

## DECRETO DEL DIRETTORE GENERALE - N. 525-DG del 31/08/2023 - Allegato Utente 1 (A01)

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| <p style="text-align: center;"><b><u>CONTRACT AMENDMENT No. 2 TO<br/>CLINICAL TRIAL AGREEMENT</u></b></p> <p style="text-align: center;">between</p> <p><b>Fondazione IRCCS Istituto Nazionale dei Tumori</b> (hereinafter called “<b>Institution</b>”), located in Via Venezian 1-20133 Milan, tax ID No. 80018230153, VAT code 04376350155, represented by the General Manager, Carlo Nicora</p> <p style="text-align: center;">And</p> <p>the company <b>Exelixis, Inc.</b>, located in 1851 Harbor Bay Parkway, Alameda, CA 94502, U.S.A. (the “<b>Sponsor</b>”).</p> <p>Under a special Power of Attorney issued on 17 July 2023, Sponsor has appointed and authorized <b>ICON Holdings Clinical Research International Limited – Italian Branch (Sede Secondaria)</b>, with a place of business at Via Benigno Crespi, Maciachini Business Park, no. 19, 20159 Milano, Italy (“<b>CRO</b>”) to execute this Contract Amendment no. 2 in the name and on behalf of the Sponsor thus binding Sponsor to the duties and obligations set out in this Contract Amendment no. 2.</p> <p>Hereinafter individually "the Party", below collectively as the "Parties", is hereby entered into by the Parties as of last signature date (“<b>Amendment No. 2 Effective Date</b>”).</p> <p style="text-align: center;"><b><u>WHEREAS:</u></b></p> <p>- on date 14 February 2018 the Parties executed a Clinical Trial Agreement, (the “<b>Agreement</b>”) to conduct a clinical study with title “<b><i>A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination</i></b></p> | <p style="text-align: center;"><b><u>EMENDAMENTO N. 2 ALLA<br/>CONVENZIONE PER<br/>SPERIMENTAZIONE CLINICA</u></b></p> <p style="text-align: center;">tra</p> <p><b>Fondazione IRCCS Istituto Nazionale dei Tumori</b> (di seguito per brevità “<b>Ente</b>”) con sede in Via Venezian 1, 20133 Milano C.F. n. 80018230153 e P.I. 04376350155, rappresentata dal Direttore Generale, Carlo Nicora</p> <p style="text-align: center;">E</p> <p>La società <b>Exelixis, Inc.</b>, con sede in 1851 Harbor Bay Parkway, Alameda, CA 94502, U.S.A. (il “<b>Promotore</b>”).</p> <p>In virtù di Procura speciale emessa in data 17 July 2023, il Promotore nomina e autorizza <b>ICON Holdings Clinical Research International Limited – Italian Branch (Sede Secondaria)</b> avente la propria sede in Via Benigno Crespi, Maciachini Business Park, no. 19, 20159 Milano, Italia (“<b>CRO</b>”) a sottoscrivere il presente Emendamento n. 2 alla Convenzione in nome e per conto del Promotore, vincolando pertanto il Promotore ai doveri e agli obblighi stabiliti nel presente Emendamento n. 2 alla Convenzione.</p> <p>Di seguito singolarmente “la Parte” collettivamente “le Parti”, - è stipulato dalle Parti a partire dall'ultima data di sottoscrizione (“<b>Data di entrata in vigore Emendamento n. 2</b>”).</p> <p style="text-align: center;"><b><u>PREMESSO CHE:</u></b></p> <p>- in data 14 febbraio 2018 le Parti hanno stipulato una convenzione, (la “<b>Convenzione</b>”) per l'esecuzione dello studio clinico dal titolo: “<b><i>A Phase 1b Dose-Escalation Study of Cabozantinib (XL184) Administered Alone or in Combination with Atezolizumab to Subjects</i></b></p> |
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| <p><b><i>with Atezolizumab to Subjects with Locally Advanced or Metastatic Solid Tumors</i></b>” Protocol XL184-021 (hereinafter referred to as “<b>Trial</b>”) under the scientific supervision of Dr. Andrea Necchi, Medical director at s.c. Oncologia Medica 1 [Medical Oncology department 1], directed by prof Filippo de Braud;</p> <p>- on 13 June 2019 the Parties executed the Contract Amendment No. 1 which became necessary in order to:</p> <ul style="list-style-type: none"> <li>- include further instrumental diagnostic activities required for the proper execution of the Trial in question with modification of the Budget annexed to the Agreement</li> <li>- update the contractual terms regarding the processing of personal data taking into account the entry into force of European Regulation No. 679/2016;</li> <li>- amend the name of the processing arm “Expansion Run-In” as follows: “021 A2 Single Agent Cabo (SAC)”;</li> <li>- extend the number of patients to be enrolled in the clinical trial in question, initially planned at about 7 to about 25;</li> </ul> <p>- it became necessary to amend again the Agreement in order to appoint by the Sponsor <b>IQVIA</b> as authorized payment agent (“<b>APA</b>”) for all administrative activities (payments) connected to the aforementioned Trial, which has accepted said appointment;</p> <p>- effective November 1, 2020, following the withdrawal of the employment relationship of Dr. Andrea Necchi with the Institution, the Institution has appointed as person responsible for the Sponsor’s Trial, following formal acceptance, <b>prof. Filippo de Braud</b>, Head of s.c. Oncologia Medica 1, to replace the Principal Investigator, Dr. Andrea Necchi, and Prof. Filippo de Braud, has agreed to conduct</p> | <p><b><i>with Locally Advanced or Metastatic Solid Tumors</i></b>”- protocollo XL-184-021 (di seguito per brevità “<b>Sperimentazione</b>”), sotto la responsabilità scientifica del dott. Andrea Necchi, Dirigente medico presso la s.c. Oncologia Medica 1 della Fondazione diretta dal prof Filippo de Braud;</p> <p>- in data 13 Giugno 2019 le Parti hanno stipulato l’Emendamento n. 1 alla Convenzione resosi necessario al fine di:</p> <ul style="list-style-type: none"> <li>- includere ulteriori attività diagnostiche strumentali necessarie per la corretta esecuzione della Sperimentazione in oggetto con modifica del Budget allegato alla Convenzione;</li> <li>- aggiornare i termini contrattuali relativi al trattamento dei dati personali tenuto conto dell’entrata in vigore del Regolamento Europeo n. 679/2016;</li> <li>- modificare la denominazione del braccio di trattamento “Expansion RunIn” come segue “021 A2 Single Agent Cabo (SAC)”;</li> <li>- estendere il numero di pazienti da arruolare nella sperimentazione clinica di cui trattasi, inizialmente previsti in circa 7 fino a circa 25;</li> </ul> <p>- si è reso necessario emendare nuovamente la Convenzione al fine di nominare da parte del Promotore la società <b>IQVIA</b> quale agente di pagamento autorizzato (“<b>APA</b>”) per tutte le attività di tipo amministrativo (i pagamenti) connesse alla Sperimentazione sopra citato, la quale ha accettato tale nomina;</p> <p>- a partire dal 1 novembre 2020, a seguito della cessazione del rapporto di lavoro del Dr. Andrea Necchi con l’Ente, l’Ente ha nominato come responsabile della Sperimentazione dello Sponsor, previa accettazione formale, il <b>prof. Filippo de Braud</b>, Direttore della s.c. Oncologia Medica 1, in sostituzione dello Sperimentatore Principale, Dr. Andrea Necchi, e il Prof. Filippo de Braud ha accettato di</p> |
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| <p>Sponsor's Trial in accordance with the Agreement;</p> <p>- the recitals are an integral part of this Contract Amendment No. 2.</p> <p><b>NOW THEREFORE, THE PARTIES AGREE AS FOLLOW:</b></p> <p>1. Exhibit A is hereby amended and supplemented as shown below:</p> <p style="text-align: center;">“...<i>ADDED</i> ...</p> <p><b>Exhibit A, Payment Schedule.</b> The Payment Schedule set forth under Exhibit A to the Agreement is hereby amended as follows:</p> <p>The invoicing information indicated in Exhibit A of the Contract Amendment No.1 to the Agreement, remain valid and effective except as regards the indication of the new Authorized Payment Agent, the company <b>IQVIA Inc.</b> and for all that is indicated below:</p> <ul style="list-style-type: none"> <li>• The amounts per visit/patients given according Exhibit A to Contract Amendment No.1 shall be paid to the Institution on a quarterly basis, upon issuance of a due invoice by the latter, and according to the statement of charges submitted by the Sponsor through the APA and validated by the Principal Investigator, to be sent to the following address:<br/>clinical_trial_payment@istitutotumori.mi.it.</li> <li>• Invoices may be uploaded directly to the IQVIA company via email address</li> </ul> | <p>condurre la Sperimentazione dello Sponsor in conformità alla Convenzione;</p> <p>- le premesse fanno parte integrante del presente Emendamento n. 2 alla Convenzione.</p> <p><b>TUTTO CIÒ PREMESSO, SI CONVIENE E SI STIPULA QUANTO SEGUE</b></p> <p>1. L'Allegato A è modificato e integrato come di seguito indicato:</p> <p style="text-align: center;">“...<i>OMISSIS</i> ...</p> <p><b>Allegato A, Programma di pagamento.</b> Il Programma di pagamento di cui all'Allegato A alla Convenzione viene qui emendato come segue:</p> <p>Le informazioni di pagamento indicate nell'Allegato A dell'Emendamento n. 1 alla Convenzione restano valide ed efficaci fatto salvo per quanto concerne l'indicazione del nuovo Agente di Pagamento Autorizzato, la società <b>IQVIA Inc.</b> e per tutto quanto indicato in prosieguo:</p> <ul style="list-style-type: none"> <li>• Gli importi per visita/paziente forniti in base all'allegato A dell'Emendamento n. 1 alla Convenzione saranno corrisposti all'Ente su base trimestrale a fronte di emissione di regolare fattura da parte della stessa, sulla base di rendiconto presentato dal Promotore tramite APA e validato dallo Sperimentatore Principale da inviare al seguente indirizzo:<br/>clinical_trial_payment@istitutotumori.mi.it.</li> <li>• Le fatture possono essere caricate direttamente tramite IQVIA</li> </ul> |
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| <p>emea@ctp.solutions.iqvia.com or physically or by regular mail to:</p> <p>Exelixis Inc.<br/>c/o IQVIA Clinical Trial Payments<br/>37 The Point, North Wharf Road<br/>Paddington<br/>London, W2 1AF<br/>United Kingdom<br/>Tax ID number: 04-3257395<br/>(Ref: Study)</p> <p>Phone Support:<br/>Global Payment Services at 1-973-659-6722<br/>Inside Italy at 800-931-574</p> <p>Institution budget contact email:<br/><a href="mailto:clinical_trial_payment@istitutotumori.mi.it">clinical_trial_payment@istitutotumori.mi.it</a></p> <ul style="list-style-type: none"> <li>Physical copies of the invoices are not required.</li> <li>The preferred method to send your invoices is emailing them to: <a href="mailto:emea@ctp.solutions.iqvia.com">emea@ctp.solutions.iqvia.com</a></li> <li>For any payment related questions please contact: <a href="mailto:emea@ctp.solutions.iqvia.com">emea@ctp.solutions.iqvia.com</a></li> </ul> <p>2. <b>Transfer from PRA to ICON.</b><br/>Effective as of 30 June 2023, any references in the Agreement, including those in the Preamble referring to the name and address of the CRO as “Pharmaceutical Rresearch Associates Italy S.r.l., located at Milano, 20122, Via Borgogna 8” are hereby deleted in their entirety and replaced with “ICON Holdings Clinical Research International Limited – Italian Branch (Sede Secondaria), with a place of business at Via Benigno Crespi, Maciachini Business Park, no. 19, 20159 Milano, Italy”.</p> | <p>all'indirizzo e-mail<br/>emea@ctp.solutions.iqvia.com o<br/>fisicamente o inviate via posta a</p> <p>Exelixis Inc.<br/>c/o: IQVIA Clinical Trial Payments<br/>37 The Point, North Wharf Road<br/>Paddington<br/>London, W2 1AF<br/>United Kingdom<br/>Codice fiscale: 04-3257395<br/>(Ref: Study)</p> <p>Contatto telefonico:<br/>Global Payment Services at 1-973-659-6722<br/>Per l'Italia: 800-931-574<br/>Indirizzo mail Referente budget per l'Ente:<br/><a href="mailto:clinical_trial_payment@istitutotumori.mi.it">clinical_trial_payment@istitutotumori.mi.it</a></p> <ul style="list-style-type: none"> <li>Non sono richieste copie cartacee delle fatture.</li> <li>Le fatture dovranno essere trasmesse al seguente indirizzo:<br/><a href="mailto:emea@ctp.solutions.iqvia.com">emea@ctp.solutions.iqvia.com</a></li> <li>Per eventuali domande relative ai pagamenti, contattare : <a href="mailto:emea@ctp.solutions.iqvia.com">emea@ctp.solutions.iqvia.com</a></li> </ul> <p>2. <b>Trasferimento da PRA a ICON.</b><br/>Con decorrenza dal 30 giugno 2023, ogni riferimento nella Convenzione al nome e all'indirizzo della CRO - ivi inclusi quelli contenuti nel Preambolo - quale “Pharmaceutical Rresearch Associates Italy S.r.l., con sede in Milano, 20122, Via Borgogna 8” sono cancellati nella loro interezza e sostituiti con “ICON Holdings Clinical Research International Limited – Italian Branch (Sede Secondaria), con sede operativa in Via Benigno Crespi, Maciachini Business Park, n. . 19, 20159 Milano, Italia”.</p> |
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| <p><b>3. Miscellaneous.</b></p> <p>This Contract Amendment No. 2 is drafted in Italian and in English and in the event of discrepancy, the Italian version shall prevail.</p> <p>With the exception of what has been expressly modified by this Contract Amendment No. 2 to the Agreement, all other provisions included under the Agreement and Contract Amendment No. 1 shall remain valid, binding and unchanged.</p> <p>Where the Parties have performed activities governed by this Contract Amendment No. 2 on a date prior to the date of the last signing of this Contract Amendment No. 2, the services performed in the meanwhile shall be deemed to be governed by the provisions contained in this Contract Amendment No. 2.</p> <p><b>IN WITNESS WHEREOF</b>, the Parties hereto, each by a duly authorized representative, have executed this Contract Amendment No. 2 that will be valid and effective as of Amendment Effective Date.</p> <p>This Contract Amendment No. 2 is signed digitally in accordance with Article 24 of legislative decree 82/2005, in accordance with the provisions of Article 15 paragraph 2bis of Law 241/1990 as supplemented by article 6, decree law 18/10/2012, no. 179, converted into Law no. 22 of 17/12/2012.</p> <p>This Contract Amendment No. 2 is written in both the Italian and English languages in case of discrepancy the Italian language will prevail.</p> | <p><b>3. Varie.</b></p> <p>Il presente Emendamento n. 2 alla Convenzione è redatto sia in lingua italiana che in lingua inglese ed in caso di discrepanza prevarrà la lingua italiana.</p> <p>Ad eccezione di quanto indicato nel presente Emendamento n. 2 tutte le altre clausole contenute nella Convenzione nonché nell'Emendamento n. 1 rimangono valide, vincolanti ed invariate.</p> <p>Ove le Parti abbiano dato esecuzione ad attività disciplinate dal presente Emendamento n. 2 in data precedente a quella dell'ultima sottoscrizione del presente Emendamento n. 2, le prestazioni eseguite <i>medio tempore</i> dovranno considerarsi regolate dalle previsioni contenute nel presente Emendamento n. 2.</p> <p><b>IN FEDE DI CIÒ</b> le Parti, ciascuna nella persona del/la proprio/a rappresentante debitamente autorizzato/a sottoscrivono il presente Emendamento n. 2 alla Convenzione, che sarà valido ed efficace a far tempo dalla data di Data di Efficacia dell'Emendamento. Il presente Emendamento n. 2 alla Convenzione viene sottoscritto con firma digitale ai sensi dell'art. 24 del D. Lgs. 82/2005, giusta la previsione di cui all'art. 15, comma 2bis della Legge n. 241/1990, come aggiunto dall'art. 6, D.L. 18/10/2012, n. 179, convertito in Legge 17/12/2012 n. 22.</p> <p>Il presente Emendamento n. 2 è redatto sia in lingua italiana sia in lingua inglese in caso di discrepanza prevarrà la lingua italiana.</p> |
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**p. il promotore / on behalf of the Sponsor:  
ICON Holdings Clinical Research  
International Limited – Italian Branch  
(Sede Secondaria), acting as authorized  
representative of Exelixis, Inc / che agisce  
come rappresentante autorizzato di  
Exelixis, Inc.**

**Fondazione IRCCS Istituto Nazionale  
Tumori**

By/Da: \_\_\_\_\_  
Authorized digital signature  
Firma digitale autorizzata

Name/Nome: Gabriella Maria Laurora  
Title/Titolo: Procuratrice

By/Da: \_\_\_\_\_  
Authorized digital signature  
Firma digitale autorizzata

Name/Nome: Dott. Carlo Nicora  
Title/Titolo: il Direttore Generale / The  
General Manager

**THE PRINCIPAL INVESTIGATOR / LO SPERIMENTATORE PRINCIPALE**  
**Following review and acceptance / Per presa visione e accettazione:**

By/Da: \_\_\_\_\_  
Authorized digital signature  
Firma digitale autorizzata

Name/Nome: prof. Filippo de Braud

Digital Signature/Firma digitale