SAFETY AND EFFICACY OF EVEROLIMUS, A mTOR INHIBITOR, AS SINGLE AGENT IN A PHASE 1/2 STUDY IN PATIENTS WITH MYELOFIBROSIS

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Paola Guglielmelli, Giovanni Barosi, Alessandro Rambaldi, Roberto Marchioli, Arianna Masciulli, Lorenzo Tozzi, Flavia Biamonte, Niccolò Bartalucci, Elisabetta Gattoni, Maria Letizia Lupo, Guido Finazzi, Alessandro Pancrazzi, Elisabetta Antonioli, Maria Chiara Susini, Lisa Pieri, Elisa Malevolti, Emilio Usala, Ubaldo Occhini, Alberto Grossi, Silvia Caglio, Simona Paratore, Alberto Bosi, Tiziano Barbui, Alessandro M. Vannucchi, on behalf of the AGIMM investigators

1 Department of Medical and Surgical Care, Section of Hematology, University of Florence and Istituto Toscano Tumori, Florence, Italy
2 Unit of Clinical Epidemiology and Center for the Study of Myelofibrosis, IRCCS PoliclinicoS. Matteo Foundation, Pavia, Italy
3 Hematology Department, Ospedali Riuniti di Bergamo, Bergamo, Italy
4 Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy
5 Hematology and Bone Marrow Transplant Unit, Ospedale A. Businco, Cagliari, Italy
6 U.O.C. di Ematologia, Ospedale San Donato, Arezzo.
7 Oncology Unit, Ospedale di Prato, Italy
8 Novartis Farma SpA, Origgio, Varese, Italy

SUMMARY:

In the pathogenesis of myelofibrosis, as well as of myeloproliferative neoplasms in general, has been studied the role of the deregulated activation of the PI3K/AKT/mTOR pathway, that is involved in the regulation of cell cycle in a broad spectrum of cancers, with a critical role in the cell growth, proliferation, survival and apoptosis.

A multicenter, phase 1 / 2 study, involving the centers of Florence, Pavia and Bergamo, was recently conducted to evaluate the safety profile and efficacy of Everolimus (RAD001), a specific m-TOR inhibitor derived from Rapamycin. Everolimus was tested as a single therapeutic agent in a total of 39 patients with myelofibrosis with intermediate or high-risk, both Primary (PMF) and post-polycythemia vera (PPV-MF) and post-essential thrombocythemia (PET-MF): in phase 1 the dose of 10 mg/day was identified as the maximum tolerated dose, then this posology was administered in the phase 2 of the study. In this second phase were enrolled 30 subjects (16 PMF, PPV-8 MF, 6 MF-PET), 21 (70%) on them were JAK2V617F mutated, two had the MPLW515L mutation and one the MPLW515K mutation.

Everolimus displayed clinical activity in this group of patients with an acceptable safety profile: in fact responses (complete or partial) were documented in terms of reduction of splenomegaly (44%), resolution of constitutional symptoms (69%), pruritus (80%), anemia (25%), leukocytosis (15%) and thrombocytosis (25%).

On the other hand, the haematological toxicity was modest, with 8 cases (27%) of grade 2 or 3 anemia, grade 2 neutropenia in 7%, grade 2 thrombocytopenia in 3% of the patients, all reversible after discontinuation of treatment. Overall, non-haematologic effects of clinical relevance were infrequent, and mainly represented by grade 1-2 stomatitis (70%).

This study has provided proof-of-concept that targeting mTOR signaling pathway in myelofibrosis is clinical relevant, suggesting the opportunity of further clinical experimentation with everolimus, either as a single agent perhaps with the use of different drug dosage and time schedules, or in combination with other novel molecules, such as histone deacetylase inhibitors or other immunomodulators.

To view the paper: http://www.ncbi.nlm.nih.gov/pubmed/21725052