



The ROYAL MARSDEN

ESMO Clinical Unit Visit 2013

Clinical Trials Fellowship at the Lung Cancer Unit of the Royal Marsden Hospital.

2 September 2013 to 30 November 2013

Fellow: Ramon Andrade Bezerra de Mello, MD, PhD

Home institution and supervisor: António Manuel Ferreira Araújo, MD, PhD

Departament of Medical Oncology, Portuguese Oncology Institute, Porto, Portugal

Host Institution and supervisor: Sanjay Popat, BSc MBBS FRCP PhD

The Royal Marsden, London, United Kingdom

Purpose

To acquire new skills in an international reference institution, concerning lung cancer clinical trials and clinical research.

Background

Lung cancer is a very aggressive disease. The 5 year overall survival considering all stages remains very poor. However, since the last decades much research has been carried out in this field and new development drugs are the current object of main interest in science. Thus, understanding particular issues of the clinical trials setting in different institutions may help a clinician acquire important skills for improving patient care.

Methods and technologies

Setting: Lung Cancer Unit of the Royal Marsden Hospital, London, United Kingdom.

Design: Postdoctoral fellowship experience in the clinical trials setting from 2 September 2013 to 30 November 2013.

Previous skills: The fellow is finalist medical resident in medical oncology (5th year). Also, he has acquired a PhD degree in lung cancer at 31 January 2013.

The fellow did the general medical council registration with full license to practice (number 7436909) in order to perform clinical activity in parallel to the research.

Plan: The applicant (fellow) has spent 3 months in the host institution and followed a schedule proposed by the host supervisor. The table 1 shows the weekly fellowship timetable.

Table 1 – weekly schedule of the postdoctoral clinical research fellowship at the Lung Unit of the Royal Marsden NHS Foundation Trust, Chelsea and Kingston units.

	Monday	Tuesday	Wednesday	Thursday	Friday
Site/time	Kingston	Chelsea	Chelsea	Chelsea	Chelsea
A.M.	New, Follow-up and chemotherapy clinic	Inpatient work	Inpatient work	Inpatient work	Chemotherapy clinic, MDU**

Lunchtime	MDT*	Joint Marsden/ Brompton Lung MDT	Administration / Research	Research	MDT* and Lung Unit Research meeting
P.M.	Administration/ Research	New and Follow-up outpatient clinic	Administration/ Research	Ward round	Administration/ Research

*MDT stands for multidisciplinary decision team

**MDU stands for medical day unit

Dr. Popat's team work in the Lung Unit at Kingston Hospital and Chelsea Unit of the Royal Marsden Hospital. The fellow was based at the Chelsea branch of the Marsden mostly, and at the Kingston branch on Mondays.

Costs: The costs were in part supported by the fellow (€4,000.00) and the other part was supported by a grant (€5,000.00) from ESMO Clinical Unit Visit 2013.



Expected transferable skills

During the fellowship, the fellow learned about administrative and clinical issues of clinical trials. Also, the fellow has acquired a new experience at an international reference cancer institution and may bring to the home institution clinical and organizational skills in order to improve patient care.

Relevance in host applicant country

The Royal Marsden Hospital is considered in Portugal and Europe as a very important cancer care institution due to its excellence in patient care and cancer research. Thus, the shared experience will be important for improving future approaches in this field.

Relevance in your home institute

The fellowship has provided important technical skill to allow the fellow to be involved in future clinical trials and also improve his clinical practice.

Reason for choice the host institute

The host institution is an international reference institution with known excellence in lung cancer clinical trials and patient care.

Facilities available to continuous the work, apply and disseminate newly acquired skills

The applicant works in a comprehensive cancer institute that is reference in Portugal and south Europe. There are a large number of lung cancer patients (about 400 per year) and many medical facilities which allow provision of good care for oncology patients.

References to recent publications in the project field which contributed to the fellow earn the ESMO grant

1. **de Mello RA**, Marques DS, Medeiros R, Araujo AM. Epidermal growth factor receptor and K-Ras in non-small cell lung cancer -molecular pathways involved and targeted therapies. World J Clin Oncol 2011; 2(11): 367-376.
2. **De Mello RA**, Costa BM, Reis RM, Hespanol V. Insights into angiogenesis in non-small cell lung cancer: molecular mechanisms, polymorphic genes and targets therapies.

- Recent Patents on Anti-Cancer Drug Discovery. 2012; 7 (1): 118 – 31. (Impact Factor = 2.723)
3. **De Mello RA**, Magalhães MA, Villas-Boas A. Stridor and respiratory failure due to tracheobronchomalacia: a case report and review of the literature. São Paulo Med J. 2012; 130(1): 61 – 4 (Impact Factor = 0.711).
 4. **de Mello RA**, de Vasconcelos A, Ribeiro RA, Pousa I, Afonso N, Pereira D, Rodrigues H. Insight into p95HER2 in breast cancer: molecular mechanisms and targeted therapies. Recent Pat DNA Gene Seq. 2012;6(1):56-63 (SCM = 0.83).
 5. Araújo A, Coelho A, **de Mello RA**, Azevedo I, Soares M, Queiroga H, Teixeira E, Parente B, Barata F. Personalizing medicine - strategies for implementing the evaluation of ALK rearrangement in non-small-cell lung cancer in Portugal. Rev Port Pneumol 2012; 18 (5): 244-46. DOI 10.1016/j.rppneu.2012.04.011 (Impact factor = 0.226)
 6. **de Mello RA**, Ferreira M, Costa S, Costa BM, Pires FS, Neves I, Almeida MI, Cunha J, Oliveira P, Hespanhol V, Reis RM. Association between EGF +61 genetic polymorphisms and non-small cell lung cancer increased risk in a Portuguese population: a case-control study. Tumour Biol 2012; 36 (5): 1341 – 8. DOI: 10.1007/s13277-012-0382-7 (Impact Factor = 2.143).
 7. **de Mello RA**, Pires FS, Marques DS, Oliveira J, Rodrigues A, Soares M, Azevedo I, Peixoto A, Santos C, Pinto C, Hespanhol V, Teixeira MR, Amaro T, Queiroga H, Araújo A. EGFR exons mutation distribution and outcome in non-small-cell lung cancer: a Portuguese retrospective study. Tumour Biol 2012; 33 (6): 2061 – 8. DOI: 10.1007/s13277-012-0465-5. (Impact Factor = 2.143).

8. **De Mello RA**, Araújo A. Epidermal growth factor receptor mutation frequency and non-small cell lung cancer management: implication for treatment choices. Clinics (Sao Paulo) 2012; 67 (11): 1349. (Impact factor = 2.058).

Justification for the fellowship duration

This fellowship is an optional research fellowship integrated in the applicant's medical oncology resident program training and it is composed of 2 months of optional clinical fellowship and 1 month of research fellowship. In Portugal, the residency program time is 5 years. In 2013, the applicant was in the 5th year of his residency program training and earned valuable clinical and research skills during this fellowship.

Results from this fellowship and final remarks

During his fellowship period, Dr. de Mello had an excellent postdoctoral experience in clinical research and saw 63 lung cancer patients in the outpatient clinics. In the first week of his fellowship, he also presented to the Marsden team results from part of his research carried out in Portugal:

The role of polymorphic variants on vascular endothelial growth factor gene and non-small-cell lung cancer prognosis:

A Portuguese prospective study

He participated in more than 20 lung cancer clinical trials and also complementary research. Further, Dr. de Mello attended a course of good clinical practice from the National Institute of Health Research, Clinical Research Network, United Kingdom, in order to be co-investigator of Marsden lung cancer clinical trials. Below is listed some of the clinical trials which the fellow participated as co-investigator:

1. Capecitabine and Tarceva in Advanced Lung Cancer (CAPITAL). Sponsor: Royal Marsden Hospital, London, UK.
2. Prospective randomised controlled trial to investigate the effectiveness of inhalers for the relief of breathlessness in patients with lung cancer and COPD. Sponsor: Royal Marsden Hospital, London, UK.
3. Study of Pleural effusions to Characterize signal transduction Kinase pathways in non-small cell lung cancer (NSCLC) and malignant mesothelioma. Sponsor: Royal Marsden Hospital, London, UK.
4. A randomised study to investigate the effectiveness of acupuncture for the relief of dyspnoea in patients with non-small cell lung cancer and mesothelioma. Sponsor: Royal Marsden Hospital, London, UK.
5. EQUALITY - Expression Quantitative trait Loci mapping In Tumours collected at bronchoscopy. Sponsor: Imperial College, London, UK.
6. 200.12 - A phase 1 open label trial of continuous dosing with BIBW 2992 combined with paclitaxel and bevacizumab, Sponsor: Boehringer-Ingelheim.
7. Phase 1/2 study of LorvotuzumabMertasine (IMGN901) in combination with Carbo/Etop in ED SCLC. Sponsor: ImmunoGen.
8. LUX-LUNG 8 - A randomized, open label phase III trial of afatinibvs Erlotinib in patients with advanced squamous ca of lung as secondline therapy following first line platinum. Sponsor: Boehringer-Ingelheim.
9. FGFR: Proof of concept study of AZD4547 in patients with FGFR1 or FGFR2 amplified tumours (non-adenocarcinoma). Sponsor: GSK.

- 10.** Phase II study of selective BRAF kinase inhibitor GSK2118436 in subjects with advanced non-small cell lung cancer and BRAF mutations. Sponsor: Sponsor: GSK.
- 11.** Randomized, Multicenter, Double-Blind, Phase 3 Trial Comparing the Efficacy of Ipilimumab plus Etoposide/Platinum versus placebo in ED SCLC (adopted). Sponsor: BMS (ICON).
- 12.** A Phase II Trial of BIBW 2992 in suspected mutant EGFR lung cancer patients unfit for chemotherapy. Sponsor: BMS.
- 13.** Open-label phase II trial of erlotinib and bevacizumab in advanced NSCLC EGFR mutations. Sponsor: BMS
- 14.** A Randomized, Phase 3 Study of Ganetespib in Combination with Docetaxel versus Docetaxel Alone in Patients with Advanced Non-Small-Cell Lung Adenocarcinoma (protocol ID 9090-14). Sponsor: Synta.
- 15.** A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer(SCLC) and good performance status. Sponsor: Christie.
- 16.** Double blind randomised phase III study of maintenance Pazopanib versus placebo in NSCLC patients non progressive after first line chemotherapy. MAPPING. Sponsor: EORTC.

He also helped in a Royal Marsden retrospective study carried out by Dr. Sanjay Popat and Dr. Nadia Yousaf (medical oncology specialty registrar) which assessed the role of many immunohistochemistry biomarkers and brain metastasis in epidermal growth factor receptor (EGFR) mutated lung cancer patients. In addition, the fellow published a review article concerning lung cancer, biomarkers and innovative targeted therapies in Pharmacogenomic Journal, Future Medicine, (impact factor = 3.857) in the last month of his fellowship:

de Mello RA, Madureira P, Carvalho LS, Araújo A, O'Brien M, Popat S. EGFR and KRAS mutations, and ALK fusions: current developments and personalized therapies for patients with advanced non-small-cell lung cancer. *Pharmacogenomics* 2013 Nov; 14 (14): 1765-77. doi: 10.2217/pgs.13.177.

This article was made in partnership with Dr. Sanjay Popat and Dr. Mary O'Brien (Lung Unit, Royal Marsden Hospital, London, United Kingdom), with his previous supervisor from the home institution, Prof. António Araújo (Portuguese Oncology Institute, Porto, Portugal), and with two other colleagues from IBMC (Institute of Molecular and Cellular Medicine), University of Porto: Dr. Pedro Madureira (postdoctoral fellow) and Liliana S. Carvalho (PhD student).

In conclusion, lung cancer is a very important field of medical oncology nowadays due to the high disease incidence and the aggressiveness of the disease worldwide. Molecular oncology acquired a main role in this framework due to the possibility of personalizing therapies according to the tumor genetic profile. EGFR mutation and EML4-ALK rearrangement are currently key biomarkers in lung cancer clinical practice. Many clinical trials have assessed innovative lung cancer targeted therapies and The Royal Marsden Hospital is considered a top cancer center worldwide in this field. Thus, the fellow is delighted with the acquired postdoctoral clinical research skills during this period integrated in his medical oncology training and hopes to stay in touch with the Marsden team in order to establish future partnerships to improve cancer patient treatment.