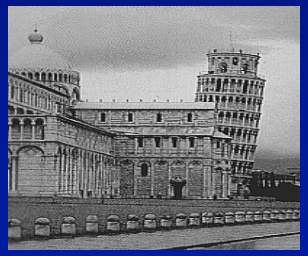


Primo Workshop
Clinical Research and Innovation
Pisa, 4 Luglio 2014

Evaluation of the anti-neoplastic activity of new tyrosine-kinase inhibitors in primary cells of patients with aggressive thyroid cancer

Alessandro Antonelli[1], Poupak Fallahi[1], Silvia Martina Ferrari[1], Concettina La Motta[2], Guido Bocci[1], Fulvio Basolo[3], Paolo Miccoli[3].

[1]Department of Clinical and Experimental Medicine, [2]Department of Pharmacy; [3]Department of Surgical, Medical, Molecular Pathology and Critical Area; University of Pisa

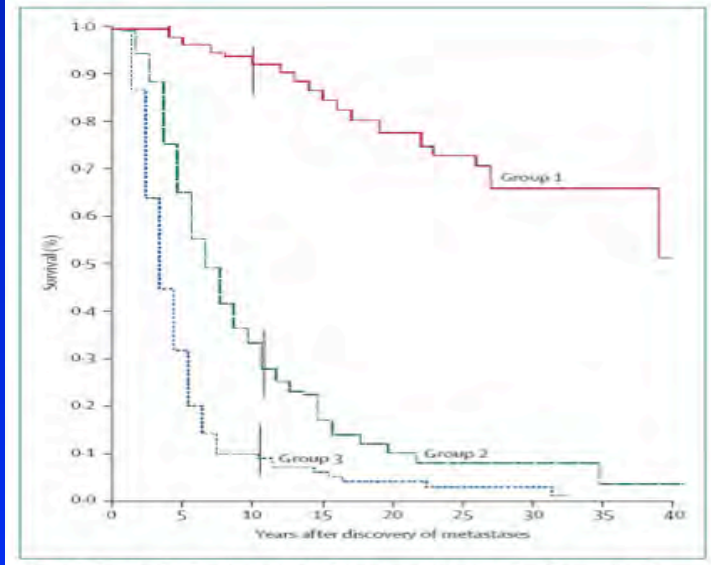
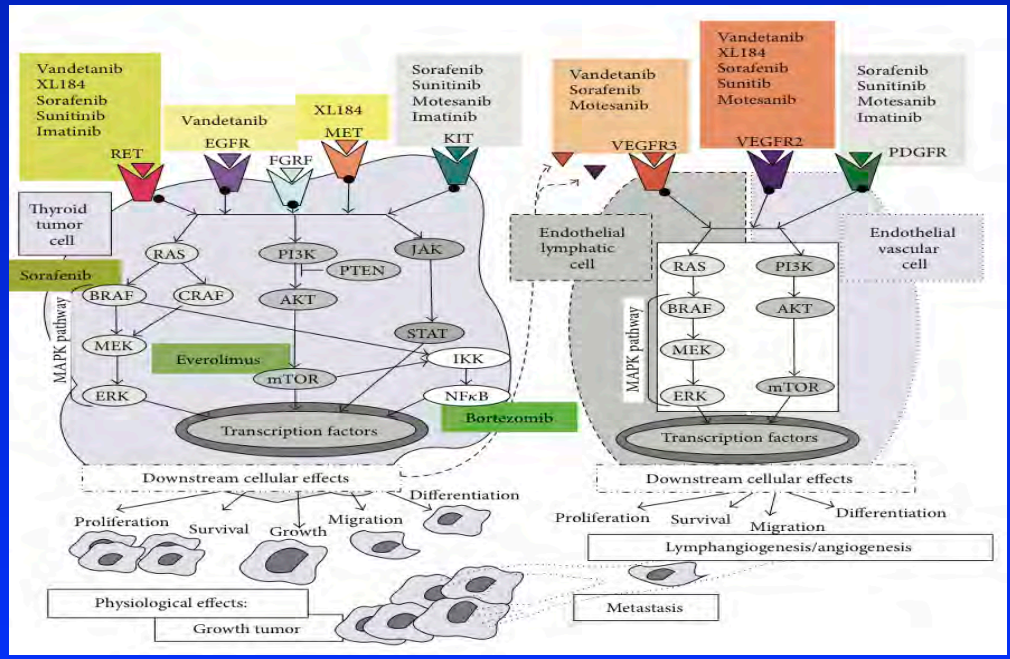


Figure 3: **Survival of patients with distant metastases after discovery of distant metastases according to presence of initial radioiodine uptake and outcome of radioiodine treatment**

Group 1: 29% of patients had initial uptake and no residual disease after treatment; survival was similar to that of general population. Group 2: 38% of patients had initial uptake and residual disease after treatment; median survival after discovery of distant metastases was 6 years. Group 3: 33% of patients had no initial uptake; median survival was 3 years. Reproduced with permission from ref 11.



Cellular signaling pathway alterations and potential targeted therapies for medullary thyroid carcinoma. Giunti S, Antonelli A, Amorosi A, Santarpia L. *Int J Endocrinol* 2013;2013:803171.

The advent of low-cost individual genomic analysis provides hope that we are entering a new era of personalized, patient-specific care. The recent advances in the pathogenesis of these diseases have revealed key targets (BRAF, RAS, RET, VEGFR, EGFR, etc.) that are now being evaluated in the clinical setting.
The lack of effective therapies for differentiated thyroid cancer (DTC), resistant to radioiodine and traditional therapies, is now being overcome by the development of targeted novel compounds that have been demonstrated to induce clinical responses and stabilization of disease. Interestingly, the most promising responses have been reported in patients treated with antiangiogenic inhibitors such as vandetanib and XL184 in medullary thyroid cancer, and sorafenib in papillary and follicular DTC.
However, the increasing complexity of the diagnostic and therapeutic tools for thyroid cancer needs, more and more, an effort to personalize the diagnosis and the treatment, to reach the maximum success, avoiding unnecessary and potentially harmful treatments.

Many new approaches for the therapy of dedifferentiated thyroid cancer are emerging, but until now a significant clinical impact on survival by the use of these drugs is still lacking.

New more effective drugs are needed.

In the future, the identification by molecular profiling of patients who are likely to benefit from each therapeutic option will be important.

Moreover, new techniques have been developed to test the effectiveness of the various treatments in each patient.

For this purpose, particular importance should be given to the development of primary cells from the single patient.

Chemosensitivity tests

in primary tumoral cells

may help in detecting

responsive patients

(60% Positive Predictive Value),

in preventing the administration of inactive drugs

to unresponsive patients

(90% Negative Predictive Value).

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Antiproliferative and proapoptotic activity of CLM3, a novel multiple tyrosine kinase inhibitor, alone and in combination with SN-38 on endothelial and cancer cells

Guido Bocci [a,*], Anna Fioravanti [a], Concettina La Motta [b], Paola Orlandi [a], Bastianina Canu [a], Teresa Di Desidero [a], Laura Mugnaini [b], Stefania Sartini [b], Sandro Cosconati [c], Rita Frati [a], Alessandro Antonelli [d], Piero Berti [e], Paolo Miccoli [e], Federico Da Settimo [b], Romano Danesi [a]

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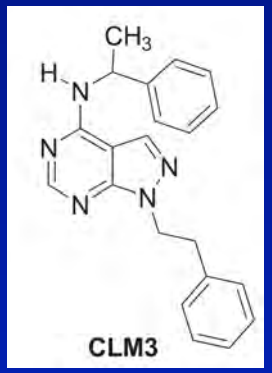
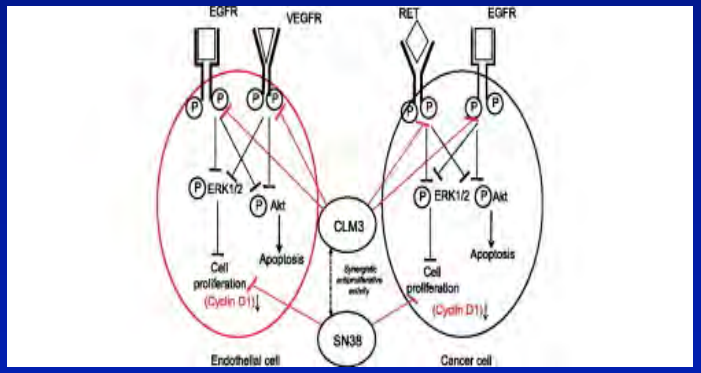
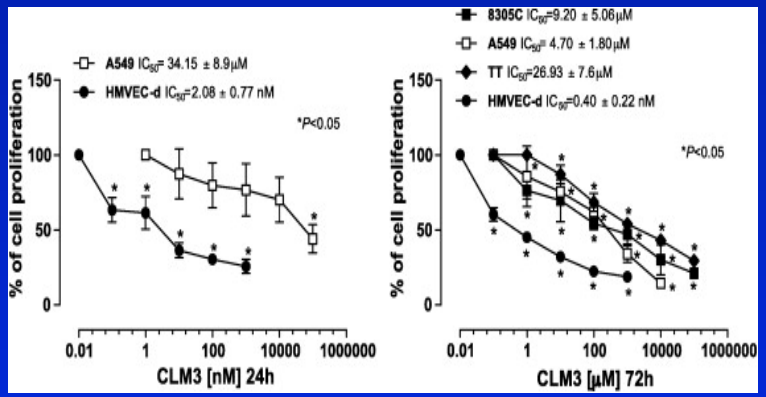
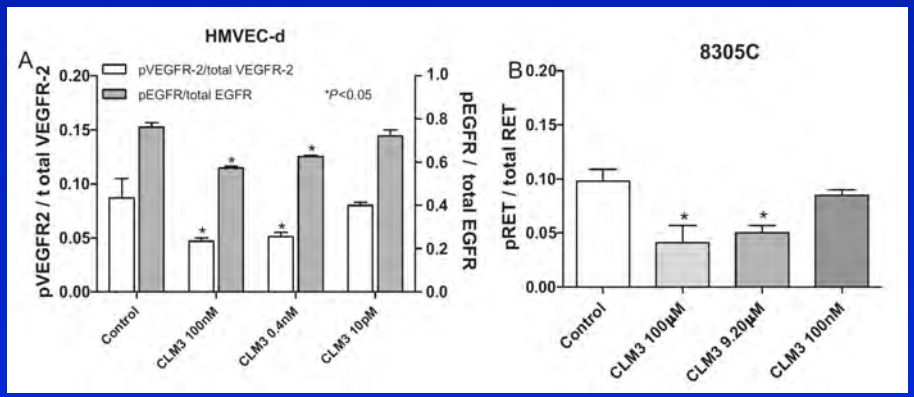
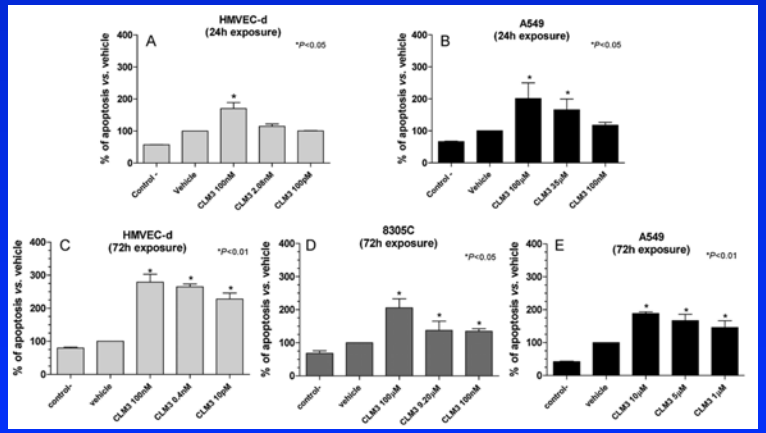
[b] Department of Pharmaceutical Sciences, University of Pisa, Pisa, Italy
[c] Department of Pharmaceutical Chemistry and Toxicology, University of Napoli "Federico II", Napoli, Italy
[d] Metabolism Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy
[e] Department of Surgery, University of Pisa, Pisa, Italy

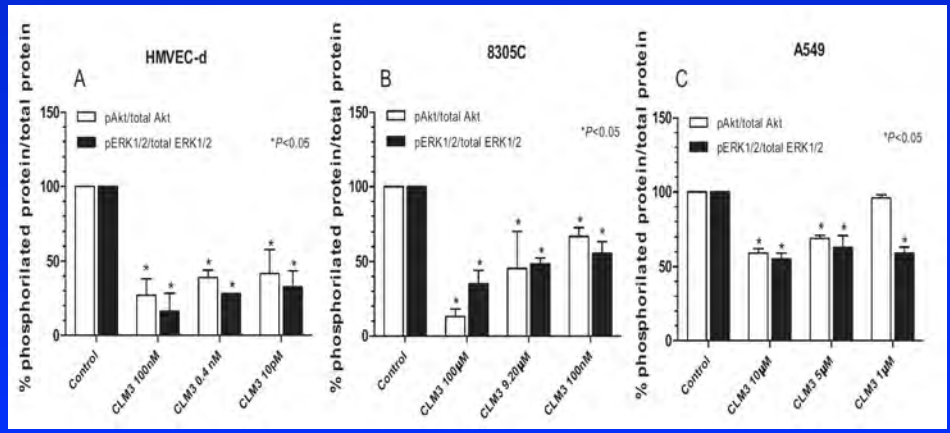








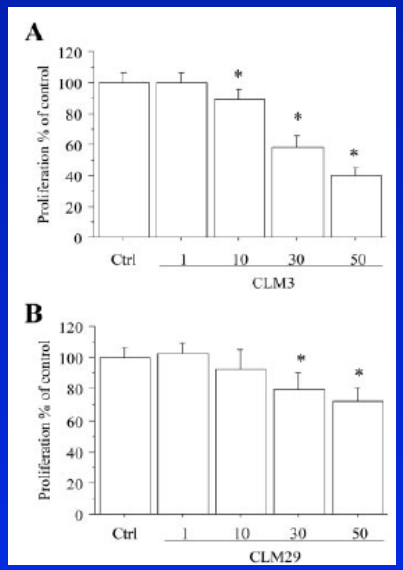


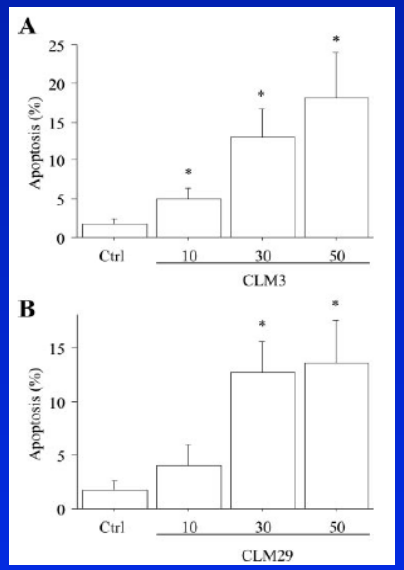


J Clin Endocrinol Metab, January 2011, 96(1):0000–0000

Novel Pyrazolopyrimidine Derivatives as Tyrosine Kinase Inhibitors with Antitumoral Activity *in Vitro* and *in Vivo* in Papillary Dedifferentiated Thyroid Cancer

Alessandro Antonelli, Guido Bocci, Concettina La Motta, Silvia Martina Ferrari, Poupak Fallahi, Anna Fioravanti, Stefania Sartini, Michele Minuto, Simona Piaggi, Alessandro Corti, Greta Alì, Piero Berti, Gabriella Fontanini, Romano Danesi, Federico Da Settimo, and Paolo Miccoli





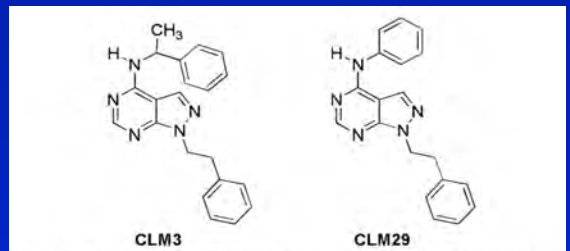
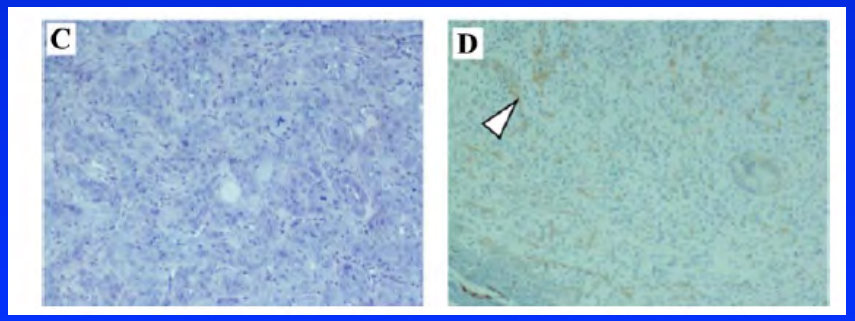
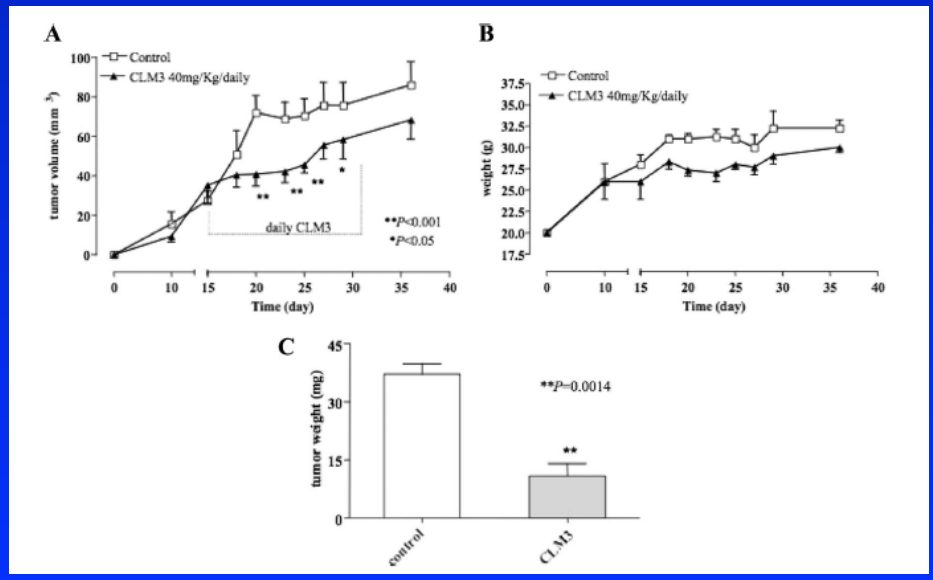


FIG. 1. Two novel pyrazolo[3,4-*d*]pyrimidine derivatives have been used, named CLM3 and CLM29. The structure of each compound is given in figure.

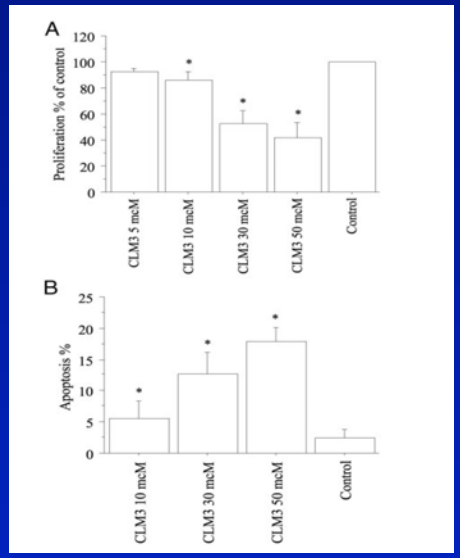


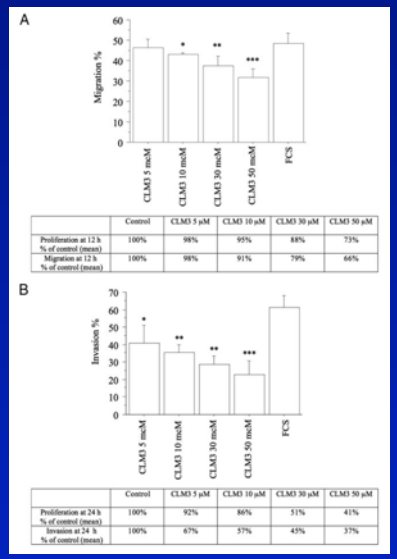


J Clin Endocrinol Metab, 2014

CLM3, a multitarget tyrosine kinase inhibitor with antiangiogenic properties, is active against primary anaplastic thyroid cancer *in vitro* and *in vivo*

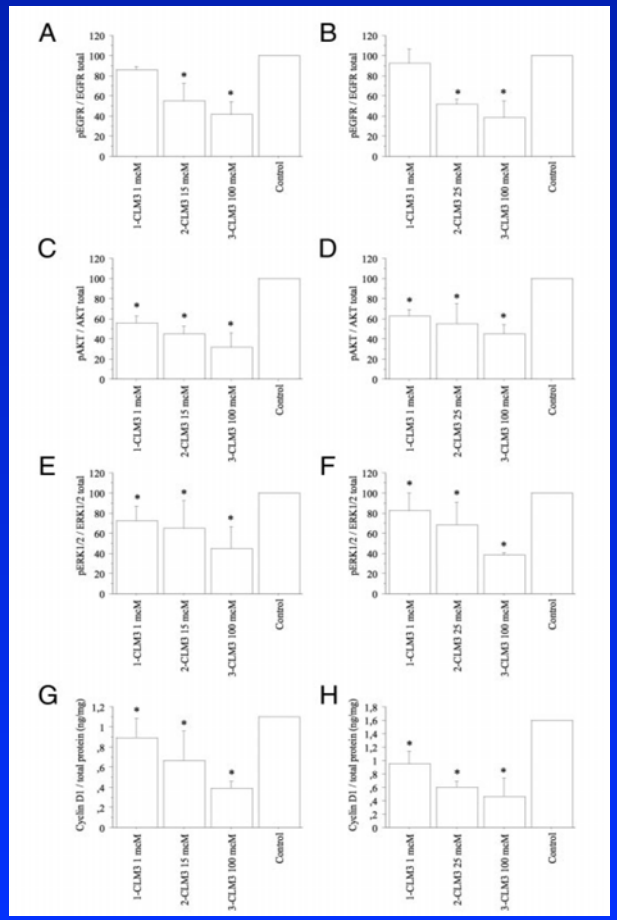
Alessandro Antonelli[1], Guido Bocci[1,2], Poupak Fallahi[1], Concettina La Motta[3], Silvia Martina Ferrari[1], Caterina Mancusi[1], Anna Fioravanti[1], Teresa Di Desidero[1], Stefania Sartini[3], Alessandro Corti[4], Simona Piaggi[4], Gabriele Materazzi[5], Claudio Spinelli[5], Gabriella Fontanini[5], Romano Danesi[1], Federico Da Settimo[3], Paolo Miccoli[5]

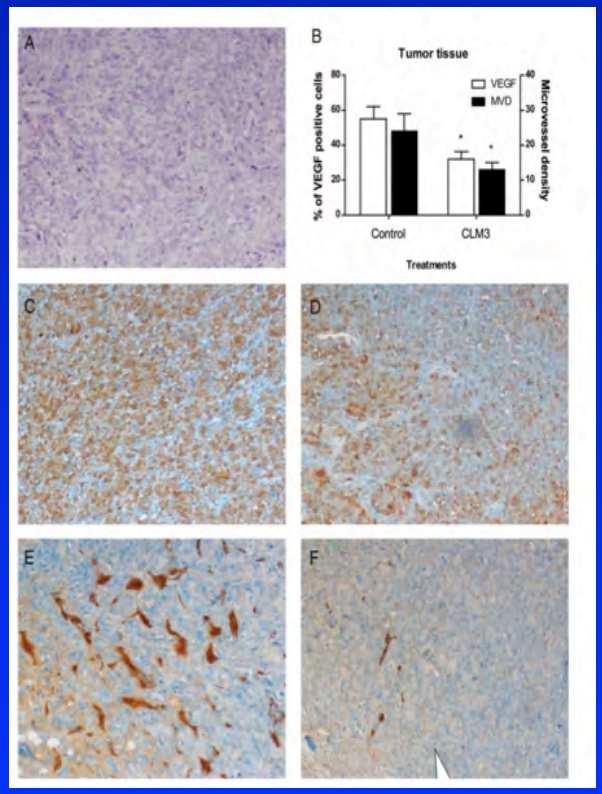


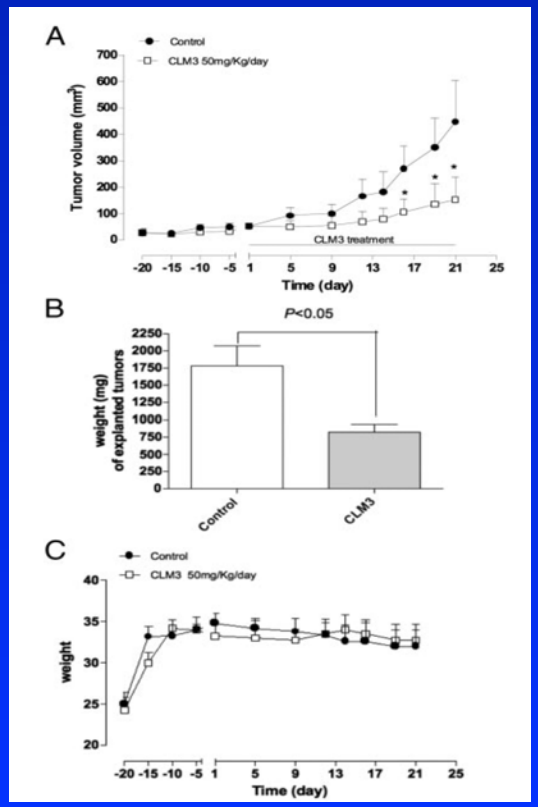


	Control	CLM3 5 μM	CLM3 10 μM	CLM3 30 μM	CLM3 50 μM
Proliferation at 12 h % of control (mean)	100%	98%	95%	88%	73%
Migration at 12 h % of control (mean)	100%	98%	91%	79%	66%

	Control	CLM3 5 μM	CLM3 10 μM	CLM3 30 μM	CLM3 50 μM
Proliferation at 24 h % of control (mean)	100%	92%	86%	51%	41%
Invasion at 24 h % of control (mean)	100%	67%	57%	45%	37%







Molecular and Cellular Endocrinology 393 (2014) 56–64

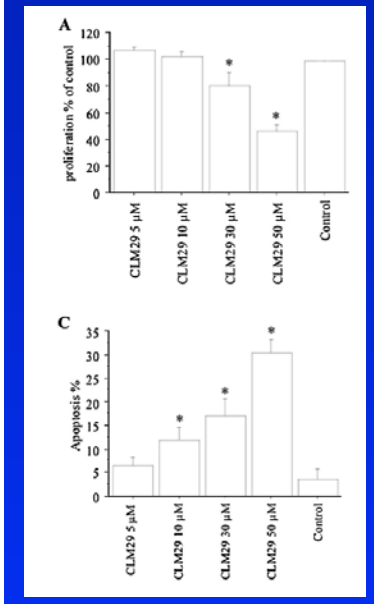
Contents lists available at ScienceDirect

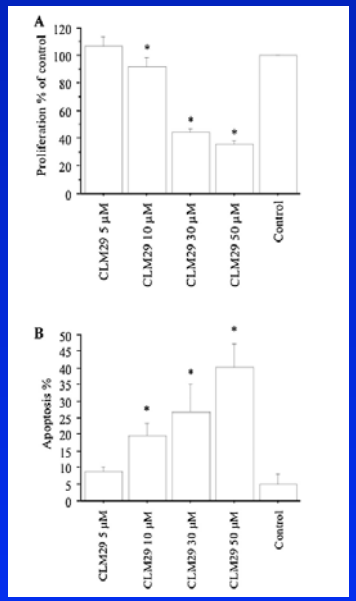
Molecular and Cellular Endocrinology

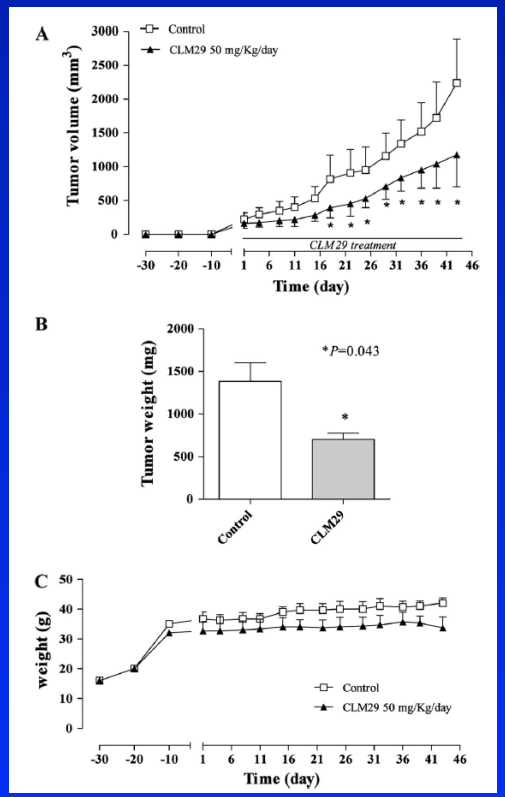
journal homepage: www.elsevier.com/locate/mce

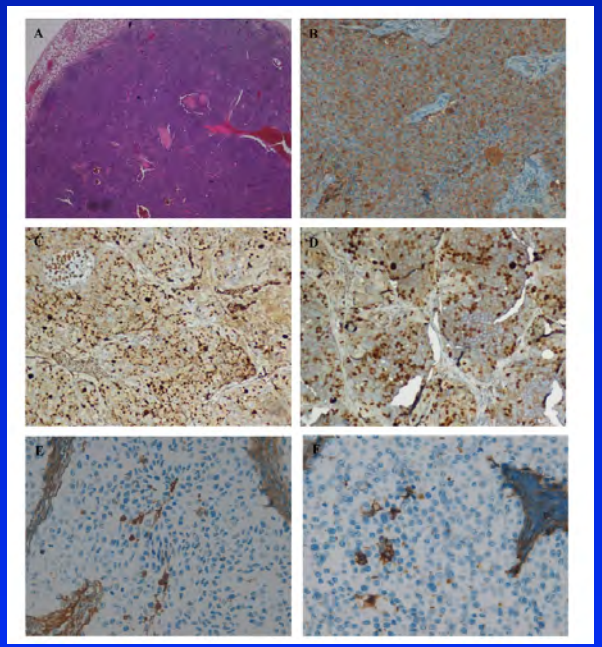
CLM29, a multi-target pyrazolopyrimidine derivative, has anti-neoplastic activity in medullary thyroid cancer *in vitro* and *in vivo*

Alessandro Antonelli [a,*], Guido Bocci [a,b], Concettina La Motta [c], Silvia Martina Ferrari [a], Poupak Fallahi [a], Alda Corrado [a], Anna Fioravanti [a], Stefania Sartini [c], Paola Orlandi [a], Simona Piaggi [d], Alessandro Corti [d], Gabriele Materazzi [e], David Galleri [e], Salvatore Ulisse [f], Gabriella Fontanini [e], Romano Danesi [a], Federico Da Settimo [c], Paolo Miccoli [e]





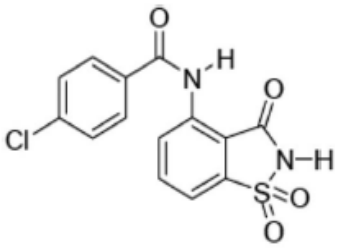




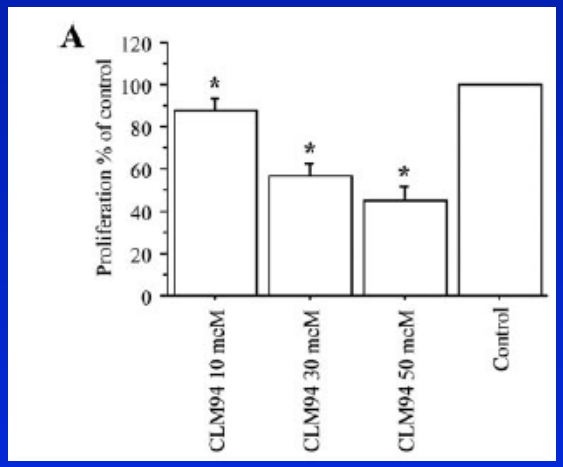
J Clin Endocrinol Metab, April 2012, 97(4):0000–0000

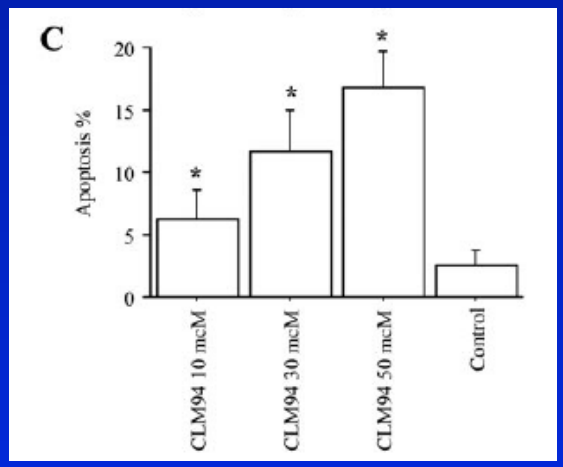
CLM94, a Novel Cyclic Amide with Anti-VEGFR-2 and Antiangiogenic Properties, Is Active against Primary Anaplastic Thyroid Cancer *in Vitro* and *in Vivo*

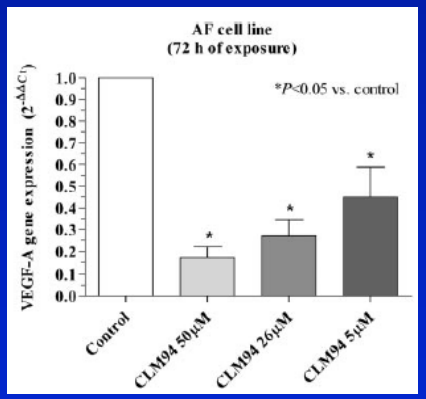
Alessandro Antonelli, Guido Bocci, Concettina La Motta, Silvia Martina Ferrari, Poupak Fallahi, Ilaria Ruffilli, Andrea Di Domenicantonio, Anna Fioravanti, Stefania Sartini, Michele Minuto, Simona Piaggi, Alessandro Corti, Greta Alì, Teresa Di Desidero, Piero Berti, Gabriella Fontanini, Romano Danesi, Federico Da Settimo, and Paolo Miccoli

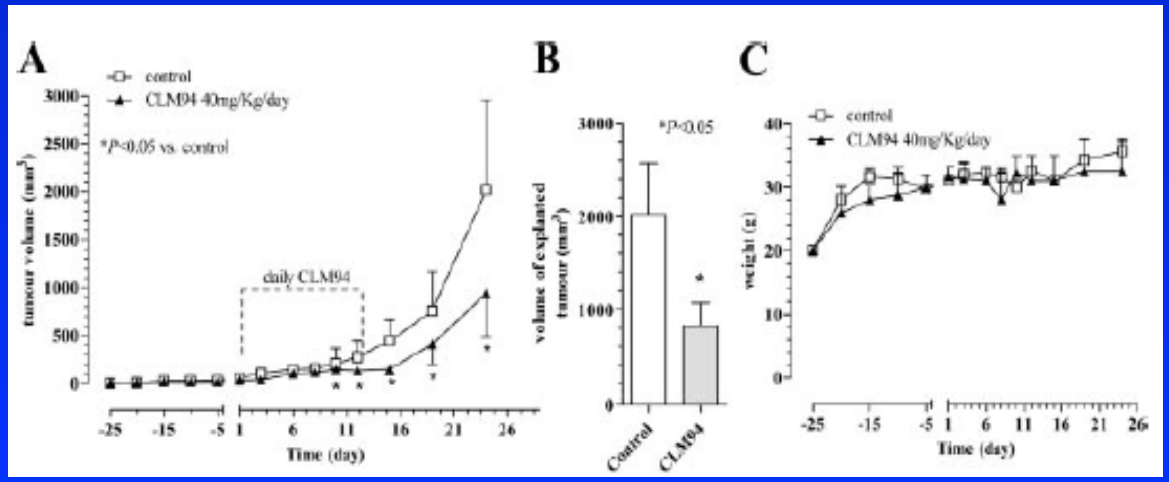


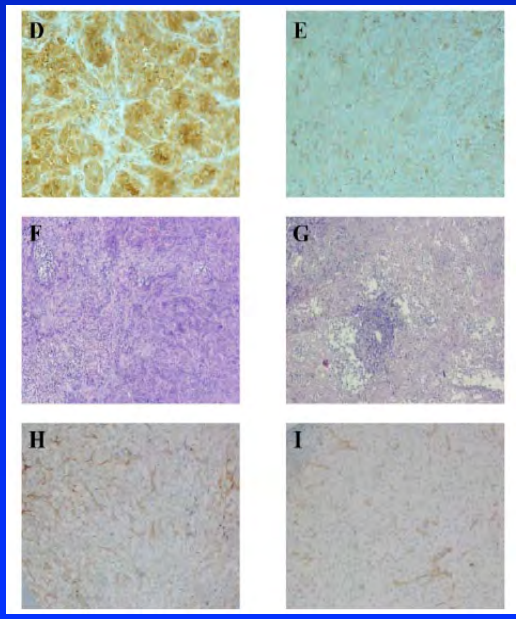
CLM94











Future perspectives

To produce new and more active drugs to be used in humans.

Journal of Medicinal Chemistry

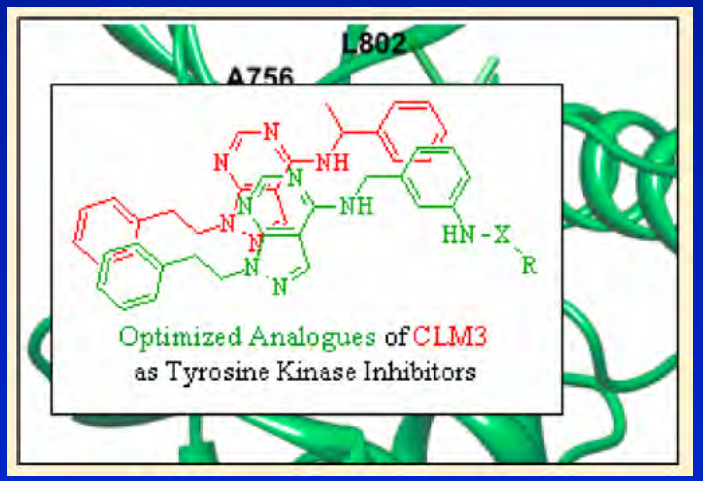
Article

pubs.acs.org/jmc

Structure-Based Optimization of Tyrosine Kinase Inhibitor CLM3. Design, Synthesis, Functional Evaluation, and Molecular Modeling Studies.

Stefania Sartini,[†] Vito Coviello,[†] Agostino Bruno,[‡] Valeria La Pietra,[‡] Luciana Marinelli,[‡] Francesca Simorini,[†] Sabrina Taliani,[†] Silvia Salerno,[†] Anna Maria Marini,[†] Anna Fioravanti,[§] Paola Orlandi,[§] Alessandro Antonelli,[§] Federico Da Settimo,[†] Ettore Novellino,[‡] Guido Bocci,[§,∥] and Concettina La Motta*[,†]

J. Med. Chem. 2014, 57, 1225−1235



To personalize the therapy in patients with thyroid cancer, through chemosensitivity tests in primary cells obtained from the single patient with tyrosine kinase inhibitors (approved for the treatment of aggressive thyroid cancer, such as vandetanib and XL184 in medullary thyroid cancer, and sorafenib in papillary and follicular DTC), to increase the responsiveness to the treatments (60% positive predictive value), preventing the administration of inactive drugs to unresponsive patients (90% negative predictive value), avoiding dangerous side effects, and reducing the costs of treatments.