COLLABORATIVE RESEARCH AGREEMENT

This Collaborative Research Agreement (hereinafter called "**Agreement**"), effective as of the date of the last signature (hereinafter called "**Effective Date**"), is made

BY AND BETWEEN

Fondazione IRCCS Istituto Nazionale dei Tumori, located at Via Giacomo Venezian 1, 20133 Milano, Italy, organized under Italian laws, under the Ministero della Salute and Regione Lombardia, represented by the General Manager, Dr. Carlo Nicora (hereinafter referred to as "**INT**")

AND

The Royal Marsden NHS Foundation Trust, located at Fulham Road, London, SW3 6JJ, (hereinafter referred to as "**RMH**")

AND

The Institute of Cancer Research: **Royal Cancer Hospital,** whose registered office is at 123 Old Brompton Road, London, SW7 3RP, United Kingdom legally represented by Dr Jon Wilkinson, Interim Director of Business and Innovation (hereinafter referred to as "**ICR**")

INT, RMH and ICR may each be referred to as "**Party**" or collectively as "**Parties**."

WHEREAS

INT is the Sponsor of an observational study entitled *"Reversion of resistance to mTOR inhibitors with the addition of exemestane in patients with malignant PEComa"* (hereinafter referred to as "**Study**"), performed under the scientific responsibility of Dr. Roberta Sanfilippo, MD at s.c. Oncologia Medica 2 – Tumori mesenchimali dell'adulto e Tumori rari (hereinafter referred to as "**INT Lead Researcher**") within which human biological Material, (hereinafter referred to as "**Material**"), has been collected and is intended to be analysed. INT has asked to ICR, to Dr. Paul Huang in particular (hereinafter referred to as "**ICR Lead Researcher**") and to RM, with Dr. Andrea Napolitano (hereinafter referred to as "**RMH Lead Researcher**") to collaborate in the Study and to perform the analysis foreseen in the Study Protocol, as indicated in the attached APPENDIX A- MATERIAL SPECIFICATION.

TERMS AND CONDITIONS

It is hereby agreed as follows:

NOW, THEREFORE, in consideration of the premises described above and the mutual promises and agreements set forth in this Agreement, the Parties agree as set forth below.

1. DEFINITIONS

"**Activities**" shall mean the activities under the Study to be performed by the Parties using the Material as described in the **APPENDIX A.**

"Affiliates" shall mean a business entity that directly or indirectly through one or more intermediaries, controls, is controlled by or is under common control with a Party, with "control" meaning direct or indirect ownership of 50% or more of the voting interest in such other entity, and in the case of a partnership control of the general partner, or the power to direct the management of any such entity.

"**Applicable Law**" shall mean applicable laws (including the Freedom of Information Act 2000), rules and regulations, including any rules, regulations, guidelines or other requirements, of the Governmental Authority(ies), that may be in effect from time to time.

"**Background Intellectual Property**" means any Intellectual Property used, conceived, developed or reduced to practice by a Party prior to the Effective Date of this Agreement or which are independently used, conceived, developed or reduced to practice by personnel of a Party independently and outside of the scope of this Agreement.

"**Commercial Purposes"** means the sale, lease, license or other exploitation of the Material, Information or Modifications to a person for profit, including, but not limited to, use of the Material, Information or Modifications by Recipients or any individual or organization to perform contract research, to screen compound libraries, to produce or manufacture products for general sale, or to conduct research activities that result in any sale, lease, license or other exploitation of the Material, Information or Modifications to any individual or organization for profit. For greater certainty, academic research sponsored by government or industry does not fall within the definition of "commercial purposes" unless the sponsor retains rights, title or interests in and to the Material, Information or Modifications; or unless the research activities result in any sale, lease, license or other exploitation of the Material, Information or Modifications to any individual or organization for profit.

"Confidential Information" means information that is owned or controlled by the Disclosing Party or its Affiliate(s) and is directly or indirectly disclosed or otherwise made available hereunder, whether written, graphic, oral, visual, tangible or intangible, in any form or format (including machine or computer readable code), including information that may be disclosed in connection with an audit or inspection that is conducted by (or on behalf of) the Recipient. Confidential Information includes, without limitation, any and all of the clinical data and research results, technical and non-technical data, formulae, ideas, know-how, Materials, methods, operational information, patent applications, plans, procedures, pre-clinical data and results, processes, product information, projections, specifications, standards, strategies, technical information, techniques, trade secrets, tools, or other clinical, technical or business information. For the avoidance of doubt, the Results shall be treated as Confidential Information.

"**Data**" means data, including raw data, processed data and data summaries, accounts, notes, records, technical reports, information obtained or produced in the course of performing the Study.

"Data Protection Legislation" means any applicable data protection or privacy laws, including:
- The Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR"),
- Other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition, including but not limited to all applicable data protection and privacy legislation in force from time to time in the UK including the GDPR; the Data Protection Act 2018 (DPA 2018) (and regulations made thereunder).

"**Disclosing Party**" means the Party/Parties to this Agreement or any of its Affiliates that discloses Confidential Information directly or indirectly, under or in anticipation of this Agreement, to the Receiving Party.

"**Governmental Authority**" shall mean any governmental agency or body, any State government, or if applicable the government of any foreign country (including without limitation agencies such as the National Institutes of Health).

"**Intellectual Property**" means any and all information, data, know-how, methods, models, formulas, formulations, compositions, materials (including, but not limited to biological and chemical materials, cell lines and cell models), inventions (whether patentable or not), discoveries, techniques, methodologies, processes, libraries, tools and technologies, computer programs, source code and test results.

"**Invention**" shall mean any result deemed useful discovery or invention, whether patentable or not, conceived, reduced to practice or otherwise made in connection with this Agreement from use of the Material.

"**Material**" for use in the Study shall mean the Material being transferred to Recipients as described in "APPENDIX A" of this Agreement and Unmodified Derivatives of the Original Material.

"**Modifications**" means substances created by Recipients, which contain or incorporate any form of the Material (including Original Material or Unmodified Derivatives).

"**Personal Data**" means any information relating to an identified or identifiable natural person, including health and genetic data ("Data Subject"), including without limitation pseudonymized information, as defined in Data Protection Legislation.

"**Personal Data Breach**" means a breach of security leading to accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to Personal Data transmitted, stored, or otherwise processed.

"**Provider**" means any Party providing Materials or Data.

"**Receiving Party**" means the Party/Parties to this Agreement or its Representatives that receives Confidential Information directly or indirectly from the Disclosing Parties.

"**Recipient**" means any Party receiving Materials or Data.

"**Researchers**" are respectively:
Dr. Roberta Sanfilippo and Dr. Chiara Fabbroni for INT, and Dr. Paul Huang for ICR, Dr Robin Jones and Dr Andrea Napolitano for RM.

"**Results**" shall mean the results generated in the course of performing the Study.

"**Term**" shall mean the period beginning on the Effective Date of this Agreement and ending upon termination or expiration of this Agreement pursuant to Section 11, whichever is shorter.

"**UK GDPR**"**:** has the meaning given to it in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018. "Controller", "Data Subject", "Processing", and "Appropriate Technical and Organizational Measures" shall be interpreted in accordance with the UK GDPR

"**Unmodified Derivatives**" means substances created by Recipients, which constitute an unmodified functional subunit or product expressed by the Original Material.

2. MATERIAL

INT shall be the Provider of Materials, ICR shall be the Recipient of the Materials. RMH shall provide the funding for the analysis of the Material and won't be involved in any exchange of the latter.

2.1. Recipient hereby agrees that Material is the sole and exclusive property of Provider and accepts to use it only for the Study, in compliance with (i) the attached APPENDIX A-MATERIAL SPECIFICATION, (ii) possible instructions herein contained (including possible limitations to the use of Material and relevant data indicated), as well as the applicable law. (iii) the Study has been approved by an appropriate ethics committee and all other governmental, regulatory or similar bodies from whom an approval is required in order to safely and legally undertake the Study. Nothing herein shall be deemed to grant to the Recipient any rights under Provider's Material.

2.2. The Material is not for use in human subject.

2.3. Recipients represent to fully agree with the scope of Study.

2.4. The Material is property of the Provider and is made available to Recipient for Activities, in compliance with the APPENDIX A, as well as the applicable law. Nothing herein shall be deemed to grant to Recipient any rights under Provider's Material.

2.5. This Agreement and the resulting transfer of Material constitute a right to use the Material only for scientific research purposes and the Recipient represents that Material will be used only for not-for-profit purposes. Any right to use the Material for commercial purpose is excluded from this Agreement and should be discussed and determined through a different written agreement between the involved Parties.

2.6. Recipient acknowledges that Material is or may be the subject of a patent application; no express or implied licenses or other rights are provided to the Recipient under any patents, patent applications, trade secrets or other proprietary rights of Provider, including any altered forms of Material made by Provider.

2.7. The Material will not be further distributed to third parties without Provider's previous written consent. Recipient shall refer any request for the Material to the Provider.

2.8. Recipient is committed to always make Material available to the respective Provider, should the Provider make a written request for its return. Furthermore, Recipient accepts to promptly inform Provider in case it runs out of provided Material and, on Provider's written request, to give adequate evidence proving the usage of the whole provided quantity. Recipient hereby declares to respect the operative instructions and procedures adopted by Provider for return of unused provided Material and/or of any derivatives given in the APPENDIX A-MATERIAL SPECIFICATION ("Instructions and Procedures").

2.9. Recipient agrees to acknowledge the source of the Material in any publication reporting use of it. Where appropriate according to scientific custom, any publication will be made jointly by INT, ICR and RMH Researchers jointly and will include the following names: Dr. Roberta Sanfilippo and Dr. Chiara Fabbroni for INT, Dr. Paul Huang for ICR and Dr. Robin Jones and Dr Andrea Napolitano for RM, collectively referred to as (**"Researchers").**

2.10. Recipient will not:

a) make Modifications of the Material without the express written consent of the Provider, except for the Activities described in APPENDIX A;
b) use the Material, Modifications or Confidential Information for Commercial Purposes;
c) use the Material or Modification in human subjects, whether in clinical trials or otherwise and whether for therapeutic, preventive, diagnostic or other purposes;
d) use the Material, Modifications or Confidential Information in research projects that grant sublicense, ownership or other proprietary rights in the Material, Modifications or Confidential Information to a third party; or
e) use the Material, Modifications or Confidential Information for purposes that are not compliant with the Study;
f) supply or make available to anyone outside of Recipient Lead Researcher's direct supervision, or to any third party for any purpose whatsoever the Material, Confidential Information or Modifications without the prior written consent of Provider whose consent may be withheld at its sole discretion.

2.11. Any Material delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. Provider makes no representations and extends no warranties of any kind, either express or implied with respect to the nature and properties of the material, which is made available by provider "as is". There are no express or implied warranties of merchantability or fitness for a particular purpose, or that the use of the material will not infringe any patent, copyright, trademark, or other proprietary rights.

2.12. Unless prohibited by law, Recipient assumes all liability for claims for damages against it by third parties which may arise from the use, storage or disposal of the Material except that, to the extent permitted by law, Provider shall be liable to Recipient when the damage is caused by the gross negligence or willful misconduct of Provider.

2.13. Under no circumstances shall any Party be liable to the other, whether in contract, tort (including negligence or breach of statutory duty) or otherwise howsoever arising for any loss of profit, business, reputation, contracts or anticipated savings or any other indirect, special or consequential losses which arise, directly or indirectly, from any default on the part of any other Party.

2.14 Nothing in this Agreement is intended to limit or exclude any liability for fraud, death or personal injury caused by negligence, or any other liability which may not be so excluded or restricted under the applicable law.

2.15. Recipient acknowledges that Material is equipped with a univocal reference code, which allows for its traceability. Therefore, Recipient agrees to use anonymized Personal Data ever received from Provider in compliance with all applicable statutes and regulations and to protect the integrity and confidentiality of certain information disclosed or otherwise made available to Recipient by Provider, concerning the processing of Personal Data in the exercise of scientific research, by adopting the highest security measures and giving access to the Data only to the person/s duly appointed.

2.16. Material is provided at Recipients' charge.

3. DATA PROTECTION

Each Party shall be the Provider of Data when providing Data to any other Party. Each Party shall be the Recipient of Data when receiving Data from any other Party. The Parties agree that they act as a Controller

as defined under article 4 (7) of the EU n°2016/679 General Data Protection Regulation ('GDPR') and all other applicable laws. Consequently, the Parties must be considered as separate Controllers, as they independently determine on the purposes and means of their own Data processing of Personal Data in the course of the Agreement.

The Parties commit themselves to comply with Data Protection Laws, including the GDPR and all other applicable laws. The Parties agree to set out this Data Protection Clauses to determine their own respective responsibilities, but also their rights and how to assist each other with their respective obligations while processing Personal Data.

For the purposes of the following Data Protection Clauses, RM, ICR and INT shall act as Data Controller and Data Exporters and the Lead Researchers shall act as a separate Data Controller and Data Importer of the Personal Data transferred related to the Material.

3.2. Responsibilities of the Parties

The Parties agree that they will:

a) Comply with the Data Protection Legislation
b) Process Personal Data received from the other Party only to the extent necessary to the Agreement. They agree they are both responsible to comply with the Data Protection Legislation principles regarding their own sphere of responsibility.
c) Conduct the Relations with Data Subjects as it follows:

   i) Right of information
   Data Subjects must receive information about the Processing of their Personal Data in accordance with Article 13 or 14 GDPR. The Parties agree that each Party is only responsible for giving correct and complete information about its own Data processing to the corresponding Data Subjects and shall not be responsible for other Parties' conduct.

   ii) Request of Data Subjects
   Each Controller is responsible to comply with the provision of Chapter III GDPR for its own Data processing. The Parties agree that they are responsible for managing Data Subjects' requests exercising their rights and shall provide a response to these requests within 30 days when such requests occur within their respective sphere of responsibility.
   If one Party receives Data Subject's request concerning Personal Data processing in respect of which the other Party is Controller, this Party shall forward such request to the other Party without undue delay, but not later than within five (5) business days. The other Party shall acknowledge receipt of such communication.
   The Parties shall cooperate and provide each other with reasonable assistance to facilitate the handling of such requests.
   Furthermore, in accordance with article 19 GDPR, the controller sharing Data with the other shall communicate any rectification or erasure of Personal Data or restriction of processing to the other controller to whom the Personal Data have been disclosed, unless this proves impossible or involves disproportionate effort.

d) Guarantee Security measures:
   Taking into account the state of the art, the costs of implementation and the specific circumstances at stake, each Party shall implement Appropriate Technical and Organizational Measures in relation to its own Processing of Personal Data to ensure a level of security appropriate to the risk.

e) Conduct International transfers of Personal Data shared in the course of the Agreement as it follows:
Each Party shall ensure that any transfer of Personal Data, carried out for the performance of the Agreement, to third parties located in countries outside of the European Union or the European Economic Area, is made only,
   i) to a jurisdiction deemed by the European Commission to have an adequate level of protection based on an adequacy decision pursuant to Article 45 GDPR;
   ii) in the absence of an adequacy decision, subject to the implementation of appropriate safeguards pursuant to Article 46 GDPR, including but not limited to the European Commission's Standard Contractual Clauses.

   It is hereby agreed that the use of derogations pursuant to Article 49 GDPR is hereby restricted, except for non-repetitive and exceptional transfers.
   In case where the transfer tool as per Article 46 GDPR does not ensure a sufficient level of protection than the one guaranteed at the European level, the adoption of supplementary measures should be considered to legitimately support the transfer.

f) In the case of Personal Data Breach, each Party shall be responsible for notifying the breach to the competent supervisory authority and, where appropriate, for communicating the breach to the affected Data Subjects. The Party, within whose sphere of responsibility the Personal Data Breach occurs, shall comply with the obligations set forth under Articles 33 and 34 GDPR.
   Parties will notify each other as soon as possible of any potential or actual loss of shared Personal Data and/or any breach of the technical and/or organizational measures taken (Personal Data Breach), but, in any event, within twenty-four (24) hours after identifying any potential or actual loss and/or breach. Each Party shall support the respective other Party by providing reasonable assistance as required to facilitate the handling of any Personal Data Breach and to assist the other Party with its obligation to notify and communicate the data breach. Personal Data Breach

4. EXPENSES OF THE STUDY

According to Article 2.14 of the Agreement, all expenses necessary for the transfer and the shipment of the Material are borne by Recipient.

5. INTELLECTUAL PROPERTY

The Provider retains all rights, title and interest in and to the Material and Confidential Information pertaining to the Material. The Provider retains all rights, title and interest in and to the Material contained whole or in-part, within Modifications. Material and Information may be subject to patent protection.

INT will provide the RMH and ICR with a written report on the progress of the Activities within 60 days of the end of each calendar year of this Agreement.

In case of Invention/discoveries, its ownership shall be determined by mutual agreement between the Parties, on fair and reasonable conditions and in accordance with applicable law, taking into account the role and contribution of each Party. Terms regarding equitable sharing of patent costs, licensing income, and invention management responsibility shall be included. Each Party will not license its own rights pertaining to the new joint inventions without the previous written authorization of the other Party. If a Party is the sole inventor of any invention, that Party shall be free to dispose of such sole invention as it deems appropriate.

To avoid any doubt, all Intellectual Property used in connection with the Project which has been generated prior to or outside the scope of the Project ("Background IP") shall remain the property of the Party contributing the same. The Parties agree that any improvements or modifications to a Party's Background

IP arising from the Project which are not severable from that Background IP will be deemed to form part of that Party's Background IP and be owned by that very same Party. No license to use any Background Intellectual Property is granted or implied by this Agreement except the rights expressly granted in this Agreement.

6. RESULTS

Provider agrees to provide Recipient a copy of their Results upon the completion of the Activities. Each Party shall own the Results it generates as part of its performance of the Activities. In the event where Results are generated by more than one Party and it is not possible, for the purpose of applying for, obtaining and/or maintaining the relevant patent protection or any other intellectual property right, to separate the contributions made by the respective Parties to such Results, they shall be jointly owned by the Parties that generate them proportionally to each Party's inventive contribution.
If Recipient's Research results in an Invention, to the extent such Invention incorporates or contains, in whole or in part, or necessarily relies on use of Materials or Modifications, Recipient agrees to promptly disclose the Invention to Provider, in confidence, before a patent application is filed. Inventorship of any such Invention (if patentable) shall be determined by the law of the country where it will be utilized or by mutual agreement between the Parties (if not patentable) and ownership shall follow inventorship, taking into account the role and contributions of individuals involved in the development of the Invention as well as the contribution of the Material itself. In the case of a jointly owned Invention between Provider and Recipient, the Parties agree to negotiate a joint invention agreement in good faith which shall provide for fair and equitable sharing of patent costs, income, and invention management responsibilities. Each Party is granted a non-exclusive license to use the Results generated by any of the other Parties in the performance of the Study, free of charge, for their own research and educational purposes. Publication of Results shall be handled in accordance with Article 7. Notwithstanding the foregoing, during the Term, each Party agrees not to collaborate with any third party on any Activities related to the Study, as may be amended from time to time, without the prior written consent of the other Parties.

7. PUBLICATION AND DISCLOSURE TO THIRD PARTY

The Parties intend that the first public dissemination of the Results arising from this Study will be jointly made by all the Parties. The Parties shall have co-authorship and the Researchers shall mutually agree as to the most effective manner to accomplish this.

Notwithstanding clause 8, each Party shall be entitled to publish articles directly arising from its solely owned Results prior to the publication of articles directly arising from the work of more than one Party on the Study, as long as it does not affect any possible future Inventions under article 5 and 6 nor hinder or prevent the Parties to submit any patent application or obtain one.

Each Party may publish the results of the Study subject to the following:

a copy of each such proposed abstract or publication manuscript (and a reasonably detailed description of any such oral presentation or other public disclosure) is submitted by the Publishing Party to the other Party at the earliest practicable time, but in any event within the following time frames:

(b) At least 30 days prior to any proposed submission for publication of any manuscript or any presentation or other public disclosure date; and

(b) At least 15 days prior to proposed submission for publication of any abstract.

Any publication will include the following names: Dr. Roberta Sanfilippo and Dr. Chiara Fabbroni for INT, and Dr. Paul Huang for the ICR, Dr Robin Jones and Dr Andrea Napolitano for RM. Researchers will collaborate on manuscripts resulting from the Study, approve of the content and jointly select journals to target for publication; however, if requested by a Party, the Researchers making the publication or presentation shall delete Confidential Information of any Party that may be contained therein. If a Party feels that information contained in such publication is patentable and communicates such situation in writing to the other, the Parties agree to delay submission or delivery of such abstract, publication or presentation, as the case may be. Such delay shall not exceed 90 additional days unless mutually agreed between relevant parties to file the patent application on same. Notification of the requirement for delay in submission for publication must be received by the publishing Party within thirty (30) days after the receipt of the material by the other Party/Parties, failing which the publishing Party shall be free to assume that the other Party/Parties has no objection to the proposed publication. The provisions of this sub-clause 7 shall survive termination or expiry of this Agreement for the period of 2 years. Any other publication of the Data or the results of the Study, other than in those journals and symposia shall require the consent of both Parties.

The authorship and contents (including scientific conclusions and professional judgments) of any paper submitted shall be determined according to international scientific and academic practice on publication.

8. CONFIDENTIALITY

Each Party shall be the Disclosing Party when providing Confidential Information to any other Party. Each Party shall be the Recipient of Confidential Information when receiving Confidential Information from any other Party.

All information shared between the Parties which is expressly marked as confidential or which a reasonable person would reasonably consider to be confidential including, but not limited to, any Parties' employees, agents and/or contractors, shall be considered Confidential Information. This Agreement and the terms and conditions hereof shall be classed as falling within the definition of Confidential Information and the Party seeking disclosure of any Confidential Information shall not, without the prior written permission of the Party to whom the Confidential Information relates, disclose the same to any third party except to the extent this may be required by a regulatory authority or by applicable laws and regulations or as necessary for the conduct of the Study.

Confidential Information does not include information to the extent that:

(a) is now in the publicly known or subsequently becomes part of the public through no breach of this Agreement;

(b) the Receiving Party lawfully receives it from any third party without restriction as to use or confidentiality as shown by written or other tangible evidence;

(c) it is independently developed by or for the Receiving Party by persons without access to the Confidential Information; or

(d) it was already known by the Receiving Party at the time of its disclosure under this Agreement as shown by written or other tangible evidence.

(e) which, after disclosure to a Party, is subsequently published or comes to be publicly known by means other than an action or omission on the part of any Party

(f) is required to be disclosed to any regulatory authority or court of competent jurisdiction, or which is required to be disclosed pursuant to a request under the Freedom of Information Act 2000 or applicable law.

8.2 Required Disclosures

If Receiving Party receives a subpoena or other validly issued administrative or judicial process demanding Confidential Information, Receiving Party will (a) promptly inform the Party or entity issuing such subpoena or other government process of the existence of this Agreement; (b) immediately notify the Disclosing Party of the disclosure requirement (which will include a copy of any applicable subpoena or order); (c) afford the Disclosing Party a reasonable opportunity to oppose, limit or secure confidential treatment for the required disclosure; and (d) not oppose any effort by the Disclosing Party to quash any such subpoena or other government process. If the Disclosing Party fails to intervene to quash said subpoena or other government process after being given notice and a reasonable opportunity to do so, or if such motion is denied by a court of competent jurisdiction, the Receiving Party will disclose only that portion of the Confidential Information of the Disclosing Party that the Receiving Party is legally required to disclose. In the event that any Confidential Information is ordered produced in an action or proceeding, it will not lose its confidential status through such use and Receiving Party will take all reasonable and necessary steps to protect its confidentiality.

8.3 Return of Confidential Information

Upon the termination or expiration of this Agreement, or at any other time upon the written request of Disclosing Party, Receiving Party will promptly return to Disclosing Party all Confidential Information in Receiving Party's possession or control, together with all copies, summaries and analyses, regardless of the format in which the information exists or is stored. At the Disclosing Party's request, the Receiving Party will promptly destroy all such information instead of returning it. In case of destruction, Receiving Party will promptly send a written certification that destruction has been accomplished to the Disclosing Party. However, Receiving Party is entitled to retain one copy of Confidential Information for the sole purpose of determining its obligations under this Agreement.

8.4 Permitted Disclosures

Receiving Party agrees that it will not disclose Confidential Information to any third party without prior written consent of Disclosing Party. Notwithstanding the foregoing, Receiving Party may disclose Disclosing Party's Confidential Information to an agent of Receiving Party performing services for the Receiving Party related to the Research, provided the Receiving Party's consent and provided that such agent is under obligations of confidentiality regarding Disclosing Party's Confidential Information at least as restrictive as those within this Agreement. Receiving Party agrees to disclose Confidential Information only to those of its or its Affiliates' officers and employees whose duties justify the need to know the Confidential Information for the Research. Upon disclosing Confidential Information to its or its Affiliates' officers and employees, Receiving Party will advise said officers and employees of the confidential nature of the Confidential Information and the relevant obligations contained in this Agreement. Receiving Party will be liable for unauthorized disclosure of Confidential Information by its or its Affiliates' officers or employees.

8.5 Use of Confidential Information

Receiving Party shall use Confidential Information solely for the Study.

8.6 Term and Duration of Confidentiality

The obligations of confidentiality survive for five (3) years following the expiration or earlier termination of this Agreement.

9. WARRANTIES AND DISCLAIMERS.

Material is provided by Provider "AS IS." Provider MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, WITH RESPECT TO THE DATA AND EXPRESSLY DISCLAIMS ALL IMPLIED WARRANTIES OF MERCHANTABILITY AND OF FITNESS FOR A PARTICULAR PURPOSE OR USE.

10. COMPLIANCE

Each Party agrees to comply with Applicable Law in connection with this Agreement.

11. TERM AND TERMINATION

This Agreement will expire at the conclusion of the Study but in no event later than 2 (two) years from the Effective Date unless earlier terminated or extended in writing by the Parties. Any Party may terminate their involvement in this Agreement forthwith by notice in writing to the other Party if any of the other Parties commits a substantial breach of this Agreement, which in the case of a breach capable of remedy shall not have been remedied within sixty (60) days of receipt by the Party in default of the notice identifying the breach and requiring its remedy.

Upon termination or expiration of or withdrawal from this Agreement, Recipient’s right to continue to use the Material shall cease and they will arrange for the return to the Provider or for the lawful disposal of all unused Material, as elected by the Provider.

Articles 2, 4, 5, 6, 7, 8 and 9 will survive the expiration or earlier termination of this Agreement.

12. MISCELLANEOUS

(i) This Agreement shall be governed and construed in accordance with the laws and jurisdiction of the State (where applicable) of the country of the defending Party, namely the laws of England and Wales when RMH or ICR is the defending Party, or the laws of Italy when INT is the defending Party. Similarly, the venue for any such proceeding shall be in the country of the defending Party, without regard or giving effect to its principles of conflict of laws.

(ii) Nothing herein creates or is intended to create an employment relationship, partnership, joint venture, agency relationship or any other fiduciary relationship between the Parties.

(iii) This Agreement, including its APPENDIXES, constitutes the entire agreement and understanding of the Parties and supersedes any prior agreements, promises or understandings, written or verbal, relating to the subject matter hereof.

(iv) This Agreement may not be modified or supplemented, nor may any provision or the benefit thereof

be waived, except by a written instrument duly signed by both Parties.

(v) This Agreement may not be assigned by the Parties without the prior written approval of the other Party, and any purported assignment in violation of approval shall be void *ab initio*. This Agreement shall inure to the benefit of each Party's successors and assigns.

(vi) This Agreement is signed by digital signature. The exchange of digital signatures and a fully executed copy of this Agreement delivered by electronic mail shall have the same effect as a wet ink original.

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their duly authorized representatives.

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For INT

Fondazione IRCCS Istituto Nazionale Tumori
The General Manager
(Dr. Carlo Nicora)

_____

Read and acknowledged by
INT LEAD RESEARCHER

By: _____
Name: Dr. Roberta Sanfilippo

GIOVANNA ROBERTA SANFILIPPO
Firmato digitalmente da GIOVANNA ROBERTA SANFILIPPO
ND: dnQualifier=202350457211, c=IT, serialNumber=TINIT-SNFGNN79E51E573S, sn=SANFILIPPO, givenName=GIOVANNA ROBERTA, cn=GIOVANNA ROBERTA SANFILIPPO
Data: 2023.11.29 15:38:49 +01'00'

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Digital signature

Certification of Recipients Scientist: in my capacity as INT Lead Researcher, I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

For RMH
The Royal Marsden NHS Foundation Trust

Name: Mark Brandon-Grove
(Authorized Official)

Digitally signed by Mark Brandon-Grove, Head of Clinical Research Performance & Quality
Date: 2023.09.14 09:15:18 +01'00'

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Digital signature

Read and acknowledged by
RMH LEAD RESEARCHER

By: _____
Name: Dr. Andrea Napolitano

DocuSigned by:
Andrea Napolitano 14-09-2023
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Certification of Recipients Scientist: in my capacity as RMH Lead Researcher, I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

For ICR
The Institute of Cancer Research :Royal Cancer Hospital

Name: __Dr Jon Wilkinson, Interim Director of Business and Innovation_____
(Authorized Official)

DocuSigned by:
Jon Wilkinson 19-09-2023
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Digital signature

Read and acknowledged by
ICR LEAD RESEARCHER

By: _____
Name: Dr Paul Huang

DocuSigned by:
Paul Huang 18-09-2023
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Digital signature

Certification of Recipients Scientist: in my capacity as ICR Lead Researcher, I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

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APPENDIX A

RESEARCH PLAN

Material specification

Requested by:
Prof. /Dr. Paul Huang
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Requested Material
Tumor tissue, Paraffin embedded

Shipment
At Recipients' charge

Activities of the Parties

The Royal Marsden NHS Foundation Trust:

- will provide the funding for the analysis of the Material and the other activities carried out by ICR and won't be involved in any exchange of the Material itself.

Fondazione IRCCS Istituto Nazionale dei Tumori:

- will provide the Material at Recipient's charge.
- will conduct retrospective analysis of all advanced malignant PEComa cases treated with medical therapy at INT, here below better described.

The Institute of Cancer Research: Royal Cancer Hospital:

- will receive the Material.
- will undertake transcriptomic and proteomic profiling of PEComa tumour specimens from INT, here below better described.

Scope of the Study

Rationale
PEComas can harbor alterations of TSC1 or TSC2 genes, with a constitutive activation of the mTOR pathway. TSC1 acts to stabilize TSC2, and loss of TSC1 leads to lack of TSC2 expression. TSC2 encodes

for tuberin, which interacts with hamartin, the product of TSC1, determining a heterodimer. In particular, tuberin inhibits the mTORC1 kinase. Activated mTORC1 drives the mTOR/p70S6K metabolic pathway, which leads to increased cell growth, and regulates vascular smooth muscle differentiation. A small subset of malignant PEComas harbor TFE3 gene fusions, known to be mutually exclusive with TSC1/TSC2 loss-of-function mutations. TFE3 is a member of the MiT family, which is involved in the differentiation of melanocytes and also osteoclasts.

Given such alterations of the mTOR pathway, the systemic treatment of PEComas is based on mTOR inhibitors. Sirolimus (also called rapamycin) is an mTORC1 inhibitor, which has provided tumor responses in a number of (but definitely not all) patients with malignant PEComas. Notably, in the phase 2 study of nab-sirolimus (an albumin-bound intravenous mTOR inhibitor with high intratumoral drug accumulation) in patients with advanced disease, 25 in 34 patients were assessed for their mutational status. Most (89%), but not all, TSC2 mutations were associated with a response to the drug. Responses were seen even in patients with TSC1 mutations or no TSC1/TSC2 mutations 12.

Growing evidence supports a close interaction between the mTOR pathway and estrogen (ER) or androgen receptors signaling in a wide range of malignancies. The combination of mTOR inhibitors and antiestrogen treatment, such as the nonsteroidal aromatase inhibitor exemestane, has been deeply studied in breast cancer and represents the standard of care in a specific subset of patients with ER-positive breast cancer upon progression to hormonal therapy alone13-15. Interestingly, a cross-talk between estrogen and mTORC1 pathways was also demonstrated in PEComas using a patient-derived model of lymphangioleiomyomatosis.16 This provided us with a rationale for combining antiestrogens and mTOR inhibitors in patients with locally advanced or metastatic PEComa progressing to mTOR inhibitors alone. A reversion of sirolimus resistance was achieved in more than one half of progressing patients in a small series, and further translational and genetic analyses are needed to fully understand the molecular mechanisms behind such results.

Methodology

We will conduct retrospective analysis of all advanced malignant PEComa cases treated with medical therapy at Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy, from 2014 to 2021. Up to now, we treated 20 patients with the combination of an mTOR inhibitor + exemestane upon progression to sirolimus alone.

Work to be carried out by the ICR as part of the Study

ICR will undertake transcriptomic and proteomic profiling of PEComa tumour specimens from IRCCS Istituto Nazionale dei Tumori. In addition, analysis of the mutational status of all exons of *TSC1* and *TSC2* will be conducted using clinically validated targeting sequencing. Transcriptomic and proteomic data will be subjected to further bioinformatic analysis to identify Omic features associated with clinicopathological features including TSC1/2 mutational status.

Bibliography

1. Sanfilippo R, Jones RL, Blay JY, Le Cesne A, Provenzano S, Antoniou G, et al. Role of chemotherapy, VEGFR inhibitors, and mTOR inhibitors in advanced perivascular epithelioid cell tumors (PEComas). Clin Cancer Res 2019;25: 5295–300

2. Sanfilippo R, Fabbroni C, Fucà G, Fumagalli E, Morosi C, Sbaraglia M, Gronchi A, Collini P, Dei Tos AP, Casali PG. Addition of Antiestrogen Treatment in Patients with Malignant PEComa Progressing to mTOR Inhibitors. Clin Cancer Res. 2020 Oct 15; 26(20):5534-5538.