent to the exclusive jurisdiction of the courts of England for any action, suit or proceeding arising out of or relating to this Agreement that is not resolved in accordance with the above and, subject to Section 19.9, agree not to commence any action, suit or proceeding related thereto except in such courts.

19.6. **Notices**. Any notice or other communication required or permitted to be given by either Party under this Agreement shall be in writing and shall be deemed given as of: (a) the date delivered if delivered by hand, or reputable courier service; (b) the second (2nd) business day (at the place of delivery) after deposit with an internationally recognised overnight delivery service; or (c) the fifth (5th) business day after mailing if mailed by registered or certified mail, postage prepaid and return receipt requested, in each case addressed to the other Party at the addresses specified below, to such other addresses of which notice shall have been given in accordance with this Section. This Section 19.6 is not intended to govern the day-to-day business communications necessary between the Parties in performing their obligations under the terms of this Agreement.

Address for Notices

Institution	To: Via Elio Chianesi 53, 00144 – Rome, Italy. Attention: Scientific Director, Head of Translational Oncology Research Unit, Technology Transfer Office	With a copy to: dirscire@ifo.it Attention: Scientific Director Prof. Gennaro Ciliberto giovanni.blandino@ifo.it; sabrina.strano@ifo.it Attention: Head of Translational Oncology Research Unit technologytransfer@ifo.it Attention: Technology Transfer Office (TTO)
AZ	To: AstraZeneca UK Limited 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, England CB2 0AA Attention: Senior Director, Global Collaboration Agreements, Oncology R&D	With a copy to (which shall not constitute effective notice): OncologyRDCollaborationAgreements@astrazeneca.com Attention: Senior Director, Global Collaboration Agreements legalnotices@astrazeneca.com Attention: Legal Department

19.7. **Relationship of the Parties**. The status of a Party under this Agreement shall be that of an independent contractor. Nothing contained in this Agreement shall be construed as creating a partnership, joint venture or agency relationship between the Parties or, except as otherwise expressly provided in this Agreement, as granting either Party the authority to bind or contract any obligation in the name of or on the account of the other Party or to make any statements, representations, warranties or commitments on behalf of the other Party. All persons employed by a Party shall be employees of such Party and all costs and obligations incurred by reason of any such employment shall be for the account and expense of such Party.

19.8. **Construction**. Except where the context requires otherwise, whenever used the singular includes the plural, the plural includes the singular and the word "or" has the inclusive meaning represented by the phrase "and/or." The headings of this Agreement are for convenience only and do not define, describe, extend or limit the scope or intent of this Agreement or any of its provisions. The term "including" or "includes" as used in this Agreement means including, without limiting the generality of any description preceding such term. References to legislation shall be construed as a reference to that legislation as amended, re-enacted or replaced whether in whole or in part, and to any legislation implementing the foregoing. The wording of this Agreement shall be deemed to be the wording mutually chosen by the Parties and no rule of strict construction shall be applied against any Party.

19.9. **Equitable Relief**. The Parties recognise that any threatened breach or breach of Sections 11 (Intellectual Property), 12 (Confidentiality) or 13 (Publication of Results) may cause irreparable harm that is inadequately compensable in damages and that, in addition to other remedies that may be available at law or equity, the non-breaching Party is entitled to seek injunctive relief for such threatened or actual breach in any court of competent jurisdiction.

19.10. **Amendment; Waiver**. No amendment, modification or waiver of any of the terms of this Agreement shall be deemed valid unless made in writing and duly executed by authorised representatives of both Parties. Each Party shall have the right to enforce the Agreement in strict accordance with its terms. The failure of either Party to enforce its rights strictly in accordance with terms shall not be construed as having in any way modified or waived the same.

19.11. **Severability**. If any provision of this Agreement is held to be invalid, illegal or unenforceable in any respect, then to the fullest extent permitted by Applicable Laws: (a) such provision will be given no effect by the Parties and shall not form part of this Agreement; and (b) all other provisions of this Agreement shall remain in full force and effect.

19.12. **No Third Party Rights**. A person who is not a Party to this Agreement shall not have any rights to enforce any of its terms. The Parties may amend, renew, terminate or otherwise vary all or any of the provisions of this Agreement without the consent of any other person.

19.13. **Entire Agreement**. This Agreement and all Schedules constitute the entire agreement and understanding between the Parties with respect to the subject matter hereof and supersede all prior oral and written agreements, understandings, promises and representations with respect thereto. In the event of any inconsistency between any such Schedules and this Agreement, the terms of this Agreement shall govern.

19.14. **Counterparts**. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original and all of which shall together be deemed to constitute one agreement. The Parties agree that execution of this Agreement by industry standard electronic signature software or by exchanging PDF signatures shall have the same legal force and effect as the exchange of original signatures, and that in any proceeding arising under or relating to this Agreement, each Party hereby waives any right to raise any defence or waiver based upon execution of this Agreement by means of such electronic signatures or maintenance of the executed agreement electronically.

[*Remainder of page intentionally left blank. Signatures follow.*]

Execution

THIS AGREEMENT IS EXECUTED by the authorised representatives of the Parties as of the Effective Date.

SIGNED for and on behalf of **AstraZeneca UK Limited**		**SIGNED for and on behalf of** **IRCCS Istituto Nazionale Tumori Regina Elena**	
Signature:	..... *Electronically signed by: Katy Montague Date: May 30, 2024 19:17 GMT+1*	Signature:	..... *Electronically signed by: Gennaro Ciliberto Date: Jun 5, 2024 16:51 GMT+2*
Name:	Katy Montague	Name:	Prof. Gennaro Ciliberto
Title:	Senior Director, External R&D	Title:	Scientific Director

The Principal Investigator acknowledges that he/she has read this Agreement and understands the obligations Institution has undertaken on his/her behalf.

Acknowledged and Agreed to:

By: _____ *Electronically signed by: Giovanni Blandino Date: Jun 4, 2024 12:44 GMT+2*

Name: Dr. Giovanni Blandino

Title: Principal Investigator

Date: 04-Jun-2024

By: _____ *Electronically signed by: Sabrina Strano Date: Jun 4, 2024 12:48 GMT+2*

Name: Dr. Sabrina Strano

Title: Researchers (Institution)

Date: 04-Jun-2024

SCHEDULE 1

RESEARCH PLAN

Title: Circulating microRNAs as biomarkers for monitoring mucositis insurgence and progression upon Datopotamab Deruxtecan (Dato-DxD) treatment.

PI (Institution): Dr Giovanni Blandino (giovanni.blandino@ifo.it)

Researchers (Institution): Dr Sabrina Strano (sabrina.strano@ifo.it)

Scientific Lead (AZ): Dr Alice Barkell (alice.barkell@astrazeneca.com)

AZ Materials and Data to be provided by AZ to Institution are:

AZ Materials	**Amount**
Datopotamab deruxtecan (DS1062)	50 mg
Data	**Amount**
Data relating to the AZ Materials	N/A

SYNOPSIS

Oral mucositis (OM) is an inflammatory process characterized by erythema and ulceration of the mucous membranes of the oral cavity. It is a common painful side effect that accompanies cancer patients receiving high doses of chemotherapy and radiotherapy treatments. Approximately 90 % of patients with Head and Neck cancer and over 75 % of leukemia patients who undergo to bone marrow transplantation experience mucositis (Elting et al, 2007). Although the infections, the immunosuppression, the poor nutritional state favour the insurgence of OM, the main causative agent is the citotoxicity of the treatment. The extent, the severity of OM and the time of healing are site-dependent: They are also related to dose and schedule of treatment (Kuderer et al, 2022). OM appears 3-5 days after starting of the therapy, reaches the peak at day 7 and complete healing at the second week of the treatments. The pathophysiology of OM is a multistage phenomenon that involves a cascade of inflammatory events that have been recapitulated in five phases: Initiation, upregulation of inflammation, signalling amplification, ulceration and wound healing (Sonis et al, 2004). The initiation of OM involves two main events: oxidative stress with production of ROS and release of damage-associated molecular patterns (DAMPs) that bind receptors and initiate the inflammatory signalling cascade. The progression of OM requires the activation of NFKB that induces the transcription of proinflammatory cytokines and chemokines such TNFa and IL1, IL6 that recruit blood leukocytes to the site of lesion and secrete proteases disrupting the tissue matrix (Pulito et al, 2021). Although the pathological condition is self-limiting, altered oral intake, dehydration and increased risk of infection impair the patient ‘s compliance evolving frequently either halting therapy or in the hospitalization. The advent of new therapeutic regimens as targeted and checkpoint inhibitors therapies highlighted the

potential onset of distinct oral mucosal toxicities for pathogenesis and clinical presentation (Jacob et al,2021; Schaberg et al,2022; Foster et al,2022). microRNAs are small noncoding RNAs (19-24 nucleotides) originating from precursors RNAs that are involved in post-transcriptional regulation of coding genes (Garzon et al,2009). The regulation of gene expression occurs at post-transcriptional level through the interaction of 3'untraslated region UTR (3'UTR) of messenger RNAs. The canonical function of miRNAs is to repress post-transcriptionally the expression of specific target proteins by either promoting mRNA decay or quenching translation (Dragomir et al, 2022). miRNAs are highly stable and tissue specific and their expression profile can represent a specific signature of the disease (Mitchell et al,2008). Easily detectable in formalin fixed tissues and in body fluids, circulating miRNAs are very stable and resistant to endogenous RNAses. A variety of evidence has suggested the possibility of using microRNAs as important molecular analytes for biomarker development by examining their expression in the saliva and serum of cancer patients (Cortez et al, 2011; Anfossi et al, 2018)

At present, there is no evidence regarding the use in clinical practice of blood biomarkers for the stratification of cancer patients at high risk of insurgence of mucositis.

Statement and impact for the National Health System

Mucositis is one of the most prominent side effects of cancer therapy. It has a significant impact on quality of life of patients. Currently, several agents and management approaches are available to medical practitioners with variable efficacy (Brown et al,2020). The identification of biomarker which would determine whether there is mucositis and thereby establish the severity would be useful (Shetty et al,2022). The setting of a diagnostic protocol of patients 'molecular stratification might improve their outcome. Since mucositis affects 40% of treated cancer patients and 80% of chemo-radiotherapy HNSCC patients, the dissection of mucositis development, the identification of early biomarkers and novel treatments might have paramount implications for Healthy System. With the advent of target therapies and immunotherapies reports of new oral mucosa toxicities and relate adverse events are increasing. In addition, mucositis increases rates of hospital admission, clinic visits, and nutritional consults that impact severely on the National Health System.

Preliminary findings

Mucosal inflammation and atrophy of the mouth and gastrointestinal tract, collectively known as alimentary tract mucositis, are debilitating adverse effects observed in cancer patients undergoing cancer treatments.

A) In order to mimic the OM inflammatory process "in vitro", we used primary gingival keratinocytes and epidermis (HEKa) that were treated with different classes of antineoplastic agents used in the treatment of patients suffering from HNSCC tumors and known to induce mucosal lesions of various degrees in the patient (see Fig.1).

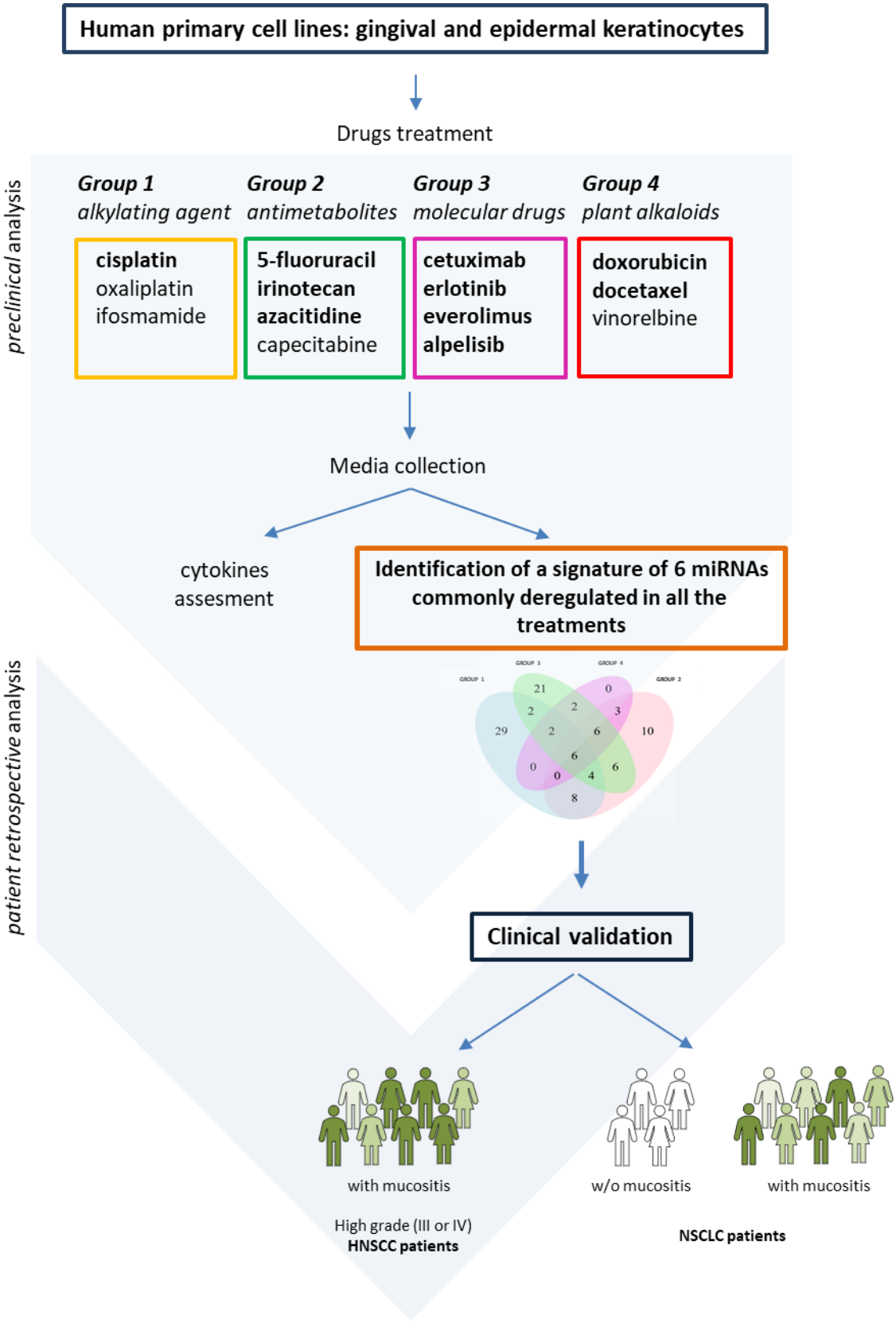
B) We identified sub-apoptotic concentrations and after the treatment we extracted from gingival culture media circulating miRNAs that were used as probe to hybridize Agilent slides containing specific oligos of 2549 microRNAs. We identified six microRNAs that are specifically related to the development of mucositis following anti-tumour treatments, such as chemo or radiotherapy treatments. In particular, miR signature (which has been institutionally patented) levels were found to be commonly up-regulated in culture media tested regardless of the type of treatment carried out (see Fig.1).

C) We conducted a bioinformatics analysis on miRNA SeQ data from the TGCA of mirX expression levels in normal versus tumor tissues. Such analysis did not show any involvement of miR signature in the tumor process. This reinforces our initial hypothesis of the specificity of miR signature as a biomarker of the mucosal inflammatory process secondary to the iatrogenic damage.

D) We assessed miR signature circulating levels in two retrospective casuistries of cancer patients with oral mucositis induced either by radio-chemotherapy (HNSCC n=26) or by Pembrolizumab (Lung

cancer n=15) treatments, respectively. Notably, we found that the circulating levels of miR signature are enriched only in patients affected by oral mucositis (see Fig.1).

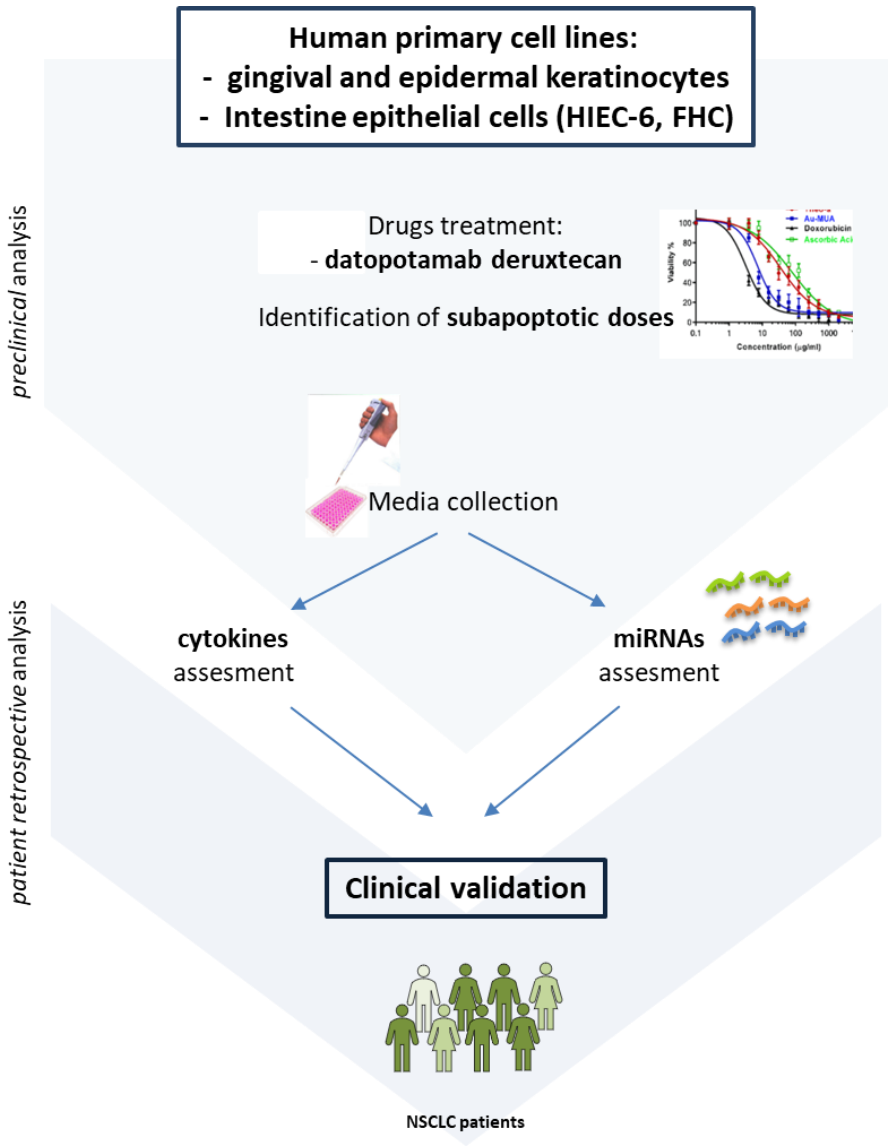
Figure 1



Primary Objective / Research Activities to be performed by Institution

Our aim will be to dissect the cytotoxic effects of Dato-DxD against normal primary mucosa cell lines. To this end Primary Epidermal (HEKa) and Gingival keratinocytes and intestinal epithelial cells (HIEC-6, FHC) will be treated with Datopotamab-DxD at different concentrations and at different time points (0.24,48,72 hours). After establishing the half maximal effective concentration (EC50) and the half maximal lethal concentration (LC50) for each cell line (Atplite,Perkin Elmer), we will perform functional assays by using sub-apoptotic doses of Dato-DxD (see Fig.2). As there are no existing reports in the literature regarding Trop2 expression in primary cell lines, we plan to test protein expression by either Western blot (using the EPR20043 antibody which commercially available from Abcam) or by Flow cytometry (using a commercially available flow antibody for Trop2). Subsequently the culture media derived from of primary cells will be collected and assessed for the expression of cytokines that are released modulated during mucosal inflammation such as IL1b, IL6 and TNFa with the aid of ELLA Technology. The culture media derived from primary cells treated with sub-apoptotic doses of Dato-DxD will be collected and analyzed against a signature of circulating microRNAs previously found that are involved in oral mucositis process.

Figure 2



GANTT Project timeline

Months	1		2		3		4		5		6	
Identification of subapoptotic doses of DATOPOTAMAB-DxD/ Evaluation of TROP2 expression levels												
Assessment of released cytokines in gingival and intestinal primary mucosal cells												
Assessment of released microRNAs in gingival and intestinal primary mucosal cells												

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Reporting:

Reports to be provided every six (6) months, or as otherwise agreed between the Parties.

Information Exchange:

Results, Data and reports to be exchanged via a secure online platform, to be advised by AZ, and not via email.

Time frame of the project:

Six (6) months

SCHEDULE 2

RESEARCH BUDGET

Total Research Budget (in Euros):

	Total	Details
1 Staff salary	0.00	
1b Researchers contracts	0	
2 Equipment	0	
3a Supplies	50000	
primary cell lines (HIEC-6, FHC, gingival and epidermal keratinocytes)		8500
cell media and plasticware		1800
viabilty assay		2700
cytokine assessment		7500
miRNA array		5800
digital PCR reagents		6500
RNA extraction		2500
RT-PCR reagents		3700
	subtotal	39000

Payment Schedule:

50% of total Research Budget upon execution of the Agreement

50% of total Research Budget upon completion of all deliverables and AZ's receipt and approval of a Final Report.

Institution shall invoice AZ for each instalment of the Research Budget on, or promptly after, the achievement of the relevant deliverables or the relevant date(s) set out above (as applicable)**.**

SCHEDULE 3

INVOICE REQUIREMENTS

Transmission of Purchase Orders. Institution agrees to participate in the electronic transaction program for Purchases Orders. AZ will indicate the electronic transaction program applicable to Institution for each Purchase Order, details of which can be found on www.astrazeneca.com on the "Supplier Information" tab or by going to https://www.astrazeneca.com/az-suppliers.html, as amended from time to time. Participation in the electronic transaction program includes the preparation and regular maintenance of electronic catalogues to support a high-quality ordering process and accepting the electronic transmission of Purchase Orders from AZ. Institution agrees to provide the required data and to designate a representative to assist in ensuring implementation and maintenance of the electronic transaction program.

Invoices and Credit Notes. Institution agrees to submit all invoices and any corresponding credit notes to AZ electronically through the electronic transaction program designated by AZ details of which can be found on www.astrazeneca.com on the "Supplier Information" tab or by going to https://www.astrazeneca.com/az-suppliers.html, as amended from time to time. AZ will indicate the electronic transaction program applicable to Institution for each invoice. Institution should only submit invoices through the electronic transaction program and only valid invoices or credit notes submitted through the electronic transaction program will be considered received by AZ. The electronic transaction program will allow Institution to either (i) transmit invoices and credit notes electronically or (ii) create those invoices or credit notes within the electronic transaction program. AZ may reasonably reject any invoice or credit note that does not meet at least the following relevant standards.

The relevant standard for an invoice is one that:

1. complies with local law, the European standard and any of the syntaxes published in Commission Implementing Decision (EU) 2017/1870;

2. documents the different goods and services within the invoice;

3. does not duplicate a pre-existing invoice or credit note for the goods or services;

4. contains the full details of the AstraZeneca party, including legal name, address and when applicable the Indirect Tax ID number; and

5. is raised by Institution, in all circumstances, unless AZ and Institution mutually agree in writing a self-invoicing scheme.

Credit notes should be used to amend incorrect invoices and should inform of the error being corrected and the invoices affected.