INTRODUCTION

It is well assessed that Gc protein-derived macrophage activating factor (GcMAF) when is associated with oleic acid in a conjugated molecular complex (OA-GcMAF), is a powerful tool in the immunotherapy of cancer. It has been demonstrated that advanced cancer patients treated with a protocol centred on OA-GcMAF exhibit a tumour volume reduction of approximately 25% in about one week (Ruggiero M, Ward E, Smith R, Branca JJ, Noakes D, Morucci G, Taubmann M, Thyer L, Pacini S. Oleic Acid, deglycosylated vitamin D-binding protein, nitric oxide: a molecular triad made lethal to cancer. Anticancer Res 2014; 34(7): 3569-78). Here we describe the case of a patient with metastatic renal carcinoma successfully treated with this protocol also known as “The Swiss Protocol®” and we describe for the first time the molecular mode of interaction between OA-GcMAF and the product of the human oncogene \textit{myc}.

MATERIALS and METHODS

A 78-year-old man was diagnosed with metastatic renal carcinoma. OA-GcMAF (Goleic®, Immuno Biotech Ltd, Channel Islands, GBG) was administered daily by alternating nebulisation (880 ng), and subcutaneous injections (880 ng).

OA-GcMAF was used in combination with:
1. A proprietary fermented milk product containing naturally produced OA-GcMAF (Les Alpes, Ltd, Wellington, NZ), 120 ml per day.
RESULTS
After 4 weeks of integrative immunotherapy, one of the kidney lesions taken as representative, measured with ultrasonography, showed a decrease of its volume from approximately 16ml (figure 1 a) to about 6ml (figure 1 b).

DISCUSSION
Although the research on GcMAF dates back to the nineties (Yamamoto N, Naraparaju VR, Asbell SO. Deglycosylation of serum vitamin D3-binding protein leads to immunosuppression in cancer patients. Cancer Res 1996; 56(12): 2827-31), only recently we demonstrated that GcMAF in vivo is not assembled as a “pure” protein, but it is associated with fatty acids, notably oleic acid (Thyer L, Ward E, Smith R, Fiore MG, Magherini S, Branca JJ, Morucci G, Gulisano M, Ruggiero M, Pacini S. A novel role for a major component of the vitamin D axis: vitamin D binding protein-derived macrophage activating factor induces human breast cancer cell apoptosis through stimulation of macrophages. Nutrients 2013; 5(7): 2577-89). From this observation, we developed OA-GcMAF a molecular complex that represents the physiological form of GcMAF. At variance with the previously used GcMAF molecules that were not associated with oleic acid, OA-GcMAF can be administered to patients through routes other than injection. In fact, due to its physical-chemical properties, OA-GcMAF can be administered through nebulisation, nasal sprays or through the sublingual route.
In addition, the presence of the fatty acid moiety in the OA-GcMAF molecular complex allows direct interaction with a number of proteins encoded by oncogenes that are involved in human cell carcinogenesis. In particular, here we describe for the first time that oleic acid mediates the hydrophobic interaction between GcMAF and the protein encoded by the human oncogene myc, a nuclear oncogene involved in the pathogenesis and progression of kidney cancer (Allory Y, Culine S, de la Taille A. Kidney cancer pathology in the new context of targeted therapy. Pathobiology 2011; 78(2): 90-8).

As depicted in figure 3, there is one molecular site of hydrophobic interaction between the fatty acid-binding site of GcMAF and the functional part of the human myc oncogene. At this molecular level, oleic acid acts as a hydrophobic stabiliser, thus allowing specific interaction between the proteins (figure 4).

The oleic acid-mediated interaction between GcMAF and the human myc oncogene explains at the molecular level the powerful anti-cancer effects of OA-GcMAF, a molecule that is about 200 fold more effective than the GcMAF molecule without the oleic acid moiety conjugated to it.

In fact the protein encoded by myc is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. The oncogene myc is found in many human neoplasms with resulting unregulated expression of a number of other genes, some of which are involved in cell proliferation, and results in the formation of cancer. Thus, myc regulates the expression of 15% of all genes through binding on Enhancer Box sequences (E-boxes) and recruiting histone acetyl-transferases. This means that in addition to its role as a classical transcription factor, myc also functions to regulate global chromatin structure by regulating histone acetylation both in gene-rich regions and at sites far from any known gene. Therefore, the interaction between OA-GcMAF and the protein encoded by the human myc oncogene might explain the ubiquitous anti-cancer efficacy of OA-GcMAF.