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M-TOR inhibitors in the treatment of advanced renal cell carcinoma

Rafał Stec[1], Michał Mączewski[2], Marta Smoter[1], Lubomir Bodnar[1], Cezary Szczylik[1]

[1]Department of Oncology, Military Institute of Health Services, Warsaw, Poland
[2]Department of Clinical Physiology, Medical Centre of Postgraduate Education, Warsaw, Poland

Renal cell cancer (RCC) accounts for approximately 3% of all registered malignancies in Poland. According to the most recent National Cancer Register, 2283 men and 1483 women were diagnosed with renal cancer in 2006. Up to 30% of patients with RCC present with metastatic disease. M-TOR inhibitors became a new therapeutic option for patients with metastatic RCC. Two of them, temsirolimus and everolimus, are currently approved for clinical use for patients with advanced renal cancer. Anticancer activity of m-TOR inhibitors is related to cellular cycle regulation and inhibition of uncontrolled angiogenesis. Based on clinical trials, temsirolimus is indicated as the first line of chemotherapy for patients with at least three poor prognostic factors. Everolimus should be administered as the second line of treatment, for patients who relapsed after antiangiogenic therapy.

Key words: renal cancer, m-TOR inhibitors, temsirolimus, everolimus.

Introduction

Renal cancer is a rare malignancy in Poland, accounting for approximately 3% of all registered malignancies. In 2006, 2283 men and 1483 women were diagnosed with renal cancer [1].

Risk of renal cancer is increased by exposure to chemical compounds, e.g. nitrosamines, carcinogens found in cigarette smoke. A certain proportion of renal cancer cases is related to genetic abnormalities – impaired VHL protein function (von Hippel-Lindau disease) [2].

Five-year survival for stage I cancer ranges from 70% to 90%, for stage II 55–70%, stage III 20–30%, and for stage IV it does not exceed 10%.

Metastases appear in more than 30% of patients undergoing radical surgical treatment (radical nephrectomy) [3]. The most common locations of metastases include: extraperitoneal lymph nodes, lungs, bones, brain and liver.

Clinical studies identified several prognostic risk factors in patients with metastatic renal cancer. Adverse prognostic risk factors related to short survival include Karnofsky's performance status below 80%, lack of nephrectomy, corrected peripheral blood calcium concentration above 10 mg/dl, haemoglobin level below the sex-specific normal limit, and lactate dehydrogenase (LDH) activity in the peripheral blood exceeding 1.5-fold the normal upper limit. Patients without adverse prognostic factors are qualified to the group of good prognosis (median overall survival is 20 months), patients with one or two factors to the group of intermediate prognosis (median overall survival is 10 months), and patients with three or more factors to the group of adverse prognosis (median overall survival is 4 months) [3].

Molecular targeted drugs that are currently approved for the treatment of metastatic renal cancer include, apart from bevacizumab, sunitinib and sorafenib, inhibitors of serine-threonine kinase mTOR (mammalian target of rapamycin).

Inhibitors of serine-threonine kinase mTOR are an important component of therapy for patients with metastatic renal cancer, in particular in patients from the group of adverse prognosis and in patients previously treated with tyrosine kinase inhibitors (sunitinib, sorafenib).

In this paper we review phase I, II and III clinical trials of m-TOR inhibitors in the treatment of metastatic renal cancer and the possibility of their use in Poland.

M-TOR inhibitors – mechanism of action

PI3K/AKT/mTOR pathways

One of the three main signalling pathways related to activity of receptor tyrosine kinases is the PI3K pathway (phosphatidylinositol 3 kinase)/AKT/mTOR. Activation of receptor tyrosine kinases results, through autophosphorylation of a cytoplasmic domain, in activation of a regulatory subunit (p85) and then a catalytic (p110) subunit of phosphatidylinositol 3 kinase (PI3K). Activation of the latter results in formation of phosphatidylinositol 3,4,5-trisphosphate (PIP3) from phosphatidylinositol 4,5-bisphosphate (PIP2) through transfer of a phosphate moiety from adenosine-5'-triphosphate (ATP). Formation of PIP3 on the inner surface of the cellular membrane results in activation of serine-threonine kinase AKT (phosphorylation in the Thr308 position). The phosphorylation is performed by phosphoinositide-dependent kinase1 (PKD1). On the other hand, maximum AKT activity is related to additional phosphorylation (in the Ser473 position) performed by phosphoinositide-dependent kinase 2 (PKD2) [4, 5]. Activated AKT kinase is transported to the cytoplasm and cellular nucleus where it activates e.g. mTOR kinase. This pathway is used by the tumour cells to change phenotype and biology of the tumour [6].

mTORC1 and mTORC2

mTOR forms two complexes: mTOR complex 1 and mTOR complex 2. Furthermore, mTOR complex 1 includes raptor (regulatory associated protein of mTOR), while mTOR complex 2 includes rictor (rapamycin-insensitive companion of m-TOR).

Activated mTOR complex 1 acts through two signalling pathways: S6 kinase (S6K1) and protein binding early eukaryotic initiating factor 4E (eIF4E-4EBP1). 4EBPI, following its activation by mTOR and other kinases, dissociates from eIF4E. Then free eIE4F associates with other eukaryotic initiating factors (A, B, G) and forms eIF4F complex that is involved in the initiation of the protein translation process (c-MYC, cyclin D1, ornithine decarboxylase) required to enter phase S from phase G1 of the cellular cycle [7]. On the other hand, activation (phosphorylation) of S6K1 results in 5'STOP mRNA translation of a coding ribosomic protein, elongating factors and other proteins that are involved in the transit from phase G1 to phase S of the cellular cycle [8].

mTOR complex 2 causes AKT phosphorylation (in the Ser473 position) resulting in phosphorylation and inactivation of "FOXO" proteins that play the role of a transcriptional factor and are involved in apoptosis activation [9]. Normal function of mTOR complex 2 depends on a factor that stabilizes the whole complex, protein mSIN1, which may be of importance for development of drugs that inhibit mTORC2 function [6].

Regulation of transcription of HIF-1α (hypoxia inducible factor-1α and 2α) (mTORC1 and mTORC2) and HIF-2α (only mTORC2) is an important function of mTORC1 and mTORC2 [10].

Mechanism of action

mTOR inhibitors are phase-specific drugs and act mainly in phase G1 of the cellular cycle, selectively inhibiting mTOR kinase. mTOR inhibitors associate with an intracellular protein called FKBP-12 [11], resulting in inhibition of mTOR kinase activity that is involved in cellular division [12, 13]. Inhibition of mTOR kinase activity results in blockade of protein translation (type D cyclins, c-myc, ornithine decarboxylase) involved in regulation of the cell cycle. Apart from regulation of the cell cycle, mTOR kinase is involved in translation of transcriptional factors (HIF-1α and HIF-2α) engaged in adaptation of a tumour cell to hypoxia and production of vascular endothelial growth factor (VEGF) responsible for abnormal angiogenesis. "Control" of a malignant process by mTOR inhibitors mainly depends on regulation of the cell cycle and inhibition of abnormal angiogenesis [13, 14].

A precursor of currently used mTOR inhibitors was found (isolated from *Streptomyces hygroscopicus*) in 1975 and named "rapamycin" after the place where it was found (the Pacific island Rapa Nui). Initially it was found to have potent antifungal and antibacterial properties. Later its antitumor and immunosuppressive actions were demonstrated.

Both rapamycin and its derivatives deforolimus, temsirolimus and everolimus are currently used in clinical practice. Both temsirolimus and everolimus are used in the treatment of metastatic renal cancer.

Temsirolimus

In a phase I clinical trial (Raymond *et al.* [15]), administration of various dose levels of temsirolimus (7.5-220 mg/m^2 – at least one full course – four weekly administrations) in 24 patients resulted in a partial objective response in two patients (one of them received 15 mg/m^2) and so-called smaller objective response in another two patients. The most common drug-related adverse effects included mucositis and skin lesions.

In a phase II clinical trial, 111 patients with advanced cytokine-resistant renal cancer were randomized to 3 different dose levels of temsirolimus, given as weekly intravenous infusions: 25 mg (n = 36), 75 mg (n = 38), and 250 mg (n = 37). The objective response rate was 7% for the whole population (2, 3 and 3 patients for dose levels 25 mg, 75 mg and 250 mg, respectively). Median time to progression for all patients was 5.8 months, and median overall survival was 15 months, without any difference between individual patient groups receiving different doses of the drug. Since no benefits of higher dose levels were demonstrated, a dose level of 25 mg temsirolimus was recommended for further clinical trials.

Median overall survival was two- or even three-fold higher in patients with beneficial or intermediate prognosis versus patients with adverse prognosis (23.8 months, 22.5 months and 8.2 months, respectively). When the results were compared to historical results for patients treated with first line interferon α, patients with intermediate or adverse prognosis were found to benefit the most from the treatment [16].

In a phase I/II clinical trial (Motzer *et al.* [17]) of temsirolimus combined with interferon α (71 patients), the recommended dose levels for phase III clinical trials were 15 mg temsirolimus and 6 MU interferon α. The most common grade 3 and 4 adverse effects in patients receiving the recommended dose level included leucopenia (33%), hypophosphataemia (28%), anaemia (23%), malaise (23%) and hypertriglyceridaemia (13%). Among patients who received recommended dose levels, median time to progression was 7.6 months (95% CI: 5.5 to 11 months) vs. 9.1 months (95% CI: 6.2 to 13 months) for the whole study population, median overall survival was 22.1 months (95% CI: 11 to 26 months) vs. 18.8 months (95% CI: 15.5 to 25 months) and clinical benefit (stable disease + objective response) was found in 44%

(95% CI: 28% to 60%) and 46% (95% CI: 35% to 59%), respectively.

Efficacy of temsirolimus was confirmed by a multicenter, randomized, phase III clinical trial (Hudes *et al.* [18]) that enrolled patients with treatment-naïve advanced renal cancer, presenting with at least three of six adverse prognostic factors such as lactate dehydrogenase activity in peripheral blood exceeding 1.5 × upper normal limit, haemoglobin level below the sex-specific normal limit, corrected peripheral blood calcium concentration above 10 mg/dl, time between diagnosis of renal cancer and treatment initiation more than 1 year, Karnofsky performance status above 80% and presence of multiorgan metastases. Patients were randomized in 1 : 1 : 1 ratio, to one of three treatment arms receiving:

1) interferon α-2a three times weekly, at a dose of 3 MU in week one, 9 MU in week two and 18 MU in week three, provided it was well tolerated (n = 207),
2) temsirolimus at a dose of 25 mg as a weekly intravenous infusion (n = 209),
3) combination treatment: temsirolimus at a dose of 25 mg as a weekly intravenous infusion and interferon α-2a three times weekly, at a dose of 3 MU in week one, 9 MU in week two and 18 MU in week three, provided it was well tolerated (n = 210).

It should be emphasized that the study also enrolled patients with other than clear cell renal cancer (80% with clear cell type cancer and 20% with other histological subtypes) (Table 2).

In a group of patients receiving temsirolimus as monotherapy, median time of overall survival (10.9 months vs. 7.3 months; p = 0.008) and median time to progression (3.8 months vs. 1.9 months; p = 0.001) were prolonged vs. the group of patients receiving only interferon α-2a. No significant differences were found between the combination treatment group and interferon α-2a monotherapy group with regard to overall survival (8.4 months vs. 7.3 months, p = 0.70). The objective response rate and disease stabilization rate were higher in the temsirolimus monotherapy group (32.1%) or combination treatment group (28.1%) vs. the interferon α-2a monotherapy group (15.5%) (p < 0.001 and p = 0.002, respectively) (Table 3) [18].

Histological subgroup analysis demonstrated that patients with clear cell cancer and other than clear cell cancer types (mainly papillary cancer and chromophobe cancer) treated with temsirolimus had comparable median time to progression and overall survival (5.5 months vs. 7.0 months and 10.7 months vs. 11.6 months, respectively). However, patients with other than clear cell cancer types treated with interferon α-2a had shorter median time to progression and overall survival versus patients with clear cell renal cancer (1.8 months vs. 3.7 months and 4.3 months vs. 8.2 months, respectively) (Table 4) [19].

Table 1. Median overall survival in particular prognostic groups of MSKCC scale

Category of risk	Risk factors	Overall survival Median (months)
Low risk	0	20
Intermediate risk	1-2	10
High risk	3-5	4

Table 2. Tumour histological type

Histology (%)	Arm I temsirolimus	Arm II temsirolimus + + interferon	Arm III interferon
Clear cell	81	78	82
Other	9	22	18

Table 3. Efficacy of temsirolimus in comparison to temsirolimus with interferon and interferon alone

	Arm I temsirolimus	Arm II temsirolimus + interferon	Arm III interferon
Progression-free survival – Median (months; 95% CI):			
Investigator	3.8 (3.6-5.2)	3.7 (2.9-4.4)	1.9 (1.9-2.2)
IA	5.5 (3.9-7.0)	4.7 (3.9-5.8)	3.1 (2.2-3.8)
Relapse-free survival – Median (months):	3.8 (3.5-3.9)	2.5 (1.9-3.6)	1.9 (1.7-1.9)
Overall response % (95% CI):	8.6% (4.8-12.4)	8.1% (4.4-11.8)	4.8% (1.9-7.8)
Clinical benefit response (overall response + stable disease ≥ 24 weeks; 95% CI):	32.1% (25.7-38.4)	28.1% (22.0-34.2)	15.5% (10.5-20.4)
Overall survival – Median (months; 95% CI):	10.9 (8.6-12.7)	8.4 (6.6-10.3)	7.3 (6.1-8.8)

IA – independent assessment

Table 4. Progression-free survival and overall survival for patients with clear and other RCC histologies

	Temsirolimus		Interferon α		Temsirolimus vs. interferon α	
Progression-free survival – Median (months; 95% CI):					HR	95% CI
Clear cell	(n = 169)	5.5 (3.8, 7.1)	(n = 170)	3.7 (2.5, 4.6)	0.76	0.60, 0.97
Other	(n = 37)	7.0 (3.9, 8.9)	(n = 36)	1.8 (1.6, 2.1)	0.38	0.23, 0.62
Overall survival – Median (months; 95% CI):						
Clear cell	(n = 169)	10.7 (8.5, 13.0)	(n = 170)	8.2 (6.6, 10.4)	0.82	0.64, 1.06
Other	(n = 37)	11.6 (8.9, 14.5)	(n = 36)	4.3 (3.2, 7.3)	0.49	0.29, 0.85

Table 5. Toxicity of temsirolimus in comparison to temsirolimus with interferon and interferon alone

Adverse event	Arm I temsirolimus n = 208		Arm II temsirolimus + interferon n = 208		Arm III interferon n = 200	
Safety population (%)	3 and 4º AG		3 and 4º AG		3 and 4º AG	
Neutropenia	3	7	15	27	7	12
Thrombocytopenia	1	14	9	38	0	8
Leukopenia	1	6	9	31	5	17
Anaemia	20	45	38	61	22	42
Fatigue	11	51	28	62	26	64
Rash	4	47	1	21	0	6
Nausea	2	37	3	40	4	41
Diarrhoea	1	21	5	27	2	20
Vomiting	2	19	2	30	2	28
Stomatitis	1	20	5	21	0	4
Hyperglycaemia	11	26	6	17	2	11
Hyperlipidaemia	3	27	8	38	1	14
Hypercholesterolaemia	1	24	2	26	0	4
Peripheral oedemas	2	27	0	16	0	8
Loss of weight	1	19	6	32	2	25
Anorexia	3	32	8	38	4	44
Fever	1	24	3	60	4	50
Infection	5	27	11	34	4	14
Pain	5	28	6	20	2	16
Dyspnoea	9	28	10	26	6	24

AG – all grades

Higher toxicity, related to hyperglycaemia, hyperlipidaemia, erythema and peripheral oedema, was observed in the group of patients receiving temsirolimus or combination therapy. Grade 3 and 4 malaise was a common adverse effect in patients receiving interferon therapy or combination therapy and occurred in as many as 26% of patients receiving only interferon ($p < 0.001$) and in 28% of patients receiving combination therapy. This adverse effect was found only in 11% of patients receiving only temsirolimus ($p < 0.001$). Haematological toxicity, manifesting as anaemia, neutropenia and thrombocytopenia, occurred more often in patients receiving combination therapy, as compared to patients treated with interferon ($p < 0.001$) and patients treated with only temsirolimus ($p < 0.001$ for neutropenia and thrombocytopenia; $p = 0.002$ for anaemia) (Table 5) [13].

Currently temsirolimus is approved in Poland for first line therapy of patients with advanced renal cancer (all histological types) with at least three of six adverse prognostic factors. This drug is administered as weekly 30-minute intravenous infusions as a single dose of 25 mg. In case of toxicity development, the dose can be reduced to 20 or 15 mg. Before temsirolimus is used, due to the risk of hypersensitivity or anaphylactic reactions during the first or subsequent infusions, antihistaminic (H1 blocker) premedication and close patient monitoring are recommended.

Temsirolimus, like other rapamycin derivatives, may cause non-infectious pneumonia [20] and therefore spirometry should be considered before the treatment initiation. Aetiology of this adverse effect is unclear. One of the hypotheses stipulates hypersensitivity related to T cells. This hypothesis is supported by results of biopsies of patients with non-infectious pneumonia that demonstrated lymphocytic alveolitis, lymphocytic, interstitial pneumonia, focal fibrosis, bleeding and obliterative bronchopneumonia [21].

Increased incidence of hyperglycaemia and hyperlipidaemia in patients treated with mTOR inhibitors is related to inhibition of mTOR dependent regulation of lipid and glucose metabolism [11, 22].

Everolimus

A phase II clinical trial of everolimus enrolled 41 patients with advanced renal cancer. Most of the patients (83%) received first line therapy based mainly on cytokines (61%) and on other therapy, including antiangiogenic therapy (22%). Clear

Table 6. Efficacy of everolimus group in comparison to "control" group

	Arm I everolimus	Arm II placebo	*p*	HR
Progression-free survival – Median (months; 95% CI): ICR*	4.0	1.9	< 0.0001	0.30
Good risk group (n = 118)	5.8	1.9	< 0.0001	0.35
Intermediate risk group (n = 231)	4.5	1.8	< 0.0001	0.25
Poor prognosis (n = 61)	3.6	1.8	< 0.009	0.39
Probability of progression-free survival after 6 months:	26%	2%		
Overall response %:	1%	0%		
Clinical benefit response (overall response + stable disease ≥ 56 days):	64%	32%		
Overall survival – Median:	NS	NS	0.23	0.83

ICR – Independent Central Review
NS – not significant

cell histology predominated (95%). All study subjects received everolimus 10 mg daily until the disease progression, occurrence of unacceptable toxicity or withdrawal of informed consent for treatment. Six-month progression-free survival was 70%, median time to progression was 11.2 months (95% CI: 1.7 to 36.2 months), median overall survival was 22.1 months (95% CI: 1.4 to 36.4 months) and clinical benefit (stable disease + objective response) was found in 87% of patients (14% partial objective response and 44% stable disease). The most common grade 3 adverse effects included pneumonia (17.9%), blood biochemical abnormalities (30.8%) and haematological abnormalities (thrombocytopenia – 7.7%). No grade 4 adverse effects were observed [23].

In 2008 Motzer *et al.* published the results of a randomized, double blind, phase III clinical trial to compare safety and effectiveness of everolimus versus placebo treatment in patients with metastatic renal cancer, previously treated with sunitinib and/or sorafenib [24]. The study enrolled patients who progressed on therapy based on tyrosine kinase inhibitors (sunitinib, sorafenib), bevacizumab or interferon α.

Patients were randomized in a 2 : 1 ratio to one of two study groups receiving:

1) oral everolimus 10 mg administered daily (n = 272),
2) placebo (n = 138).

In the event of disease progression on therapy, treatment could be unblended and patients could cross over from the placebo group to the everolimus treatment group.

When everolimus was compared to placebo, median time to progression was significantly longer in the everolimus treatment group and was 4.0 months vs. 1.9 months in the control group (p < 0.0001). Subgroup analysis demonstrated prolongation of time to progression in all prognostic groups. No significant prolongation of median time of overall survival was found, which was probably related to patients crossing over from the placebo group to the everolimus group (79 patients who progressed in the placebo group crossed over to open label everolimus) (p = 0.23). The objective response and stable disease rate was higher in the everolimus treatment group (64% vs. 32% in the placebo group) (Table 6).

The following grade 3 and 4 adverse effects were more common in the everolimus treatment group: oral mucositis (p = 0.03), infections (p = 0.03), lymphopenia (p = 0.002), hyperglycaemia (p < 0.0001), hypophosphataemia (p = 0.01), and hypercholesterolaemia (p = 0.03). Furthermore, more cases of non-infectious pneumonia and fatigue were observed but the difference did not reach statistical significance [24]. Table 7 presents a complete list of toxicities.

Everolimus is approved for the treatment of patients with advanced renal cancer (irrespective of its histological type) who progressed on or after antiangiogenic therapy. This drug is administered orally, at a daily dose of 10 mg. In case of side effects, its dose can be reduced to 5 mg.

Everolimus, like temsirolimus and other rapamycin derivatives, can cause non-infectious pneumonia [20] and therefore spirometry should be considered before the treatment initiation. In case of impairment of liver function, dose adjustment is required.

Summary and conclusions

mTOR inhibitors are a new generation of anticancer drugs, used as palliative therapy for metastatic renal cancer irrespective of its histological subtype. Currently their role in clinical practice is strictly determined – temsirolimus as first line chemotherapy for patients with at least three adverse prognostic factors and everolimus as second line chemotherapy after failure of previous antiangiogenic therapy. Comparable efficacy of temsirolimus in all histological types of renal cancer is an advantage of temsirolimus, while its disadvantage is the requirement for administration as weekly intravenous infusions which reduces convenience of the therapy and requires frequent hospital visits, in contrast to everolimus, which is given orally. When we compare toxicity (grade 3 and 4) of both mTOR kinase inhibitors based on two independent (no direct comparison of these two drugs)

Table 7. Toxicity of everolimus group in comparison to "control" group

Adverse event	Arm I everolimus n = 269		Arm II placebo n = 135		Arm III between 3 and 4º
Safety population (%)	3 and 4º	AG	3 and 4º	AG	AG
Neutropenia	0	11	0	3	NS
Thrombocytopenia	< 1	20	< 1	2	NS
Leukopenia	0	26	< 1	8	NS
Lymphopenia	15	42	5	29	0.002
Anaemia	10	91	5	76	NS
Fatigue	1	18	< 1	8	NS
Rash	< 1	25	0	4	NS
Nausea	0	15	0	8	NS
Diarrhoea	1	17	0	3	NS
Vomiting	0	12	0	4	NS
Stomatitis	3	40	0	8	0.03
Hyperglycaemia	12	50	1	23	< 0.0001
Hypertriglyceridaemia	< 1	71	0	30	NS
Hypercholesterolaemia	3	76	0	32	0.03
Hypophosphataemia	4	32	0	7	0.01
Infection	3	10	0	2	0.03
Non-infectious pneumonitis	3	8	0	0	NS
Anorexia	< 1	16	0	6	NS
Asthenia	3	20	< 1	16	NS
Dyspnoea	1	8	0	2	NS

AG – all grades
NS – not significant

phase III clinical trials, we may presume that everolimus is less toxic than temsirolimus. However, such conclusions must be confirmed in a head-to-head comparison of these drugs.

A new direction of studies to optimize treatment of advanced renal cancer is to create a so-called "sequential model" of treatment. It involves use of 1st line bevacizumab combined with interferon α treatment, 2nd line sorafenib, 3rd line sunitinib, and 4th line everolimus in a group of patients with favourable or intermediate prognosis, to obtain time to progression exceeding 27 months and overall survival reaching 40 months [25]. Obviously, this treatment model must be confirmed in a prospective clinical trial.

Off-label use of temsirolimus is also an interesting direction of clinical trials. Currently two phase 3 clinical trials are recruiting patients: temsirolimus versus sorafenib as second line therapy in patients with advanced renal cancer after failure of sunitinib therapy [26] and temsirolimus plus bevacizumab vs. bevacizumab plus interferon α as first line therapy for patients with advanced renal cancer. What is interesting, this study enrols patients from all prognostic groups [27]. Results of these studies will be available soon.

Apart from studies of mTOR kinase inhibitors in the treatment of renal cancer, there are also attempts to use this group of drugs to treat other solid tumours (small cell lung cancer, hepatocellular carcinoma, sarcomas, non-small cell lung cancer, breast cancer, gliomas) [28-33] as well as haematological malignancies [34, 35].

In summary, mTOR inhibitors are a new therapeutic option for patients with advanced renal cancer that should be considered in view of results of conducted clinical trials.

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Address for correspondence

Rafał Stec MD, PhD
Department of Oncology
Military Institute of Medicine
128 Szaserów
04-141 Warsaw
phone/fax +48 22 681 84 37
e-mail: drrafals@wp.pl