

ESMO Translational Research Fellowship
(January 2013 – January 2015)

“Feasibility of the evaluation of proliferation and nucleoside transport using FLT-PET imaging in advanced pancreatic cancer patients”

Angela Lamarca

FINAL REPORT

Host Institute: The Christie NHS Foundation Trust, Manchester, United Kingdom

Mentor: Juan W. Valle

Project title: Feasibility of the evaluation of proliferation and nucleoside transport using FLT-PET imaging in advanced pancreatic cancer patients

Home Institute: Hospital Universitario La Paz, Madrid, Spain

Rationale and Aim

In this study, we hypothesised, that gemcitabine-based chemotherapy can induce a decrease in tumour [18F]FLT uptake after a single cycle of treatment which exceeds test-retest variability. We are assessing the magnitude and variability of such changes across pancreatic tumours. We are evaluating if tumour [18F]FLT uptake prior to therapy is related to hENT1 expression. Our results will enhance understanding of pathophysiological (i.e. proliferation) changes following treatment and may be used to guide future clinical trial work in relation to patient outcome.

Study objectives

Primary objective:

-To assess feasibility of imaging proliferation and nucleoside transport using FLT-PET in patients with locally advanced or metastatic pancreatic cancer

Secondary objectives:

-To assess the test-retest variability of FLT-PET imaging

-To assess the relationship between pancreatic tumour proliferation/nucleoside transport using FLT-PET and hENT1 expression.

Experimental design

Eligibility criteria

Inclusion criteria

-Patients able to give informed consent.

-Adults (>18 years) with clinical diagnosis of locally advanced, or metastatic pancreatic cancer who are scheduled to have gemcitabine-based chemotherapy with palliative intent.

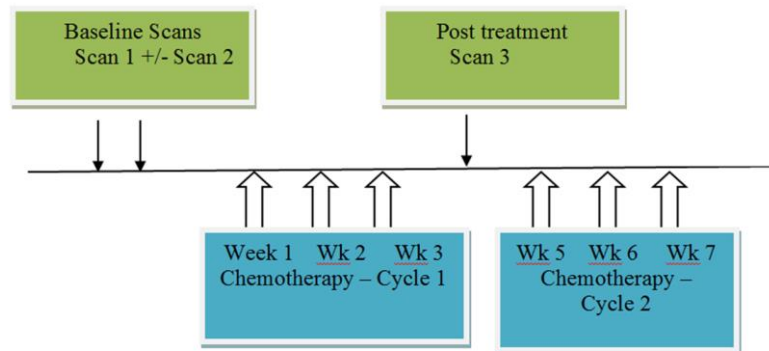
-At least one potentially PET evaluable lesion (about 2cm or more on CT/MRI): This may be locally-advanced pancreatic tumour or metastatic lesion (usually liver, lung, lymph node). Bone metastases are not considered evaluable by FLT PET due to high physiological uptake in normal bone.

- WHO/ ECOG performance status (PS) 0-2
- Able to lie comfortably on back for up to 65 minutes at a time.

Exclusion criteria

- Pregnant or breast feeding females (if of child bearing potential, pregnancy will be excluded by WMIC standard operating procedures).
- Known allergy to IV contrast agent.
- Other uncontrolled intercurrent illness including, but not limited to, any of the following:
 - Ongoing or active infection
 - Other conditions including psychiatric illness/social situations that in the view of the investigator would limit compliance with study requirements.

Study design



Study procedure

- Chemotherapy administration: Administration at the Christie hospital of a gemcitabine-based chemotherapy regimen (gemcitabine monotherapy, gemcitabine-capecitabine, others).
- Imaging procedures: All PET scans are performed as outpatient procedures at the University of Manchester Wolfson Molecular Imaging Centre (WMIC). The target dose of [18F]FLT administered is 330MBq on each occasion; venous blood samples are taken throughout the duration of the [18F]FLT scans for measurement of total plasma and whole blood radioactivity and for radiolabelled metabolites. Tissue uptake parameters including area under the time-activity curve (AUC) and the SUV are being calculated.
- hENT1 analysis will be performed once all patients have been enrolled using a commercially available Immunohistochemistry assay (Clovis Oncology) following the standard operating procedures described with the product.

Results, Conclusions and Future Perspectives

I joined Professor Valle’s team at The Christie NHS Foundation Trust in January 2013. The aim of my fellowship was to be actively involved in this translational project (“Feasibility of the evaluation of proliferation and nucleoside transport using FLT-PET imaging in advanced pancreatic cancer patients”) while I gained further clinical experience (special interest in clinical and translational research) in HPB (hepto-pancreato-biliary) cancers and NETs (neuroendocrine tumours) in a high-volume specialized HPB-NET unit.

During the two years of my fellowship, I was involved in the identification (through the multidisciplinary teams [MDTs] and new patients attending the clinic), recruitment, consent, scanning and interpretation of imaging results for patients in this study. The first six months of my fellowship were employed in obtaining all the ethical approvals for running the FLT study. This study involved the collaboration of multiple centres in Manchester requiring intense co-ordination between them:

- The weekly HPB MDT (including pathologists, radiologists, HPB surgeons and oncologists) was undertaken in North Manchester General Hospital. I attended this meeting every week. This was the first step in patient identification, before referral to The Christie for further chemotherapy treatment. At this point potentially suitable patients were identified for the FLT-PET trial; verbal and written information was provided and screening assessments were performed in consenting patients. All members of the MDT have been involved in this translational project design and development. The pathology department at Central Manchester Foundation Trust (previously North Manchester General Hospital prior to surgical reconfiguration on 01.10.2014) will be the responsible for the immuno-histochemical analysis of the tumour samples once the recruitment has been completed.
- The Christie NHS Foundation Trust (<http://www.christie.nhs.uk/>), has been my host centre. The Christie is the reference centre for Greater Manchester and Cheshire Cancer Network, including a population of around 3.2 million. Through our HPB clinic, I identified and approached eligible patients. After giving written information I followed-up all patients with a phone call, arranging for a further appointment for consent for patients interested in the study. Thirty-percent of patients who were given information consented to participate in the study (see below for summary of the reasons).
- The Wolfson Molecular Imaging Centre (WMIC), Manchester University (<http://www.bii.manchester.ac.uk/facilities/findus/WMIC/>) is specialized in imaging research. All the FLT-PET scans were performed in the WMIC, where the FLT was produced in-house. All the Pharmacokinetic studies of the blood samples performed during the scanning was performed in the WMIC laboratory.

After completing all regulatory approval, the trial opened to recruitment in June 2013. Due to the design of the study and the target population (locally advanced or metastatic pancreatic adenocarcinoma), the recruitment was expected to be challenging. We planned to patients for an FLT-PET study prior to and 1-month after starting gemcitabine-based chemotherapy. Therefore, eligible patients needed to be fit enough to lie down for more than one hour (the duration of the research scan), which is extremely difficult for patients with advanced pancreatic cancer (due to the co-existence of disease-related abdominal/back pain).

Due to the reasons above (as expected) the recruitment in this study has been slow with many patients declining the study and several drop-outs ([Table 1](#) and [Figure 1](#) below show the recruitment status and progress during the last year-and-a-half of recruitment).

In December 2013, six months after patient recruitment started, we applied for the second year prolongation of the ESMO Translational Fellowship: at that point, the recruitment of this study was around 25% of the target. Having the opportunity of completing a second year of fellowship gave me the chance to continue the recruitment of the study and to continue my personal development at The Christie.

Since the study opened we have given an information sheet out to 46 potential patients. Fourteen patients have consented to the study (unfortunately, three of them were never scanned due to fitness impairment before starting chemotherapy). Up to 22nd December 2014, 20 FLT studies have been completed. The most frequent reasons for declining to take part in the study were the extra visits needed for the protocol-driven imaging. Uncontrolled abdominal pain (which is one of the most common symptoms in patients with pancreatic cancer) was the second main reason, as detailed above.

Therefore, this translational project recruitment is still ongoing (55% of recruitment has been reached by November 2014 and two further patients have been consented since then). Even though FLT-PET scan are continuously reviewed (See [Figure 2](#) for example of obtained images) no final results will be available until the recruitment is completed.

Finally, and although the ESMO Translational Fellowship period has now been completed, I will extend my attachment at The Christie and I will continue being involved in this project until recruitment is completed which is expected for June 2015. This will subsequently lead to presentations and publication in a peer-reviewed journal; the ESMO Fellowship will be fully acknowledged.

Total patients approached		46
	first	10/07/2013
	last	04/12/2014
Total patients consented		14
	first	11/07/2013
	last	11/12/2014
Total patients scanned		11
Patients consented but not scanned		3
	Patient withdraw	1
	Patient unfit for performing the scan	2
Total scans performed		20
	first	17/07/2013
	last	17/12/2014
Total evaluable scans		18
Total of not evaluable scans		2
	Due to protocol deviation	1
	Due to patients movement, bad quality imaging	1
Patients pending further scanning		1
	Baseline scan performed, reassessment scan pending	1
Total of patients evaluable		5
	For baseline scans (patient with two evaluable baseline scan) (target: 4)	2
	For reassessment scan (Patient with evaluable one baseline and one follow-up scan) (target: 10)	5

Tabel 1: summary of the patients approached and consented. The recruitment of the study is now over 50%.

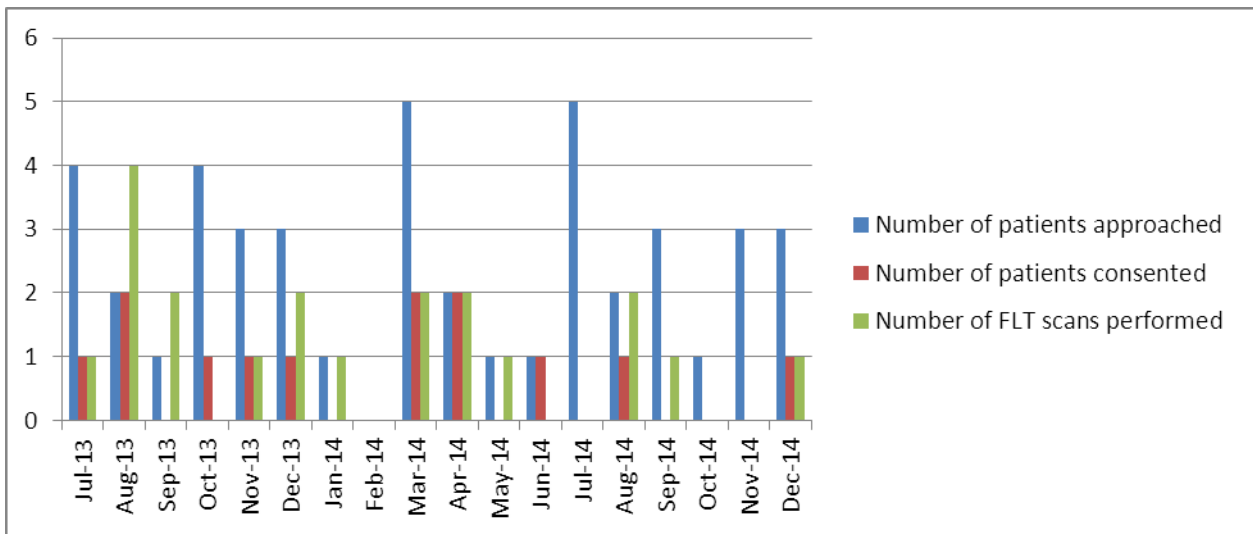


Figure 1: This figure shows the number of patients approached and consented per months since the recruitment was started. As it is shown the rate of patients declining to take part in the study is around 70%, this has been one of the main issues in patient's recruitment.

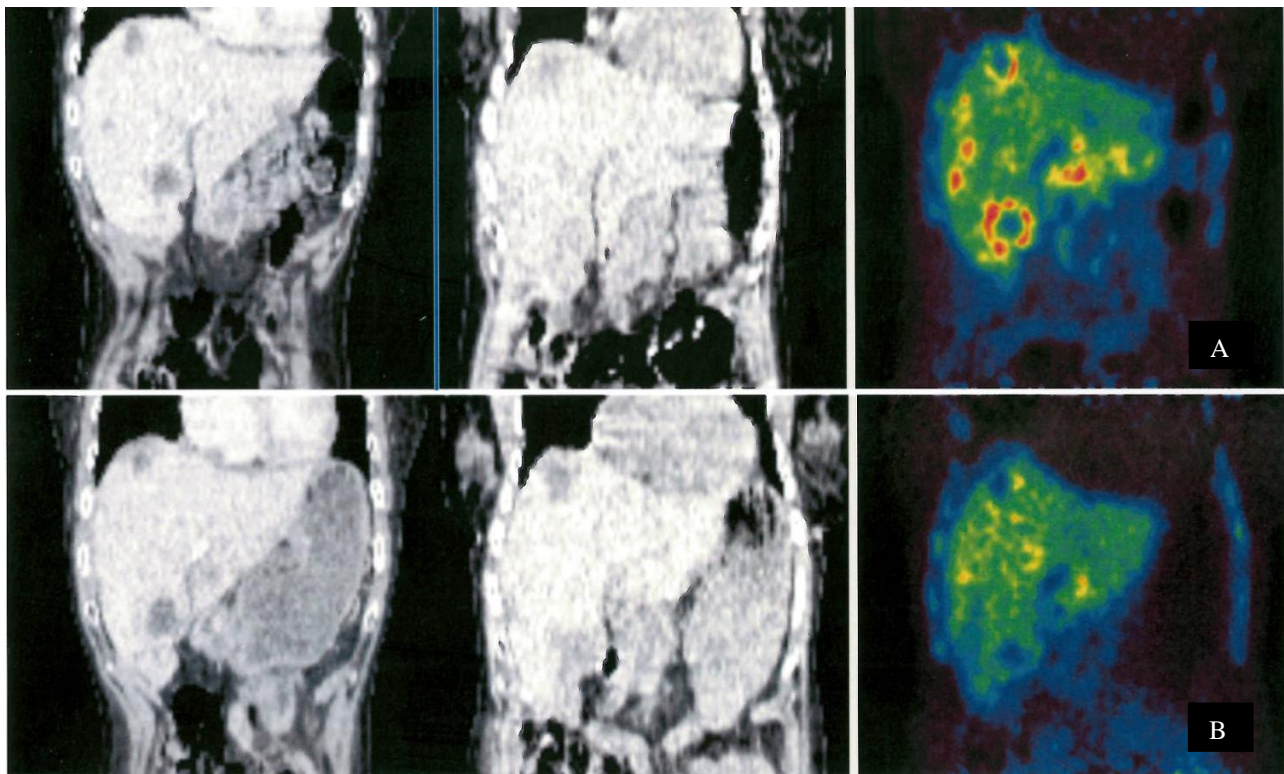


Figure 2: A: Baseline CT, contrast CT and FLT PET; B: CT, contrast CT and FLT PET after 1 month of chemotherapy. FLT uptake decreases after one month of treatment with gemcitabine-based chemotherapy. Correlation with response is ongoing.

List of Publications Resulting from the Translational Research Project “Feasibility of the evaluation of proliferation and nucleoside transport using FLT-PET imaging in advanced pancreatic cancer patients” since January 2013.

Because the translational project recruitment is ongoing, no final results are available from this particular project yet. However, the study design was accepted for poster presentation in the American Society of Clinical Oncology Annual Meeting (ASCO) 2013 in the trial in progress category.

***Angela Lamarca**, Prakash Manoharan, Marie-Claude Asselin, Ioannis Trigonis, Pamela Hindmarsh, Sarah Wood, Ray McMahon, Madhu Rao, Richard Hubner, Tamal Mahbubunnabi, Derek O'Reilly, Rahul Deshpande, Juan W. Valle, Azeem Saleem. Pilot, proof-of-concept studies for determining the feasibility of the use of FLT-PET in patients with pancreatic adenocarcinoma. ASCO 2013, TPS4146 (trials in progress poster).

Moreover, a review paper addressing the role of FLT-PET scanning in pancreatic adenocarcinoma is currently in development and is expected to be submitted during Q1 2015.

List of Publications/Presentations Resulting from other projects(other than the FLT-PET study)in which I have been involved in the Host Centre since January 2013

I have combined my activity in the FLT-PET study with other clinical and translational research activity. This has produced a number of publications and conference presentations, detailed below:

Publications:

Lamarca A, Hubner RA, Ryder WD, Valle JW Reply to the letter to the editor 'Second-line chemotherapy in advanced biliary cancer: the present now will later be past' by Vivaldi et al..Ann Oncol. 2014 Aug 19. pii: mdu382. [Epub ahead of print]

Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol. 2014 Apr 25. pii: mdu162. [Epub ahead of print]

Omar Abdel-Rahman, **Angela Lamarca**, Juan Valle, Richard Hubner. Somatostatin receptor expression in hepatocellular carcinoma (HCC); prognostic and therapeutic considerations. Endocrine-Related Cancer, Endocr Relat Cancer. 2014 Dec;21(6):R485-R493. Epub 2014 Oct 21.

Angela Lamarca, Juan W Valle. Should patients with resected bile duct cancer receive an adjuvant treatment? Journal of OncoPathology, in press

A Lamarca, R Hubner, J Valle. Looking beyond chemotherapy in patients with advanced, well-differentiated, pancreatic neuroendocrine tumours. The Journal of OncoPathology, in press, September 2013.

Book Chapters:

Angela Lamarca, Jorge Barriuso, Juan W Valle. Cholangiocarcinoma; Chapter title: Targeted therapies; In press

A Lamarca, J Valle. Neuroendocrine tumours. Challenging Concepts in Oncology. In press. August 2013, Book chapter, Oxford University Press.

Presentations in International Conferences:

Daisuke Nonaka, **Angela Lamarca**, Paul Fulford, Juan Valle and Bipasha Chakrabarty. Clinico-Pathologic Study of Goblet Cell Carcinoid of the Appendix. USCAP Conference 2015. Abstract confirmation #1207

Ms Lynne McCallum, **Dr Angela Lamarca** and Professor Juan Valle ESMO 2014: Poster presentation: Pancreatic Malignancy and Nutrition: a study of clinical practice.

Angela Lamarca, Daniel Palmer, Harpreet Wasan, W David Ryder, Linda Davies, Helen Flight, Jane Rogan, Richard Hubner, John Bridgewater, Juan W Valle. ESMO 2014: Poster presentation: ABC-06: A randomised phase III, multi-centre, open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy for patients with locally advanced / metastatic biliary tract cancers (ABC) previously treated with cisplatin / gemcitabine chemotherapy.

Angela Lamarca, Richard A Hubner, Was Mansoor, Juan W Valle. ENETS 2014: Poster presentation: Chemotherapy for Advanced Neuroendocrine Tumours (NETs): Patient Selection Should be Independent of Primary Tumour Site.

Angela Lamarca, Sarah Benafif, John Bridgewater, Paul Ross, Juan W Valle. Efficacy and safety of cisplatin and gemcitabine (CG) chemotherapy for advanced biliary tract cancer (ABC) in jaundiced patients (pts). ASCO GI 2014, Submitted September 2013. Abstract #122648

Presentations in National (United Kingdom) Conferences:

Angela Lamarca, Cristina Lopez Escola, Bipasha Chakrabarty, Richard Huber, Daisuke Nonaka, Paul Fulford, Juan Valle. Goblet cell carcinoid (GCC) tumours from the appendix: lessons from a single centre experience. UKINETS 2014, poster presentation (P27).

Lynne McCallum, **Angela Lamarca**, Juan W Valle. Pancreatic Malignancy and Nutrition: the patient's perspective. UKINETS 2014, poster presentation (P31).

Lynne McCallum, Angela Lamarca, Juan W Valle. Pancreatic Malignancy and Nutrition: A study of clinical practice. UKINETS 2014, poster presentation (P32).

A Lamarca, R Hubner, J Valle. "Use of second-line chemotherapy for patients with advanced biliary tract cancer (ABC): A systematic review of the literature". NCRI 2013, poster 67.

Judith King, et al (including **A Lamarca**). Outcomes for UK patients with advanced HCC. NCRI 2013, poster 142.

Angela Lamarca, Was Mansoor, Richard A Hubner, Juan W Valle. Responsiveness to chemotherapy is independent of primary tumour site in well differentiated neuroendocrine tumours (NETs). UKINETS 2013, Abstract #0023.

Awards:

- ✓ ECCO-ESMO 2013 Travel Grant Award
- ✓ UKINETS 2013 Travel Grant Award
- ✓ ENETS 2014 Travel Grant Award
- ✓ FLIMS Workshop Grant 2014
- ✓ ESMO 2014 Travel Grant Award
- ✓ UKINETS 2014 Travel Grant Award

List of Publications/Presentations Resulting from the Ongoing Collaboration with my Home Centre Since January 2013

During these 2 years I also continued to be in touch with my home centre in Spain (La Paz University Hospital), and have been involved in some collaborative works. Some publications and congress communications have resulted from this ongoing collaboration.

Publications:

Lamarca A, Feliu J. Pancreatic biomarkers: could they be the answer? World J Gastroenterol. 2014 Jun 28;20(24):7819-29. doi: 10.3748/wjg.v20.i24.7819.

Molina R*, **Lamarca A***, Martínez-Amores B, Gutiérrez A, Blázquez A, López A, Granell J, Alvarez-Mon M. Perioperative chemotherapy for resectable gastroesophageal cancer: A single-center experience. Eur J Surg Oncol. 2013 Aug;39(8):814-22. doi: 10.1016/j.ejso.2013.05.003. Epub 2013 Jun 5. *Both authors contributed equally to this work.

Angela Lamarca, Enrique Espinosa, Jorge Barriuso, Jaime Feliu. Biliary tract tumors: past, present and future. Chinese-Germ Journal of Clinical Oncology. January 2013 (DOI 10.1007/s10330-012-0996-7).

Book Chapters:

Angela Lamarca. Valoración del daño corporal [Work medicine and Physical Injury Evaluation]; Chapter title: Principios generales de la oncología [General principles in oncology]; ISBN 978-84-458-2499-3

Angela Lamarca. Cardiac Angiosarcoma; Chapter title: Rare Diseases, diagnoses, challenges and developing treatments; ISBN 978-1-62948-525-6

Presentations in International Conferences:

Lamarca A, Molina R, Martínez-Amores B, Gutiérrez A, Blázquez A, López A, Granell J, Alvarez-Mon M. Routine use of perioperative chemotherapy for resectable gastroesophageal cancer. WORLD GASTROINTESTINAL CANCER CONGRESS 2013, Poster 274.

Angela Lamarca, Marta Mendiola, Elsa Bernal, Victoria Heredia, Ester Díaz, María Miguel, Emilio Burgos, Jaime Feliu, Jorge Barriuso. Study of the expression of connective tissue growth factor (CTGF) and hypoxia-inducible-factor (HIF) in hepatocellular carcinoma (HCC). ECCO-ESMO 2013. Abstract 2644 (P472) (The first author won a travel fellowship to attend this congress)

Presentations in National (Spain) Conferences:

Elsa Bernal, Marta Mendiola, Laura G. PASTRIAN, Jaime Martínez, Cristina Alvarez, **Angela Lamarca**, Jose Tomas Castell, Emilio Burgos, Jaime Feliu, Jorge Barriuso SEOM (Spanish Society of Medical Oncology) 2014: Oral presentation: Molecular prognostic subgroups in gastro-entero-pancreatic neuroendocrine tumours [Pronostico de diferentes subgrupos moleculares de tumores neuroendocrinos pancreaticos].

Ángela Santiago, **Ángela Lamarca**, Eugenia García Fernández, María Miguel, Elsa Bernal, Laura Guerra, Victoria Heredia, Emilio Burgos, Marta Mendiola, Jaime Feliu. SEOM (Spanish Society of Medical Oncology) 2014: Poster presentation: Resected pancreatic adenocarcinoma: retrospective analysis looking for prognostic and predictive factors or relapse [Adenocarcinoma de páncreas (AdP) resecaados; análisis retrospectivo de la experiencia de un centro en busca de factores pronósticos y predictivos de recidiva].

Angela Lamarca, Marta Mendiola, Elsa Bernal, Victoria Heredia, Ester Díaz, María Miguel, Emilio Burgos, Jaime Feliu, Jorge Barriuso. Evaluación de la concordancia entre diferentes anticuerpos frente a HIF1 α y HIF2 α en hepatocarcinomas [Study of the expression of HIF1 α y HIF2 α in HCC: analysis of the concordance between two different antibodies]. SEOM 2013; poster number 267. (This poster won the prize to the “Best presented poster 2013”).

E. Bernal, M. Mendiola, A. Custodio, C. Álvarez, **A. Lamarca**, B. Jiménez, J.T. Castell, E. Burgos, J. Feliu, J. Barriuso. Estudio de la expresión de CTGF en tumores neuroendocrinos intestinales [CTGF expresión in intestinal neuroendocrine tumours]. SEOM 2013, poster 384

Awards:

- ✓ SEOM 2013 Best Poster Award

Selection of Courses & Workshops Attended During the Fellowship

During this two years I have attended the following Courses and Workshops:

- ESMO 2014, Sept 2014: poster presentation
- ECCO-AACR-EORTC-ESMO Workshop: Methods in Clinical Cancer Research (certificate attached), 21-27 June 2014: development of full protocol



- GETNE 2014, Oct 2014: oral presentation (by invitation)
- ASCO GI 2014, Jan 2014: poster presentation
- ENETS 2014, March 2014: poster presentation
- Maguire Communication Skill Training: Advance care planning conversations: 3-3-2014: attendee
- Manchester Clinical Endocrinology Symposium Series, 31-5-2014: 31-5-2014: oral presentation
- Pancreatic cancer: An extended case based discussion: 31-3-2014: oral presentation
- Selecting patients for loco-regional or systemic therapy (Hepatocellular carcinoma: 11-9-2014: attendee
- ASCO 2013: from 31/4/2013 to 4/5/2013; poster presentation
- World gastrointestinal cancer congress 2013 from 3/7/2013 to 6/7/2013; poster presentation
- ECCO-ESMO ESTRO 2013 from 27/9/2013 to 30/9/2013; poster presentation
- SEOM 2013 from 24/10/2013; poster presentation
- NCRI 2013 from 5/11/2013; poster presentation
- UKINETs 2013 from 25/11/2013; poster presentation

Acknowledgments




First of all, I would like to thank the ESMO Fellowship Programme for giving me the opportunity of having this life changing experience. A special thanks to Professor Valle for his trust in me. I would like to thank all the people involved in this project for their help and enthusiasm during its development and delivery. Thanks to Professor Juan W Valle and the rest of the Christie HPB/NET Oncology team (including the research and nursing team) at The Christie ENETS Centre of Excellence for the warm welcome and their daily support. I would also like to thank the team at the Wolfson Molecular Imaging Centre for being welcoming to both me and the patients.



European Society for Medical Oncology



The Christie **NHS**
NHS Foundation Trust

Home Institute	Host Institute	Funding
<p>La Paz University Hospital, Madrid, Spain</p>	<p>The Christie NHS Foundation Trust, Manchester, UK and Wolfson Molecular Image Centre, Manchester, UK</p>	<p>This ESMO Translational Fellowship Research Project was supported by ESMO with the aid of a grant from Amgen which has funded my fellowship since Jan 2013 to Dec 2014. The FLT Scans and trial infrastructure costs have been funded by the Pancreatic Cancer Research Fund.</p>
		



During 2013, The Christie has been acknowledged by ESMO for its contribution to its education arm, the ESMO Fellowship programme (November 2013)



Films 16: ECCO-AACR-EORTC-ESMO Workshops on 'Methods in Clinical Cancer Research' (June 2014)