**TITOLO DEL PROGETTO**

Feasibility study on personalized chemotherapy before or after pancreatic resection for ductal adenocarcinoma through EGFR, KRAS, SPARC and BRCA assessment.

<table>
<thead>
<tr>
<th>ASSEGNO FINANZIATO DA PROGETTO COMPETITIVO (barrare la casella corrispondente)</th>
<th>□ SI</th>
<th>X NO</th>
<th>Punti</th>
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<tr>
<td>SE IL FINANZIAMENTO È COMPETITIVO L'ENTE FINANZIATORE</td>
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<td>PROGETTO/ATTIVITÀ A SCOPO COMMERCIALE (es. sperimentazione profit)</td>
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<td>□ SI</td>
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<td>CARATTERISTICHE DEL PROGETTO (biomedico/osservazionale/clinico-interventistico/multidisciplinare)</td>
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<td>Osservazionale/multidisciplinare</td>
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<td>STATO DI APPROVAZIONE DEL PROGETTO DA PARTE DEL COMITATO ETICO (se necessario per il tipo di studio barrare o evidenziare la casella corrispondente)</td>
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**DESCRIZIONE DEL PROGETTO (max 800 parole)**

**STATE OF THE ART AND RATIONALE**

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with poor prognosis, making it the fourth leading cause of cancer-related death worldwide. Only pancreatic resection can provide some survival possibilities but unfortunately the benefit of chemotherapy either adjuvant, neo-adjuvant (or stand-alone) is small and there is still a long way to ameliorate outcomes through such multidisciplinary approach. One emerging research area is represented by molecular-target therapy, as already in use in colorectal cancer: considering costs and survival benefits, it is important to select those patients who could most benefit from different chemo-therapeutic regimens.

**EGFR**

The Epidermal Growth Factor Receptor (EGFR) plays a role in the pathogenesis and progression of different carcinomas. The mutation in the EGFR tyrosine kinase domain is predictive for EGFR tyrosine kinase inhibitor therapy sensitivity, conferring an increased response to these drugs. Erlotinib is an orally active selective EGFR-TKI licensed for advanced pancreatic cancer. Recent RCTs suggested longer progression-free and overall survivals in patients receiving gemcitabine+Erlotinib than in the gemcitabine alone group when EGFR was mutated.
KRAS
Mutations in the Kirsten rat sarcoma virus (KRAS) gene can be detected in about 70-90% of PDACs. The wild-type status determines improved overall survival in comparison to mutated cases. Having knowledge of KRAS mutation is mandatory to have a comprehensive picture of response to surgery and chemotherapy.

SPARC
The secreted protein acidic and rich in cysteine (SPARC) is a calcium-binding protein which promotes tumor invasion. Its overexpression is related to poorer prognosis but it is also part of the mechanisms for the intra-tumoral delivery of nab-paclitaxel, a solvent-free taxane. Patients with higher tumoral expression of SPARC show improved survival when receiving nab-paclitaxel+gemcitabine.

BRCA
Mutations in BRCA1/2 are commonly linked with breast and ovarian cancers but are now gaining wider recognition also in PDAC. Available data reports that patients with stage 3 or 4 PDAC who received platinum chemotherapy lived three-times longer than those who received non-platinum chemotherapies.

AIMS
The present one is an observational, molecular based, study, where PDAC patients will follow the usual clinical care paths in the participating units. The main aims are to assess on PDAC specimens EGFR, KRAS, SPARC and BRCA status and to correlate these findings with response to surgery and chemotherapy. Specimens will derive from surgery and/or biopsies, in the settings of adjuvant and neo-adjuvant therapy of resected or borderline-resectable/locally-advanced PDAC patients.

In the present feasibility study we sought to determine:

Target#1=the prevalence of EGFR, KRAS mutations, SPARC overexpression and BRCA1/BRCA2 mutations in a surgical/potentially surgical PDAC patients;

Target#2= the clinical outcome in relationship with the chemotherapy adopted from the oncologist in charge.

METHODS:
Target#1: Molecular profiling of tissue from PDAC patients:

1.1) Implementation of bio-banking of resected tissue from PDAC patients for molecular profiling and ex-vivo drug screening. The bio-banking is already settled at the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) of Meldola (Forlì – Cesena). This laboratory participated in external quality assessment (EQA) projects, adhered to quality control projects sponsored by the Italian Association of Medical Oncology.
1.2) **EGFR and KRAS mutation status assessment.**

1.3) **SPARC over-expression assessment.**

1.4) **BRCA1/BRCA2 mutation status assessment.**

1.5) **Data analysis and validation of the molecular alterations.**

**Target#2: Impact of molecular profile on response to different chemotherapy regimens**

2.1) **Clinical study design.** Observational longitudinal study within the usual standard of cares.

2.2) **Inclusion criteria for the study.** Potential participants are surgically treated PDAC patients and patients deemed having potential resectable PDAC (borderline-resectable) whenever they will respond to neo-adjuvant chemotherapy (locally advanced stage). Further inclusion details will be provided on request.

2.3) **Informed consent and ethics committee approval.** The consent process will fulfill the title 45, Part 46 of the Federal Regulations of the Department of Health and Human Services.

2.4) **Required sample size.** There is no a-priori assumption on the number of subjects that will be enrolled for molecular profiling. A total of 100 patients/tissue samples during 3 years represents a worthwhile end-result.

2.5) **Statistical analyses.** Common statistical approaches will be applied.

**EXPECTED RESULTS**

The possibility to identify KRAS, EGFR, SPARC and BRCA signatures can return the following end-results:

1) Amelioration of the genomic knowledge of PDAC suitable for refinement of chemotherapy adoption based on sensibilities of specific drugs pathways;

2) Increased knowledge of prevalence of mutational status and receptorial expression in PDAC patients

3) Improvement of survival in PDAC patients receiving “desirable chemotherapy”

4) Amelioration of cost-effectiveness of PDAC therapies.
“Desirable chemotherapy” is defined as that which will satisfy the molecular prerequisites of tumor response previously described. That is, it will be “desirable” to adopt Erlotinib in presence of EGFR mutation, nab-paclitaxel in presence of high SPARC expression and platinum-based chemotherapy in presence of BRCA mutations with the final aim to obtain the best achievable survival benefit for patients.

The study fulfills the European Society of Medical Oncology (ESMO) guidelines for the treatment of PDAC.

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<th>DESCRIZIONE DELLE ATTIVITÀ DELL’ASSEGNISTA</th>
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<tr>
<td>(per i <strong>nuovi</strong> assegni: max 400 parole; competenze richieste, scansione temporale della formazione, scansione temporale dell’attività, obiettivi primari e secondari)</td>
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<tr>
<td>(per i <strong>rimossi</strong>: max 600 parole – da integrare con la relazione dell’assegnista; formazione raggiunta, attività effettuata, obiettivi raggiunti/competenze acquisite, formazione ancora da acquisire (se pertinente), scansione temporale dell’attività durante il rinnovo)</td>
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The role of the research fellow will be to identify, within the multidisciplinary paths in the AUSL-Romagna, the potential participants to the study, to explain them aims, methods, risks and benefits, obtaining adequate informed consents. He/she will also provide the collection of samples of pancreatic tissue from the surgical unit involved, up to the bio-bank of IRST.

The necessary required skills of the research fellow are: 1) adequate knowledge of PDAC treatment, with a particular aspect to surgical indications as well as neo-adjuvant approach of borderline resectable patients; 2) good collaboration skills with both the surgical team and the oncologists in charge of the AUSL Romagna who will operate and/or follow the patient with PDAC during chemotherapy; 3) ability of collecting data in a prospective manner, with particular attention to biomarkers’ sequencing data, thus, maintaining good collaboration with IRST of Meldola and coordinating with them the tissue sampling.

During the first year of the research grant, the fellow will built and develop a dedicated workflow for the study development and application, including a dedicated database, adequate contacts with IRST and oncologists. He/she will eventually maintain contacts with the various Hospitals forming the AUSL Romagna to provide completeness of necessary data. At the end of the first year, at least 25 tissue sample will be collected to verify the feasibility of biomarker evaluation and the adopted workflow.

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<th>Scheda attività assistenziale (se prevista)</th>
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<td>ATTIVITÀ / N. ORE SETTIMANA</td>
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<td>18</td>
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**Note:**
- **nuovi**: nuovo assegnista
- **rimossi**: rimesso al termine dell’assegnista

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**ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA**
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AZIENDA SANITARIA PRESSO CUI SI SVOLGERÀ L’ATTIVITÀ

Azienda USL della Romagna sede operativa di Forlì. U.O. Unità operativa di Chirurgia e terapie oncologiche avanzate, Prof. Giorgio Ercolani. Ospedale Morgagni – Pierantoni, Via Carlo Forlanini, 34, 47121 Forlì FC

Si ricorda che, come previsto dagli Accordi sull’impiego nell’attività assistenziale dei Titolari di assegni di ricerca, sottoscritti tra l’Università di Bologna e le Aziende Ospedaliere di riferimento, una volta stipulato il contratto con il vincitore della selezione, il tutor deve consegnare alla Direzione Medica Ospedaliera la relativa modulistica, nella quale andranno riportate le attività qui segnalate.