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## ESMO Clinical Unit Visit Report

**Host institute:**

The Christie Hospital. NHS Foundation Trust

**Fellowship dates:**

27 January 2020– 6 March 2020

**Fellowship title:**

Phase I Clinical Trial Unit Visit



**Fellow:** Landa Magdalena  
Donostia University Hospital

**Mentor:** Natalie Cook  
The Christie Hospital. NHS Foundation Trust, United Kingdom

### ***Introduction and purpose of the Clinical Unit Visit***

The aim of the attachment is to provide an understanding of the structure and function of an experimental cancer medicine unit and the area of molecular profiling.

**Objective 1:** Completion of and understanding basic training requirements for participation in clinical trial activities

1. GCP Training: A mandatory requirement for anyone involved in the conduct of clinical research is Good Clinical Practice (GCP) training. GCP is the ethical and practical standard to which all clinical research is conducted. An online course followed by a multiple choice question exam will be completed at the start of the attachment

**Objective 2:** Clinical Research Observation

1. Dr. Landa Magdalena will observe the daily work of the clinical trial research team: Principal Investigator, lead co-investigator, lead research nurse, lead trial coordinator, lead data manager. She will see all aspects of patient care during the trial journey and it is expected that she will spend 1:1 time with each team member to learn about their roles and requirements from physicians in addition to learning about the role of the clinical trials nurses and administrative staff.
2. Attendance and participation at the team meetings is expected: weekly Patient Evaluation Meeting (evaluate the clinical status of all trial subjects on trial), weekly Patient Allocation Meeting (review trial slots and allocate patients on our waiting list to Experimental Cancer Medicine trials), monthly Protocol Review and Assessment Meeting (evaluate prospective new trials within ECMT and the trial unit), monthly molecular tumour board (see below), monthly risk management (review audit findings and safety issues), monthly ECMT journal club, Town Hall meeting and The Christie grand round.

**Objective 3:** Educational Opportunities

1. MRes in Experimental Cancer Medicine (ECM) lectures: During the attachment there will be taught lectures (as part of a Masters degree in ECM) which Dr. Landa Magdalena may choose



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to attend. This includes a comprehensive introduction into the clinical trial and clinical research portfolio of a Phase 1 unit, pharmacokinetic endpoints in trials, factors influencing the absorption, distribution, metabolism and elimination (ADME) of drugs and information about the the concept of “precision medicine”.

2. Audit: There are a number of ongoing audits where Dr. Landa Magdalena may assist clinical fellows in set-up, data collection and analysis of results.

**Objective 4: Translational Research within the TARGET Precision Medicine Trial**

This is the main project of the attachment. The Tumour Characterisation to Guide Experimental Targeted Therapy (TARGET) protocol aims to collect historical and fresh tumour tissue and blood samples from patients with advanced solid cancers who have been referred to ECMT. The principle objective is to establish a mechanism to develop and offer personalised cancer medicine to patients with advanced solid cancer based on molecular characteristics of tumour tissue and/or blood borne biomarkers (e.g. circulating tumour DNA (ctDNA)). The protocol was approved in January 2015 and has since enrolled almost 300 patients. By January 2020 it is anticipated that this study will have expanded further, in alignment with wider molecular profiling within The Christie. In addition to this, collection of clinical data regarding these patients is ongoing.

Dr. Landa Magdalena has an interest in hepatobiliary (HPB) tumours and this project will involve investigation of genomic and clinical characteristics of patients with HPB tumours enrolled onto clinical trials.

The main structure will include the following:

- To perform a literature review around genomic and clinical characteristics of patients with HPB tumours.
- To acquire basic understanding of the targeted sequencing on tumours, circulating biomarkers (ctDNA and/or circulating tumour cells) and germline DNA on a panel of genes relevant to cancer
- To attend molecular tumour board meetings and to understand how we interpret genomic results and identify potentially actionable clinically relevant abnormalities found during sequencing
- To help collect demographic data, clinical data related to patients' cancer, previous and current therapies, response to treatment, family history of cancer and survival related data
- To analyse, interpret and summarise the genomic and clinical characteristics and the treatment outcomes of patients with HPB malignancies treated within clinical trials.

There will also be an opportunity to spend time in the laboratories involved with the processing and analysis of the TARGET samples. We aim to provide 1 week of laboratory experience during this observership.

At the end of this objective a project report will be written summarising the role, objectives accomplished, preliminary results and outcomes that may have arisen as a result of Dr Landa Magdalena's involvement with the trial.

***Six-week timetable***

Activities in each weekly timetable will be described below

Week 1 (27th – 31st January)



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	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ID Budget collection	Training to access WCP	ECMT Trials Clinic	Research	ECMT Trials Clinic
					PAM
<b>PM</b>	Visit to hospital library, first contact with staff...	Research	ECMT Screening clinic	ECMT New patient clinic	ECMT Meeting: MR projects presentation

Week 2 (3<sup>rd</sup> – 7<sup>th</sup> February)

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ECMT Trials Clinics	Completion of GCP training	ECMT Trials Clinic	Research: project	ECMT Trials Clinic
	PEM	Attendance to World Cancer Day lectures			PAM
<b>PM</b>	Starting GCP training	Completion of GCP training	ECMT Screening clinic	ECMT New patient clinic	Research

Week 3 (10<sup>th</sup> – 14<sup>th</sup> February)

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ECMT Trials Clinics	Research: project	ECMT Trials Clinic	Research: project	ECMT Trials Clinic
	Supervisor meeting PEM				PAM Christie Grand Round
<b>PM</b>	Laboratory training	Research: project	ECMT Screening clinic	ECMT New patient clinic	Research

Week 4 (17<sup>th</sup> – 21<sup>st</sup> February)

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ECMT Trials Clinics	Research: project	ECMT Trials Clinic	Research: project	ECMT Trials Clinic
	PEM				PAM PRAM
<b>PM</b>	Training with: - Project development manager - Data manager - Translational Research Facilitator	Research: project	ECMT Screening clinic  Fellow Seminar: Abstract Writing	ECMT New patient clinic	Research



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Week 5 (24<sup>th</sup> – 28<sup>th</sup> February)

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ECMT Trials Clinics	Research: project	MRes Lectures: Experimental Medicine (Cancer)	Research: project	ECMT Trials Clinic MTB
	PEM	Supervisor meeting			PAM RMM
<b>PM</b>	Research: Project	Research: project	MRes Lectures: Experimental Medicine (Cancer)	MRes Lectures: Experimental Medicine (Cancer)	Research

Week 6 (2<sup>nd</sup> – 6<sup>th</sup> March)

	Monday	Tuesday	Wednesday	Thursday	Friday
<b>AM</b>	ECMT Trials Clinics	Research: project Supervisor meeting	MRes Lectures: Experimental Medicine (Cancer)	Research: project	ECMT Trials Clinic
	PEM				PAM; Project presentation
<b>PM</b>	Training: - dECMT - Research nurse: Observing patient treatment	Research: project	MRes Lectures: Experimental Medicine (Cancer)	MRes Lectures: Experimental Medicine (Cancer) Supervisor meeting	ECMT Meeting: - Developed project presentation to the ECMT.

**Activity description:**

**\*\*Preliminary training:**

During my first weeks I made some training related to the Observation of Clinical Trial Patients as well as to the use of the “Christie Clinical Web Portal” which is the informatic programme where all the patient records are stored:

- Good Clinical Practice (GCP) training: Online course of about 6 hours. I got a certificate.
- Christie Clinical Web Portal access training: Online course.

**1 .- Clinics**

- **ECMT Trials Clinic:** Is the daily clinic in which ECMT Fellows and Consultants attend and evaluate patients that are currently on treatment in an Early Phase Clinical Trial. This clinic includes patient interview, physical examination, vital signs assessment and completion of patient Trial-Workbook (description of current global situation of the patients, new symptoms detailing, review of co-medications, urine and blood analysis acknowledgment). I assisted to this clinic always as Observer and I had the opportunity to see patients with different type of cancers and enrolled in different trials.

- **Screening Clinic:** This clinic takes place only once a week (on Wednesday). It is a specific clinic for



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patients that has already consent for a trial and need to be screened by the investigators in order to confirm that they meet all the eligibility criteria (inclusion/exclusion). For that, the investigator asks the patient a list of questions about previous diseases, cancer history treatment, recent surgeries, co-medications, allergies and many other stuffs. If the investigator detects something that could be an exclusion criteria, this should be confirmed with the protocol, and, if necessary, sorted out during the screening period window.

- New Patient Clinic: This clinic takes place twice a week. I assisted on Thursday afternoon. This is the clinic where the investigators meet new patients referred to the ECMT both from different teams of The Christie Hospital or from other hospital around Manchester.

Before seeing the patients, all the new cases are discussed twice:

- First on Friday Patient Allocation Meeting (PAM), where the fellows present each case (sex, age, previous illnesses, cancer and oncological treatment history) and propose potential early phase trials in which the patient could be enrolled.
- Secondly, each patient is discussed between fellows and consultants on New Patient Clinic just before been attended, in order to update once again potential trials in which the patient could be included.

During this first clinic, the fellow always informs the patient about the meaning of an Early Phase Trial, the aims (dose and safety assessment) and expectations, as well as the potential risks.

Once the patient has been attended, the fellow tell the Consultant about the patient (ECOG, current symptoms, potential problems to be included in a trial, fitness...) and finally they visit the patient again together to explain their decision and future steps to go through the settled plan.

The patient will also be presented again on the next Friday PAM to inform the rest of the ECMT about the taken decision or discuss different options in case there are doubts.

## 2 - Meetings

### - PEM: Patient Evolution Meeting

This meeting takes place every Monday morning. During the meeting the ECMT go through every trial and to review all the patients that are currently being treated into each trial: general situation, toxicities, number of cycles, response assessment...

### - PAM: Patient Allocation Meeting

This is the weekly meeting to present new patients and discuss which trial they could be suitable for. The meeting has different parts:

- The ECMT (Consultants, Fellows and Research Nurses) go through an updated spread sheet where all the trials are included, with potential patients for each (recently sent "Patient Information Sheets", recently consented patients...). They discuss how the inclusion process is going and future arrangements of the patient (screening clinic, treatment starting date...)
- Weekly revision of disponible slots for each trial.
- Discussion about patients that has been seen in New Patients Clinics during the week. As the patient has been already visited, they can explain how de performance status and general situation of the patients is, and if any current issue has been newly identified during de new patient clinic visit. They write down in which trial the patient would be included, or for which will be pre-screened (genetic profiling test). In case they consider patient is not suitable because of performance status or just because standard of care is a better option than trial enrollment, they write down and patient will be informed.
- Discussion about new patients that will be seen at NEXT WEEK New Patients Clinics. They just present what they know according to the referral letter. They discuss about potential trials in which the patient could be enrolled (depending on the number of previous lines of treatment,



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if there is any tumor site available for new biopsy in case it would be needed...) and write it down on the "New Patient Sheet" for New Patient Clinics of the next week.

- PRAM: Protocol Review Meeting

This is a monthly meeting in which all the ECMT review the protocols of potential new trials that are going to be included in their portfolio. The protocol summary is presented by one of the Fellows and research nurses, as well as pharmacy team present their opinion and concerns.

- MTB: Molecular Tumour Board

This is a monthly meeting. Is a molecular tumour board specifically addressed to discuss the genomic profiling results of the patients enrolled in the TARGET trial (Tumour characterisation to Guide Experimental Targeted therapy). Staff from genetic laboratory also participate in the meeting.

During de MTB they go through each patient whose results has already been received to discuss those results and decide if there could be any matching trial.

- RRM: Risk Management Meeting

This is a monthly meeting for all the ECMT meet in which they share current problems or risk situations that have been observed, to discuss about them and decide which is the best way to manage with them and improve the team functioning.

- Other ECMT Meetings

I also assisted to a Friday meeting in which three people of the team that have participated in the Master of Research (MR) in Experimental Cancer Medicine presented their MR project.

3.- Educational lectures

During my attachment I assisted to the following educational lectures.

World Cancer Day lectures: The 4<sup>th</sup> February I could assist to some lectures that took place due to the World Cancer Day at the Manchester Cancer Research Center.

- Fellow Seminar:

During my attachment I assisted to a Fellow Seminar about "Abstract Writing", given by Dr. Angela Lamarca.

- Master's in research (MRes) Lectures in Experimental Cancer Medicine

During my attachment, I was also invited to attend to some of the MRes lectures.

They took the place during my last two weeks. Those are the lectures to which I attend:

- The phases of clinical drug development (Dr. Donna Graham)
- First in human and first in combination studies – I (Dr. Natalie Cook)
- Determination of pharmacokinetics in early clinical development (Dr. Natalie Cook)
- First in human and first in combination studies – II (Dr. Thomas Jaki)
- Precision Medicine 1 (Dr. Matt Krebs)
- Precision Medicine 2 (Dr. Matt Krebs)
- Phase O (Non-CTIMP) Studies – I (Jane Rogan)
- Additional considerations in Immuno-oncology trials (Dr. Fiona Thistlethwaite)
- Introduction to adoptive cell therapies (Dr. Fiona Thistlethwaite)
- Determination of tolerability in early clinical development (Dr. Louise Carter)
- Interpretation of Tolerability Data from an Ascending Dose Phase I Trial in Cancer Patients Workshop (Dr. Louise Carter)
- First in human and First in combination III-Dose escalation Workshop (Dr. Louise Carter)
- Regulatory clinical pharmacology studies and the impact on the design of trials (Dr. Fiona Thistlethwaite)
- Putting it all together in a clinical trial – Protocol Review and assessment (Dr. Louise Carter)
- Determination of efficacy in early clinical development 1 (Dr. Matt Krebs)
- Determination of efficacy in early clinical development 2 (Ciara O'Brien)



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#### 4.- Specific trainings

During my attachment, on Monday afternoons, I have the chance to spend some time with different staff of the team, to understand which is their role and how they develop their daily work.

- Laboratory training
- Project development manager activity observation
- Data manager activity observation
- Translational Research Facilitator Observation
- dECMT Observation
- Research Nurse activity Observation

#### 5.- Research Project

During my attachment Dr. Natalie Cook encouraged me to develop a Translational Research Project within the TARGET Precision Medicine Trial (See details above on Objective 4 of "**Introduction and purpose of the Clinical Unit Visit**").

As I am specially interested in pancreato-biliary cancer patients, she gave me the opportunity of reviewing data from patients with this type of cancer that have been enrolled into the TARGET trial, as well as the data from the Foundation Medicine Test performed to patients as pre-screening for another two trials (FOUNDATION EVAL and STARTRK trial).

The aim of the work was to describe the utility of ctDNA based genomic profiling in those patients, regarding both to the concordance with solid tumour genomic profiling and to the detection of potentially actionable mutations.

During the 6 weeks of attachment, specially on my "Research Days", I collected the data of the patients from the "Christie Clinical Web Portal" and I analysed the results regarding not only the concordance between ctDNA and solid tumour genomic profiling but also the detection of potentially actionable mutations, MTB decision and matching of the patients to early phase trials.

Finally, my last day, I made a presentation for all the ECMT explaining the project and the results we have obtained. And, moreover, I will try to send those results as a potential abstract to a UK Conference during 2020.

#### **Expected transferable skills on return to home institute**

Organization and functioning of a Experimental Cancer Medicine Team: Even if there is not an Experimental Cancer Medicine Unit in my home institution, I absolutely think that the Christie ECMT is a really well organized team. They can manage with many different kinds of meeting, as well as attend clinics and share work between different staff members (doctors, nurses, data managers...). Observing this daily work have been really enriching for me.

Definition and management of an Early Phase Clinical Trial: I have learnt about what is an Early Phase Clinical Trial and which are their main objectives (safety, tolerability). I think that I would be able to transfer the way people in the ECMT inform patients about the functioning, aims and expectancies of a Phase I trial, in order to let the patient know that the response options are not very high and that being enrolled in one of those trials implies such a rigorous control, with narrow evaluation of potential toxicities and recurrent visits to the hospital, especially during the first 1-2 months. They also inform the patient about the possible indication of overnight staying due to the obtention of pharmacokinetic (PK) samples.

It has also been really useful to see how the Fellows and Consultants explain to the patients the rationale of each trial and read with them the "Patient Information Sheet" and Informed Consent. They always give patients time to think about it and decide if they agree with all the sections of the trial.

Screening Clinics also have given me the opportunity of learning about how to interrogate the patients about all their previous conditions and treatments, in order to ensure that they are eligible. I have also noticed the importance of confirming that all the patient's co-medications are compatible with the study drug.



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Managing with Early Phase Clinical Trial Patients: Another skill that I think could be transferable to my home institute is the stuff that ECMT use to manage with all their trials. During the observation on clinics as well as with data managers, I have seen them completing the “Work-Books” of the patients, which are personalized “note- books” for each trial and for each patient, in which they progressively include the corresponding documents for each scheduled or unscheduled visit. Thus, they always know which information is needed in each visit according to the Study Schedule (bloods, urine, ECG, physical examination...) and it also makes easier for the data managers the completion of all the data required by the trial sponsor.

Clinical trial design and protocol understanding: Due to the continue contact with trial patients and trial protocol reviewing in daily work, I have acquired much more understanding about the contain of a Clinical Trial Protocol. Now I better know which are the most important aspects and key points that I must look to get information about the trial rational, design, recruitment issues and practical aspects regarding the event schedule. For this aim, it has also been very useful the attendance to MRes lectures, in which I have better understood how the process of drug development is, which are the main objectives of trials depending on their phase and the most common questions that can arise in daily practice.

Personalized Oncology and Genomic Profiling: Thanks to the attendance to weekly PEM and PAM, as well as to a monthly MTB and the MRes lectures, I have been able to better understand the information that could be obtained from genomic profiling tests and the way it could be matched to specific clinical trials. At the same time, due to the research project I have developed, I have deepened on the contain and meaning of different molecular profiling panels, which will be useful for my future regarding patients’ diagnosis and treatment.

Importance of research time: I would also like to emphasize the benefit of having some days during the week for research work. This time has been absolutely useful to develop my research project during the attachment and I think is also something that I could try to transfer to my home institution, where we don’t have specific time for research during our daily timetable.

### ***Conclusion and acknowledgements***

At the end of this attachment I can say that it completely was worth it. During those 6 weeks I have been able to get a very complete idea about how an Early Phase Clinical Trial Unit works, as well as about how Medical Oncology in the UK works.

On the one hand, I have achieved such a deep knowledge about how patients enrolled in Clinical Trials, specifically in Early Phase Trials, should be treated and how their complications and treatment related toxicities should be managed.

On the other hand, in an era of personalize medicine, it has been so valuable to see how this team deal with molecular and genomic profiling results from patients, in order to match them to the best trial possible. However, I also saw them discussing suitability of patients to be included in a trial because of their clinical deterioration problems or regarding to an available standard treatment option that could improve patient’s survival more than an experimental drug.

I would like to acknowledge all the ECMT: team managers who helped me with the initial administrative issues, data managers, project managers, research nurses...and many other people. They have all been so kind with me and have help me during my trainings and with my research project. Moreover, I would like to thank to all the Fellows of the team, as well as to the Consultants, for their kind explanations and their availability to let me observe patients with them.

Finally, I would like to specially acknowledge Dr. Natalie Cook, who accepted me for this Observership and encouraged me to ask for this grant. Thanks to her dedication I have been able to accomplish with all the initially stablished objectives of the attachment, including the development of a small research project that has been really interesting for my training as Medical Oncologist.





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