

Pharmacodynamic effects and recommended dose of RAD001 (mTOR inhibitor) in patients with advanced solid tumors in phase I trial

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The mammalian target of rapamycin (mTOR) is a serine/threonine-specific protein kinase, downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B) pathway. It is involved in the regulation of cell growth and proliferation, controlling this process at the translational level. There are two downstream messengers of mTOR: ribosomal p70S6 kinase (p70S6K) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4E-BP1). Phosphorylation of S6K1 enhances translation of mRNA that carries a 5'-terminal oligopyrimidine tract (TOP). Activation of 4E-BP1 results in dissociation from the RNA cap-binding protein eIF4E and formation of the eIF4F complex. The complex, consisting of the cap-binding protein eIF4E, the scaffold protein eIF4G and the RNA helicase eIF4A, enhances cap-dependent protein translation (1).

In the mammalian cells, activation of mTOR signaling to S6k1 and 4E-Bp1 depends on signal transmission through the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. PI3K and Akt lie upstream of mTOR, and are activated by growth factors or mitogenic stimuli, such as cytokines. Thus, mTOR kinase can be defined as a key element of the PI3K/Akt signaling pathway.

Activation of phosphoinositide-3-kinase (PI3K)/Akt/mTOR signaling through mutation of pathway components as well as through activation of upstream signaling molecules occurs in a majority of cancers contributing to deregulation of proliferation, resistance to apoptosis, and changes in metabolism characteristic of transformed cells (1,2). Proteins lying downstream of mTOR are also altered in several malignancies. Overexpression of eIF4E appeared to be a common event in solid tumors, especially in breast, colon, and neck cancers (4). Amplification of the eIF4E gene and eIF4E protein overexpression is associated with progression of those cancers (5). High eIF4E levels correlated with a higher rate of relapses and cancer-related deaths. In contrast to eIF4E, overexpression of 4EBP inhibits cell proliferation. 4EBP-1 expression levels correlate inversely with tumor progression (6). Moreover, activation of the mTOR/p70S6K pathway was found in a pancreatic cancer cell line (7, 8).

During my fellowship in the Medical Oncology Division of Vall d'Hebron University Hospital, Barcelona, Spain, I was actively involved in a phase I clinical trial with RAD001.

The primary objective of the study was to assess the safety and the tolerability of RAD001 (weekly 20, 50 and 70 mg or daily 5 and 10 mg) and to assess the changes in molecular markers of mTOR pathway by immunohistochemistry in a serial of skin and tumor biopsies.

In the first part of my stage I spent 3 months in the Pathology Division where I reviewed and learned all the technical aspects of processing the paraffin-embedded specimen, moreover I learned the immunohistochemistry technique.

In my training program I personally followed the 34 patients enrolled in the trial, I was also in charged of performing the skin biopsies for the pharmacodynamic study, that were obtained on 24hr post-dose and, for the weekly schedule, 5 days post-dose. The pharmacodynamic biomarkers analyzed were p-S6, p-4E-BP1 and p-Akt.

As results of the study RAD001 at 5-10 mg daily and 20-50 mg weekly was well tolerated and active; grade 3 DLT occurred in 5 patients comprising stomatitis (1 patient at 10 mg daily, 2 at 70 mg weekly), neutropenia and hyperglycemia (1 patient each at 70 mg weekly).

There was a dose- and schedule-dependent inhibition of the mTOR-pathway in the tumors; in the daily schedule pS6 and p-4E-BP1 were high inhibited at 5 mg and completely at 10 mg, pAKT appeared up regulated in some patients at 5 mg and 10 mg. In the weekly schedule pS6 was completely inhibited at all dose levels; p-4E-BP1 resulted completely inhibited at the dose of 50 mg and pAKT was higher up regulated at 50 mg. Similar effects were observed in tumor and skin, therefore skin could represent a good surrogate of mTOR inhibition. RAD001 at 10 mg daily was the selected dose for phase II/III studies.

The ESMO fellowship was a great experience; it offered me the opportunity to be involved in prestigious and stimulating trials in collaboration with an important oncology institution where I enriched my medical knowledge.

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