Title: mTOR inhibitor RAD001 promotes metastasis in a rat model of pancreatic neuroendocrine cancer

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None of the authors has a conflict of interest to declare.

Running title: Augmentation of metastatic tumor behavior by mTOR inhibition.

Keywords: metastasis, mTOR inhibition, neuroendocrine tumor, radionuclide therapy, somatostatin
Abstract

Inhibition of mTOR (mammalian target of rapamycin) is commonly considered a valid target in cancer treatment, but this assertion does not address effects on the immune microenvironment that may be detrimental to cancer treatment. Here we show how administration of the mTOR inhibitor RAD001 (everlimus) results in occurrence of distant metastasis in a rat model of pancreatic cancer. RAD001 was administered twice weekly for 4.5 weeks as a single treatment or combined with [177Lu-DOTA,Tyr3]octreotate (177Lu-DOTATATE), the latter of which targets the somatostatin receptor-2. The hypothesized synergistic therapeutic effect of RAD001 combined with 177Lu-DOTATATE was however not observed in our experiments. The combination showed to be less effective than 177Lu-DOTATATE alone. Unexpectedly, tumor metastasis was observed in 77% of the subjects treated with RAD001, either alone or as part of the combination treatment. This was a striking effect because metastasis did not occur in control or 177Lu-DOTATATE-treated animals, including if the primary tumor was surgically removed. These findings may be important clinically among non-compliant patients or patients that discontinue RAD001 therapy due to adverse effects.

INTRODUCTION

Gastroenteropancreatic neuro-endocrine tumors (GEPNETs) are usually slow growing and most patients present with already metastasized disease at time of diagnosis. As published by Missiaglia et al. (1) in many PNETs the mTOR signal transduction pathway is up regulated. This pathway plays a key role in regulating cell growth, metabolism, proliferation and angiogenesis. Inhibition of the mTOR signal transduction pathway in PNETs by RAD001 has shown promising results with a clinical benefit of 76%, given as a single treatment (n=115), and of 82%, given in combination with octreotide-LAR (n=45) (2). The RADIANT-3 study, a randomized, double blind, placebo-controlled, multicenter Phase III trial of 10 mg RAD001 daily in PNET-patients (n=410) has been finished recently. Median progression-free survival for RAD001 plus best supportive care was 11 months versus 4.6 months in
the placebo group (p<0.001) with acceptable toxicity (3). Most recently the FDA approved RAD001 for the treatment of PNET patients.

Since the late 1990s clinical Peptide Receptor Radionuclide Therapy (PRRT) studies have been performed with radiolabeled somatostatin analogs, such as \(^{177}\)Lu-DOTATATE and \(^{90}\)Y-DOTA,Tyr\(^3\)octreotide (\(^{90}\)Y-DOTATOC, Onalta™), targeting sst\(_2\) overexpressed on most GEPNETs. These studies have shown very promising results with regard to tumor response, overall survival, and quality of life (4, 5).

Considering the promising results of both RAD001 and PRRT for the treatment of GEPNETs, we combined these two therapies in the CA20948 syngeneic pancreatic tumor model in the rat. This radiosensitive model is commonly used for preclinical PRRT experiments and also showed to be susceptible to RAD001 treatment (6). For comparison, studies were also performed in the xenograft H69 tumor model in nude mice. The aim of the current study was to investigate the therapeutic effects of combined treatment with RAD001 and \(^{177}\)Lu-DOTATATE versus those of the two mono treatments.

MATERIALS AND METHODS

Cell lines

The CA20948 rat pancreatic tumor cell line (derived from a rat pancreas at our institution) is of acinar origin (7) and has high sst\(_2\) expression and was cultured as reported before (8). The cells were passaged for a maximum of 20 times and checked for mycoplasma infection and sst\(_2\) expression every 3 months.

The H69 tumor cell line is a human small cell lung carcinoma (ATCC, Wesel, Germany), has high sst\(_2\) expression, was passaged for a maximum of 10 times and was cultured according to the suppliers (ATCC) protocol.

Tumor models

The animal studies were in agreement with the Animal Welfare Committee requirements of our institution and conducted following generally accepted guidelines. For the first two experiments male Lewis rats (Harlan, Horst, the Netherlands) were used with a mean body weight of 275 g. For tumor induction, \(10^7\) CA20948 tumor cells in 0.5 ml ice cold PBS/animal were injected subcutaneously in the
lower flank. Monitoring body weight and tumor size by caliper measurements were performed by a technician blinded for the treatment groups. Tumor volume was calculated according to 0.4 x length x width x height. In the first study (fig. 1), animals were euthanized when tumor size had reached a volume of more than 4 cm$^3$ or when a tumor was bleeding due to skin penetration. In the second study the primary subcutaneous tumors were surgically removed when tumor volume exceeded 4 cm$^3$ or when the tumor was bleeding due to skin penetration, saving the animals for follow-up. Animals were euthanized when >10% loss of body weight was detected.

For the third experiment 24 male NMRI Nu/Nu mice with a mean body weight of 35 grams xenotransplanted sst2 expressing H69 cells were used. Animals were euthanized when tumor size reached a volume of more than 2 cm$^3$, when a tumor was bleeding due to skin penetration, or when >10% loss of body weight was detected.

**RAD001**

In the first experiment, RAD001 (kind gift from Novartis, Basel, Switzerland) and placebo was prepared according to the manufacturers protocol. In the second and third experiment RAD001 powder (LC laboratories, Woburn, USA) was dissolved in 2 ml ethanol and further diluted to the appropriate concentration in 5% (w/v) glucose solution. RAD001 was administered orally by gavage with a blunt needle.

**Radionuclides and peptides**

DOTA,Tyr$^3$-octreotate was obtained from Mallinckrodt, St Louis, MO. $^{177}$LuCl$_3$ was obtained from NRG, Petten, the Netherlands and was distributed by IDB-Holland, Baarle-Nassau, the Netherlands. $^{177}$Lu-DOTA,Tyr$^3$-octreotate was locally prepared as described before (9) in a specific activity of 125 MBq/3.4 μg peptide. Labeling of $^{111}$In-DTPA-octreotide (Octreoscan (Tyco Health Care, Petten, the Netherlands)) in a specific activity of 30 MBq $^{111}$InCl$_3$ / 0.5 μg DTPA-octreotide was performed as previously described (10). For the mice experiments a specific activity of 30 MBq $^{111}$InCl$_3$ / 0.1 μg DTPA-octreotide was used.

**In vitro autoradiography and HE staining**

As previously described in detail (11).
Experimental setup

In experiment 1, ten days after tumor inoculation RAD001 treatment was started, followed by $^{177}$Lu-DOTATATE injection. Animals were randomized into matching treatment groups with regard to tumor size at the start of treatment. Six treatment groups were created using one dose of RAD001 (5 mg/kg BW) twice a week and two doses of $^{177}$Lu-DOTATATE, 125 or 278 MBq, either as mono treatment or in combination (Table 1). Experiment 1 ended at day 60. To keep animal discomfort as low as possible and for practical reasons RAD001 was administered twice weekly.

Experiment 2 was essentially similar as experiment 1, variations were 2.5 next to 5 mg/kg BW dose of RAD001, alone or combined with 125 MBq $^{177}$Lu-DOTATATE (Table 1). The most important difference in comparison to experiment 1 was the resection of the subcutaneous tumor when tumor size > 4 cm$^3$. Experiment 2 was terminated at day 150. All animals still alive at the end of the experiment were checked for distant metastases by $^{111}$In-DTPA-octreotide SPECT/CT and autopsy.

In experiment 3, NMRI Nu/Nu mice bearing subcutaneous H69 tumors were first treated with 28 MBq $^{177}$Lu-DOTATATE injected intraperitoneally. Four days later three combination treatment groups were created at random. The first group received RAD001 (5mg/kg BW) daily, the second group received RAD001 (5mg/kg BW) twice a week with placebo treatment daily for the rest of the week and the third group received placebo treatment daily. RAD001/placebo treatment was given for a total of four weeks. Three weeks after the first $^{177}$Lu-DOTATATE treatment a second 25 MBq $^{177}$Lu-DOTATATE treatment was given to all animals as an alternative for surgical removal of the primary tumor. When subcutaneous tumor size exceeded 2 cm$^3$ the animal was checked for distant metastases by $^{111}$In-DTPA-octreotide SPECT/CT and autopsy.

Surgical procedure

During all surgical procedures isoflurane/O$_2$ anesthesia was applied and animals were kept warm using a heating pad. After shaving and disinfection an incision was made just beside the tumor. The capsule surrounding the tumor was carefully dissected from surrounding tissue. The wound was closed by absorbable sutures.

SPECT/CT scanning
24 (experiment 1) or 48 h (experiment 2) after intravenous (i.v.) injection of $^{177}$Lu-DOTATATE, a helical SPECT scan was acquired covering the tumor region using the four-headed NanoSPECT/CT system (Bioscan) using Nucline software (v2.01, Mediso) for quantification of $^{177}$Lu-DOTATATE tumor uptake. Just before euthanizing an animal, a whole body SPECT/CT scan was made 4 – 24 hours after i.v. injection of $^{111}$In-DTPA-octreotide for detection of distant metastasis.

RESULTS AND DISCUSSION

Our first study, described in table 1 (group 1 – 6), showed CA20948 tumor growth inhibition by RAD001 mono therapy as was previously found by Boulay et al. as well (6). Also in clinical studies mTOR inhibition generally seems to elicit a cytostatic rather than a cytotoxic response (12, 13). Boulay et al. also showed twice weekly administration of RAD001 to be as effective as daily administration in this tumor model (6). All animals in the control and the RAD001-only group had to be euthanized within 36 days post start of treatment because of tumor growth beyond 4 cm$^3$ or a ruptured tumor. As expected, all animals receiving $^{177}$Lu-DOTATATE with or without RAD001 exhibited significant antitumor response compared to controls ($p<0.05$). However, $^{177}$Lu-DOTATATE in combination with RAD001 did not show to be more effective than $^{177}$Lu-DOTATATE alone (Fig. 1A). A dose effect relationship for the low and high dose $^{177}$Lu-DOTATATE was not found, which is in agreement with similar levels of $^{177}$Lu-DOTATATE tumor uptake in these two groups 24 hours after injection, as quantified based on SPECT (Fig. 1E). Partial saturation of the sst$_2$ receptors on the tumor cells in the high dose group could play a role in this respect.

Strikingly, from day 40 post start of treatment, most animals in the combination therapy groups showed unexpected decrease in body weight (Fig. 1B). Tumor metastasis to the liver and occasionally to the lung was found in these animals upon autopsy (Fig. 1D). In the combination treatment groups 11 out of 14 animals had to be euthanized because of loss of body weight and apparent metastasis (Fig. 1C). Metastases could be visualized after injection of $^{111}$In-DTPA-octreotide by SPECT/CT, indicating sst$_2$ expression. $^{177}$Lu-DOTATATE-only treated animals did not show loss of body weight and were all free of metastasis, confirmed by negative $^{111}$In-DTPA-octreotide SPECT/CT scans and negative autopsies (Figure 1D). The occurrence of spontaneous metastasis in the subcutaneous CA20948 tumor model has not been described before, despite the fact that this model has often been used in PRRT studies with long follow-up periods (14). We therefore hypothesize that RAD001, alone
or in combination with $^{177}$Lu-DOTATATE, or the discontinuation of RAD001 treatment might be the cause of the metastasis. Unfortunately the RAD001 mono therapy treatment group in this study did not survive long enough to develop or to be tested for metastases by SPECT.

For further investigation, a second study was performed (Table 1, group 7-13) in which a subcutaneous tumor reaching a volume of 4 cm$^3$ was surgically removed to allow long term follow-up. Furthermore, in this experiment also a 2.5 mg/kg BW dose of RAD001 was applied next to the earlier used 5 mg/kg BW, combined with 125 MBq $^{177}$Lu-DOTATATE (Table 1). In an additional group (group 13) 5 mg/kg BW of RAD001 was given to control rats without tumor.

The therapeutic effects obtained in this second study were in agreement with the first study, without significant difference using the lower RAD001 dose. PRRT resulted in complete response of the CA20948 tumor in 3 out of 7 animals, whereas in all other animals the subcutaneous tumor had to be removed surgically. In one animal treated with $^{177}$Lu-DOTATATE, clear tumor spill into the wound bed was observed during the surgical procedure resulting in tumor regrowth in the wound bed and metastasis in an ipsilateral lymph node in the groin. Therefore this animal was not included in our analysis. The decrease in body weight seen in the RAD001 + PRRT animals in study 1 was less explicit in study 2 (Fig. 2B) probably because of earlier intervention. Again distant metastasis developed in animals receiving RAD001, either in high or low dose, or in combination with $^{177}$Lu-DOTATATE. (Fig. 2A), whereas control and $^{177}$Lu-DOTATATE treated animals remained metastasis free. When development of distant metastasis was suspected based on loss of body weight, $^{111}$In-DTPA-octreotide was injected and 4-24 hours later a SPECT/CT scan (Fig. 3A) was acquired. When a distant metastasis could be visualized, the animal was euthanized, followed by autopsy as illustrated by photographic images (Fig. 3B). Of tumor tissue collected, frozen sections were prepared and used for hematoxylin eosin staining (Fig. 3C + F) and $^{111}$In-DTPA-octreotide in vitro autoradiography with (Fig. 3E + H) or without (Fig. 3D + G) a 1000 x excess of unlabeled octreotide (block). All metastasis appeared to be sst$_2$-positive, in agreement with the receptor status of the primary subcutaneous tumors. In a third study, RAD001 administered daily/twice weekly combined with PRRT in a suboptimal dose did again not show any significant additional therapeutic effect on subcutaneous human H69 xenografts in nude mice compared to placebo combined with PRRT (Fig. 2C + D). In this experiment no distant metastasis was found after RAD001 therapy. A possible explanation could be
the slow growth rate of the H69 tumor; longer follow up and surgical removal of the primary subcutaneous tumor as performed in the rat experiment 2 was preferred, this was not allowed according to the animal ethical protocol for this study though.

An explanation of the mechanism of action leading to the unexpected metastases in lung, liver and lymph nodes in the rat model cannot be given, based on these studies. Understanding the pathways involved and how they are interconnected is needed to explain the current findings. As recently discussed by Ebos et al. (15) sustained suppression of the VEGF pathway may lead to a rebound in tumor growth, once discontinued. Comparable to our findings with RAD001, acceleration of metastasis was found in preclinical models after short-term treatment with the VEGFR/PDGFR kinase inhibitor sunitinib (16). The fact that in our studies RAD001 treatment was discontinued after 4.5 weeks may have resulted in such rebound effect via VEGFR as well. The twice weekly administration of RAD001 could also have resulted in an incomplete inhibition resulting in a (twice weekly repeated) upregulation of growth pathways. Discontinued mTOR inhibiton could also have stimulated glucose uptake, glycolysis and de novo lipid biosynthesis, which are considered hallmarks of cancer and cancer metastasis. A possible explanation for the higher therapeutic effects found for $^{177}$Lu-DOTATATE only treatment compared to the combination treatment of RAD001 and $^{177}$Lu-DOTATATE could be the fact that in the combination treatment the tumor cell proliferation rate is lowered by RAD001, resulting in an decreased radio sensitivity. The acceleration of metastasis could be caused by an effect on the immune system that could be unique to this particular preclinical CA20948 tumor model. Therefore comparable experiments with other preclinical tumor models, such as the H69 mice model with surgical removal of the primary subcutaneous tumor, will have to be performed. If the results of our studies can be translated to humans, mTOR inhibition treatment should be closely watched especially after discontinuation of this therapy because of adverse effects or in non-compliant patients, despite the positive therapeutic results of mTOR inhibition in different kinds of tumors.


<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>n</th>
<th>tumor volume &gt; 4 cm³</th>
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</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Control</td>
<td>Vehicle only</td>
<td>7</td>
<td>†</td>
</tr>
<tr>
<td>2 RAD001</td>
<td>RAD001 (2x/week, 5 mg/kg bw)</td>
<td>6</td>
<td>†</td>
</tr>
<tr>
<td>3 Combination of low dose ¹⁷⁷Lu-DOTATATE with RAD001</td>
<td>RAD001 (2x/week, 5 mg/kg bw) and 125 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>7</td>
<td>†</td>
</tr>
<tr>
<td>4 Combination of high dose ¹⁷⁷Lu-DOTATATE with RAD001</td>
<td>RAD001 (2x/week, 5 mg/kg bw) and 275 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>7</td>
<td>†</td>
</tr>
<tr>
<td>5 Low dose ¹⁷⁷Lu-DOTATATE</td>
<td>125 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>6</td>
<td>†</td>
</tr>
<tr>
<td>6 High dose ¹⁷⁷Lu-DOTATATE</td>
<td>275 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>7</td>
<td>†</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Control</td>
<td>Vehicle only</td>
<td>8</td>
<td>Surgery</td>
</tr>
<tr>
<td>8 Low dose RAD001</td>
<td>RAD001 (2x/week, 2.5 mg/kg bw)</td>
<td>8</td>
<td>Surgery</td>
</tr>
<tr>
<td>9 High dose RAD001</td>
<td>RAD001 (2x/week, 5 mg/kg bw)</td>
<td>8</td>
<td>Surgery</td>
</tr>
<tr>
<td>10 Combination of low dose RAD001 with ¹⁷⁷Lu-DOTATATE</td>
<td>RAD001 (2x/week, 2.5 mg/kg bw) + 125 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>7</td>
<td>Surgery</td>
</tr>
<tr>
<td>11 Combination of high dose RAD001 with ¹⁷⁷Lu-DOTATATE</td>
<td>RAD001 (2x/week, 5 mg/kg bw) + 125 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>8</td>
<td>Surgery</td>
</tr>
<tr>
<td>12 ¹⁷⁷Lu-DOTATATE</td>
<td>125 MBq ¹⁷⁷Lu-DOTATATE</td>
<td>8</td>
<td>Surgery</td>
</tr>
<tr>
<td>13 RAD001, no tumor</td>
<td>RAD001 (2x/week, 5 mg/kg bw)</td>
<td>7</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Table 1: Treatment groups in studies 1 and 2. BW = body weight, † = euthanasia, n.a. = not applicable. All animals were bearing CA20948 tumors, except for animals in group 13.

Figure 1. Anti-tumor effect by RAD001 + $^{177}$Lu-DOTATATE combination treatment did not lead to better anti-tumor effects compared to $^{177}$Lu-DOTATATE alone and unexpectedly resulted in distant metastasis. **Fig. 1A:** Subcutaneous CA20948 tumor size after treatment with vehicle of RAD001 (control), RAD001 (5 mg/kg), $^{177}$Lu-DOTATATE (125 MBq or 275 MBq) or a combination of RAD001 plus $^{177}$Lu-DOTATATE (Table 1). The red arrow depicts the administration of $^{177}$Lu-DOTATATE. The blue arrows depict RAD001 administrations. Data are presented as mean ± sem. **Fig. 1B:** Mean body weight per treatment group from start of RAD001 treatment. Both combination treatment groups showed loss of body weight beyond day 40. Data are presented as mean. **Fig. 1C:** Survival curves of the different treatment groups, a green dot represents sacrifice of at least one animal because of subcutaneous tumor size > 4 cm$^3$ or a ruptured tumor. A blue dot represents sacrifice of at least one animal because of loss of body weight or poor condition, correlating with metastasis. **Fig. 1D:** Animals with (right) and without (left) metastases in the liver as indicated by the red arrows. **Fig. 1E:** $^{177}$Lu-DOTATATE uptake in subcutaneous primary CA20948 tumors after different doses of $^{177}$Lu-DOTATATE (125 MBq/3.4 ug and 275 MBq/7.5 ug)) as quantified by SPECT.

Figure 2. RAD001 treatment (with or without $^{177}$Lu-DOTATATE) resulted in the occurrence of distant metastasis. **Fig. 2A:** Mean body weight per group from start of RAD001 treatment. Again the dip in body weight in the RAD001-treated animals is observed; from day 40 on in the high-dose RAD001 group, from day 60 on in the low-dose RAD001 group. **Fig. 2B:** Survival curve, censored for metastasis-unrelated death. All RAD001 treatment groups had significantly lower survival rate compared to control and PRRT-only groups. ‘ Animal found death in cage, no metastases upon autopsy. ” Animal did not survive subcutaneous tumor surgical resection, no metastasis upon autopsy. □ Animal with macroscopically visible tumor spill during subcutaneous tumor surgical resection. **Fig. 2C:** Subcutaneous H69 tumor size in NMRI Nu/Nu mice was monitored after treatment with $^{177}$Lu-DOTATATE in combination with vehicle of RAD001(control), RAD001 (5 mg/kg, twice a week) and RAD001 (5 mg/kg, daily). At day 21 a second $^{177}$Lu-DOTATATE treatment was given for reduction of subcutaneous H69 tumor size facilitating a longer follow-up. No additional
therapeutic effect of RAD001 on $^{177}$Lu-DOTATATE treatment is seen in this tumor model. Data are presented as mean. **Fig. 2D;** Survival curve showing no significant difference between combination treatment of $^{177}$Lu-DOTATATE with vehicle RAD001 (control), RAD001 administered twice weekly or RAD001 administered daily.

**Figure 3.** RAD001 treatment resulted in the occurrence of distant metastasis, shown by $^{111}$In-DTPA-octreotide SPECT/CT and in vitro autoradiography. **Fig. 3A;** SPECT/CT of animals representing all treatment groups. The SPECT/CT of control and $^{177}$Lu-DOTATATE treated animals were performed at the end of the experiment at day 150 and only show uptake in kidneys. The SPECT/CTs of the other animals were made just before euthanasia because of tumor growth and show clear uptake in tumor tissue and kidneys. Kd = kidney, LuM = lung metastasis, LiM = liver metastasis, LnM = lymph node metastasis, PST = primary subcutaneous tumor. **Fig. 3B;** autopsy images. Healthy livers (Liv) in control and $^{177}$Lu-DOTATATE treated animals. Distant metastasis in the liver (LvM) in RAD001 treated animals. **Fig 3C;** Hematoxylin/eosin sections of primary subcutaneous tumors (PST) **Fig. 3D;** corresponding $^{111}$In-DTPA-octreotide in vitro autoradiography images **Fig. 3E;** corresponding $^{111}$In-DTPA-octreotide in vitro autoradiography images with addition of a 1000 x excess of unlabeled DTPA-octreotide. **Fig. 3F;** Hematoxylin/eosin sections of distant metastasis in RAD001 treated animals. **Fig. 3G;** corresponding $^{111}$In-DTPA-octreotide in vitro autoradiography images **Fig. 3H;** corresponding $^{111}$In-DTPA-octreotide in vitro autoradiography images with block.
Figure 1

A. Tumor volume (cm³)

- Control
- RAD001
- 125 MBq ¹⁷⁷Lu-DOTATATE
- 275 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 125 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 275 MBq ¹⁷⁷Lu-DOTATATE

Days after start of RAD001 treatment:

B. Body weight (g)

- Control
- RAD001
- 125 MBq ¹⁷⁷Lu-DOTATATE
- 275 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 125 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 275 MBq ¹⁷⁷Lu-DOTATATE

Days after start of RAD001 treatment:

C. Survival (%)

- Control
- RAD001
- 125 MBq ¹⁷⁷Lu-DOTATATE
- 275 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 125 MBq ¹⁷⁷Lu-DOTATATE
- RAD001 + 275 MBq ¹⁷⁷Lu-DOTATATE

Days after start of RAD001 treatment:

D. Images showing tumor growth and weight changes.

E. Uptake in tumor (MBq/cm³)

- 125 MBq
- 275 MBq
Figure 2

A. Body weight (g) over time after start of RAD001 treatment:
- Control
- 125 MBq $^{177}$Lu-DOTATATE
- 2.5 mg/kg RAD001
- 5 mg/kg RAD001
- 2.5 mg/kg RAD001 + 125 MBq $^{177}$Lu-DOTATATE
- 5 mg/kg RAD001 + 125 MBq $^{177}$Lu-DOTATATE
- 5 mg/kg RAD001, no tumor

B. Survival percentage over time after start of RAD001 treatment:

C. Tumor volume (cm$^3$) over time after start of $^{177}$Lu-DOTATATE treatment:
- $^{177}$Lu-DOTATATE + control
- $^{177}$Lu-DOTATATE + RAD001 2x/week
- $^{177}$Lu-DOTATATE + RAD001 daily

D. Survival percentage over time after $^{177}$Lu-DOTATATE treatment:

* $p < 0.05$ compared to control
Figure 3
mTOR inhibitor RAD001 promotes metastasis in a rat model of pancreatic neuroendocrine cancer


Cancer Res Published OnlineFirst November 13, 2012.

Updated version
Access the most recent version of this article at: doi:10.1158/0008-5472.CAN-11-2089

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