Michael Froehner^a
Oliver W. Hakenberg^b
Manfred P. Wirth^a

^aDepartment of Urology, University Hospital, Technical University of Dresden, Dresden, and ^bDepartment of Urology, University Hospital, University of Rostock, Rostock, Germany

Molecular Therapy in Urologic Oncology

Key Words

Molecular therapy · Targeted therapy · Tyrosine kinase inhibitor · Oncology · Prostate cancer · Bladder cancer · Germ cell tumour · Renal cell carcinoma

Abstract

During recent years, significant advances have been made in the field of molecular therapy in urologic oncology, mainly for advanced renal cell carcinoma. In this hitherto largely treatment-refractory disease, several agents have been developed targeting the von Hippel-Lindau metabolic pathway which is involved in carcinogenesis and progression of the majority of renal cell carcinomas. Although cure may not be expected, new drugs, such as the multikinase inhibitors sorafenib and sunitinib and the mammalian target of rapamycin inhibitor temsirolimus, frequently stabilize the disease course and may improve survival. Fewer data are available supporting molecular therapies in prostate, bladder, and testicular cancers. Preliminary data suggest a potential role of high-dose calcitriol and thalidomide in hormone-refractory prostate cancer, whereas targeted therapies in bladder and testicular cancers are still more or less limited to single-case experiences. The great theoretical potential and the multitude of possible targets and drug combinations, however, support further research into this exciting field of medical treatment of urologic malignancies.

Copyright © 2007 S. Karger AG, Basel

Introduction

Molecular or ‘targeted’ therapy is considered to be a new strategy in medical oncology, supplementing the traditional options surgery, irradiation, and chemotherapy. To qualify as targeted therapy, three requirements should be met: the target should be an important metabolic pathway, it should be measurable, and interaction with the target should result in clinical benefit [1]. Targeted therapy differs from traditional antineoplastic chemotherapy in several ways. It has a different toxicity profile (less severe side effects, different spectrum, frequently rash or hand-foot syndrome). Most small-molecule agents can be given orally and interact with one or more molecular targets, usually involved in cellular signalling pathways. Treatment with these agents results in a different response pattern (stabilization of disease rather than measurable remission). Often, there is no clearly defined dose-response relationship. The proof of specific target expression, for instance by immunohistochemistry, enables an individualized treatment, sparing the treatment side effects in patients not expressing the target molecule [2–7].

Several approaches can be used for the interaction with target molecules in genito-urinary cancer treatment. These may consist of competitive inhibition (example: atrasentan, an endothelin receptor antagonist), antibody

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2007 S. Karger AG, Basel
0042–1138/07/0791–0001\$23.50/0

Accessible online at:
www.karger.com/uin

Michael Froehner
Department of Urology, University Hospital, Technical University of Dresden
Fetscherstrasse 74, DE–01307 Dresden (Germany)
Tel. +49 351 458 2447, Fax +49 351 458 4333
E-Mail Michael.Froehner@uniklinikum-dresden.de

Fig. 1. The von Hippel-Lindau pathway in renal cell carcinoma. Non-functioning von Hippel-Lindau gene product (VHL protein, hatched) results in decreased binding and cleavage of hypoxia-inducible factor alpha (HIF- α), subsequent transfer of HIF- α into the nucleus, and binding to HIF- β , leading to the transcription of the growth factors vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The secreted growth factors bind to their receptors (vascular endothelial growth factor receptor, VEGFR, and platelet-derived growth factor receptor, PDGFR) in an autocrine and paracrine manner, causing dimerization and autophosphorylation of the transmembrane receptor protein kinases and activation of downstream signalling pathways (flashes), causing tumour cell and vascular endothelial and stromal proliferation. Data derived from Patel et al. [2] and Rini and Small [8].

binding to a ligand (example: bevacizumab, an antibody against vascular endothelial growth factor; VEGF), antibody binding to a receptor (example: trastuzumab, an antibody against Her2; ErbB2), inhibition of the receptor tyrosine kinase (example: gefitinib, an inhibitor of the receptor of epidermal growth factor; EGF), inhibition of tyrosine kinases in the downstream signalling pathway (example: temsirolimus, an inhibitor of mammalian target of rapamycin; mTOR), or application of a ligand to a receptor (example: calcitriol, binding to the calcitriol receptor). During recent years, several targeted treatment strategies have been evaluated in urologic oncology, with differing success. Some of them offer a treatment option in hitherto almost untreatable disease states and might become a new standard of care in the years ahead. In this article, we summarize the currently available targeted treatment options in urologic oncology. In the rapidly growing field of molecular therapy, we focused on therapies with proven or probable value in clinical practice.

Renal Cell Carcinoma

In the field of urologic oncology, the greatest body of evidence is available supporting targeted therapy of advanced renal cell carcinoma. This disease is notoriously resistant to conventional chemotherapy and radiotherapy and is, therefore, particularly difficult to treat, when

surgery was unable to control the disease. The majority of clear cell renal cell carcinomas, the by far most common type of kidney cancer, harbour a loss of function of the von Hippel-Lindau gene product (chromosome 3p deletion, suppressed expression or inactivating mutations of the gene). In normal tissue, the von Hippel-Lindau protein is involved in the regulation of responses to hypoxia [2, 4]. Figure 1 illustrates the signalling pathway activated by the loss of function of this gene [2, 8]. Several targeted therapies have shown clinical activity in renal cell carcinomas. Molecular treatment may target the ligand of the VEGF receptor (bevacizumab is a monoclonal antibody against VEGF receptor), receptor tyrosine kinases VEGF receptor and platelet-derived growth factor (PDGF) receptor (sunitinib and sorafenib target these receptors), or it may intervene in the downstream signalling pathway (temsirolimus is an inhibitor of the mTOR, a serine-threonine protein kinase involved in the downstream signalling pathway). Besides its inhibitory effect on receptor tyrosine kinases, the multikinase inhibitor sorafenib also interacts with the downstream signalling cascade by inhibiting the serine-threonine Raf-1 kinase [2, 9–11]. The majority of renal cell carcinomas overexpress the EGF receptor and/or the receptor tyrosine kinase ErbB2 (Her2). Both receptor tyrosine kinases may be inhibited by lapatinib [9, 12].

At present, of all targeted therapies, the greatest body of evidence is probably available supporting the clinical

use of sunitinib in metastatic renal cell carcinoma. Sunitinib as a second-line treatment after failure of cytokine-based first-line therapy produced a high rate of partial remissions [13]. In a randomized trial comparing sunitinib with interferon alpha as first-line treatments for metastatic renal cell carcinoma [14], the median progression-free survival was significantly longer in patients receiving sunitinib than in those receiving interferon alpha (11 vs. 5 months). The response rate was higher in the sunitinib group than in the interferon alpha group (31 vs. 6%, $p < 0.001$). There was a trend towards an increased overall survival in the sunitinib arm; the significance level set for the interim analysis was, however, not reached [14]. An example for a partial remission seen during first-line treatment with sunitinib is shown in figure 2.

For sorafenib, mature data from randomized trials are not yet available for the first-line setting. Data from a second-line trial performed in patients progressing during initial systemic treatment [15], however, indicate that this substance has also a promising activity in metastatic renal cell carcinoma. As compared with placebo, the median progression-free survival was longer in patients receiving sorafenib (5.5 vs. 2.8 months, $p < 0.001$), and the partial response rate was also higher with sorafenib (10 vs. 2%, $p < 0.001$). As with the first-line sunitinib trial [14], there was a tendency towards an improved overall survival that did not fit the required significance threshold for the interim analysis [15]. Sorafenib and sunitinib have a favourable side effect profile, with rash and diarrhoea occurring most commonly. Sorafenib treatment harbours a small risk of developing coronary heart disease and myocardial infarction which, however, seems to be outweighed by the clinical benefit of the drug [14, 15].

Bevacizumab is a monoclonal antibody binding and inactivating VEGF, thus potentially developing anti-angiogenic and antitumour activities in renal cell carcinoma. This agent was the first molecular therapy showing clinical activity in metastatic renal cell carcinoma in a randomized trial [16]. As compared with placebo, high-dose bevacizumab (10 mg/kg every 2 weeks) significantly delayed progression in patients with metastatic clear cell renal cell carcinoma with progression during prior cytokine treatment or contra-indications to such treatment. There was, however, no effect on survival [16].

Blockage of the mTOR serine-threonine protein kinase (as a part of downstream signalling pathways) is another promising molecular treatment in metastatic renal cell carcinoma. In a phase 3 trial [17], 626 patients with high-risk metastatic renal cell carcinoma were random-

Fig. 2. Partial remission and reduced vascularization of a liver metastasis of a clear-cell renal cell carcinoma (arrowheads) in a 75-year-old woman after one cycle of sunitinib. **a** Before treatment. **b** After treatment.

ized into three arms: interferon alpha (up to 18 million U s.c. three times a week) versus the mTOR inhibitor temsirolimus (25 mg i.v. once a week) versus temsirolimus (15 mg i.v. once a week) plus interferon alpha (6 million U s.c. three times a week). The median survival was significantly longer in the 25-mg temsirolimus arm as compared with the interferon alpha arm (10.9 vs. 7.3 months, $p = 0.0069$), whereas the lower dose combined with interferon alpha was less effective (median survival 8.4 months, not significantly different from the interferon alpha arm). The toxicity profile was acceptable and was not appreciably different in the treatment arms [17].

Lapatinib has been tested as a second-line treatment in a randomized phase 3 trial in 417 patients with metastatic renal cell carcinoma – 94% had received cytokine therapy, lapatinib dose 1,250 mg daily; control arm: hormonal treatment [12]. Whereas there was no detectable overall survival difference in the whole study population (median 46.9 weeks for lapatinib vs. 43.1 weeks for hormonal treatment, $p = 0.29$), the overall survival was significantly improved by lapatinib treatment in the subgroup (56%) of the patients whose tumour overexpressed EGF receptor proven by immunohistochemistry (median 46.0 weeks for lapatinib vs. 37.9 weeks for hormonal treatment, $p = 0.02$). The patients with EGF receptor-overexpressing tumours apparently had a particularly poor survival when treated with hormonal therapy; this survival disadvantage seemed to be compensated by application of lapatinib. The toxicity was moderate with rash and diarrhoea, each affecting about 40% of the patients receiving lapatinib [12].

Although many molecular treatments have shown single-agent activity in renal cell carcinoma, complete remissions are extremely rare, and all patients are deemed to eventually progress and succumb to their malignancy. To improve response rates and survival or even to cure some patients, the combination of different molecular interventions is a tantalizing strategy. Molecular agents may be combined as ‘horizontal blockade’ in the case of simultaneous inhibition of different receptors (for instance VEGF and PDGF receptors by sunitinib or sorafenib plus EGF receptor by erlotinib or lapatinib) or as ‘vertical blockade’ by intervention at more than one level in the same pathway (for instance bevacizumab plus sorafenib or lapatinib plus temsirolimus). However, such interventions harbour the risk of surprising and significant toxicity and require careful investigations in controlled trials. There are first promising results from combined treatment approaches available. Partial responses were observed by combined sorafenib and bevacizumab treatment even in patients with the sarcomatoid variant of renal cell carcinoma which is a highly aggressive subtype with a particularly poor prognosis [18]. The observed toxic effects were, however, considerable [19].

There is no consensus on the necessity of nephrectomy prior to molecularly targeted therapy for metastatic renal cell carcinomas. Most patients in randomized trials demonstrating efficacy of targeted therapy for renal cell carcinoma underwent nephrectomy initially. There is, however, still no evidence that nephrectomy improves the survival in this setting, as it did in patients subsequently receiving cytokines [20].

Prostate Cancer

Docetaxel-based chemotherapy is an active treatment in patients with hormone-refractory prostate cancer. It has been shown to improve the median survival by approximately 2 months as compared with treatment with mitoxantrone plus prednisolone [21]. Two substances tested combined with docetaxel-based chemotherapy showed promising results in this setting. Although the precise mechanism of action of thalidomide is still unknown [4], it may be regarded as a ‘targeted’ cancer treatment because of its anti-angiogenic and immunomodulatory properties. In a small randomized trial comparing weekly docetaxel (30 mg/m² for 3 weeks of a 4-week cycle) with or without thalidomide (200 mg daily) [22, 23], the median survival was better in the thalidomide group (25.9 vs. 14.7 months, $p = 0.04$). This surprisingly high survival advantage contrasts favourably with the 2-month median survival gained by docetaxel treatment as compared with mitoxantrone plus prednisolone and calls for further evaluation of this regimen in patients with hormone-refractory prostate cancer.

The calcitriol receptor is another target with promising clinical potential in prostate cancer. Experimental in vitro and in vivo models suggest that calcitriol may induce apoptosis and inhibit tumour growth and metastatic spread [24]. In an interim analysis of a double-blind randomized trial comparing high-dose calcitriol with placebo in combination with weekly docetaxel (36 mg/m² for 3 weeks of a 4-week cycle) [25], patients receiving calcitriol had an improved overall survival. The difference just reached significance level in multivariate analysis ($p = 0.035$), but missed it narrowly in univariate analysis ($p = 0.07$). There was only a marginal difference in prostate-specific antigen response rates. High-dose calcitriol had a favourable safety profile [25].

Endothelin-1 is secreted by prostate cancer cells and promotes tumour growth and metastatic spread by autocrine and/or paracrine activity. It has been found to stimulate the mitotic activity in osteoblasts and to decrease osteoclastic bone resorption and osteoclast motility, thus promoting the development of osteoblastic bone metastases [26]. Besides some symptomatic improvement and biochemical responses of prostate-specific antigen and bone turnover markers, however, the clinical benefit of single-agent treatment with the endothelin-1 antagonist atrasentan is limited. In a meta-analysis of more than 1,000 patients with hormone-refractory prostate cancer [27], there was only a marginal difference from placebo concerning disease progression. A possible role of atrasen-

tan as a part of a combination treatment, particularly in patients with bone involvement, needs further evaluation in controlled trials. Based on the available clinical data, approval for atrasentan was not granted by the Food and Drug Administration [26].

Up to now, clinical trials investigating tyrosine kinase inhibitors or monoclonal antibodies as monotherapy for hormone-refractory prostate cancer yielded uniformly disappointing results [28–31].

Bladder Cancer

The molecular pathways involved in carcinogenesis and progression of invasive bladder cancer are increasingly well understood. There are several exciting options to intervene in these pathways in preclinical and clinical testing [32]. Up to now, however, there are still only a few reports on clinically meaningful benefits of molecular treatment in bladder cancer. Invasive bladder cancer cells express the receptor tyrosine kinases EGF and Her2 (fig. 3). Inhibition solely of the EGF receptor with gefitinib was without appreciable additional effect in combination chemotherapy with gemcitabine-cisplatin [33]. Lapatinib inhibits both EGF and Her2 receptor tyrosine kinases and has shown promising activity in advanced breast cancer [34]. In one study [35], patients with advanced urothelial carcinoma and immunohistochemical evidence of either EGF receptor and/or Her2 receptor overexpression who progressed after cisplatin-based first-line chemotherapy received 1,250 mg lapatinib daily as monotherapy. There were no complete and only one (although marked) partial remission by independent radiological review. However, patients with strong expression of one or both markers seemed to benefit from the treatment in terms of stabilization of the disease. The toxicity was mild, with diarrhoea and rash representing the most common side effects [35].

Testicular Cancer

Although a majority of seminomas and a subset of non-seminomas express c-kit [36], identifying them as potential candidates for imatinib treatment, there are no published reports on successful imatinib application in refractory germ cell tumours up to now. Among 6 patients with incurable chemotherapy-refractory germ cell tumours with c-kit expression (no difference between seminomas and non-seminomas was made), only 1 pa-

Fig. 3. Immunohistochemical reactions demonstrating strong staining of the complete surface membrane for the receptor tyrosine kinases EGF(EGFR) (a) and Her2 (Her2neu) (b) in a primarily metastatic urothelial carcinoma of the bladder in a 65-year-old woman. Original magnification $\times 40$.

tient experienced transient stabilization of disease and tumour marker decrease [37]. A minority of refractory germ cell tumours overexpress Her2 [38]. In one case of a cisplatin-refractory germ cell tumour with Her2 expression, treatment with the monoclonal antibody trastuzumab resulted in disease remission [39]. Leydig cell tumours rarely cause metastatic disease that, however, is largely resistant to conventional treatment with chemotherapy or radiotherapy. Since Leydig cell tumours express PDGF, kit ligand, and their receptors, PDGF receptor and c-kit, they are potential candidates for imatinib

treatment. Studies in cell lines and animal models were promising [40]. Experimental treatment in a 76-year-old man with metastatic Leydig cell tumour was, however, without detectable effect [41].

Other Urologic Malignancies

Due to the low frequency of other types of urologic cancers, there are only very sparse data on potentially beneficial molecular treatment strategies. In one study [42], a dramatic clinical improvement has been achieved by a combination of imatinib and thalidomide in a patient with chemotherapy-refractory recurrent undifferentiated prostate sarcoma. Adrenal carcinomas might be attractive targets for molecular therapy [43]; there are, however, still no reports on clinical advances in this field.

Conclusions

Molecular treatment is currently changing the standards of medical treatment of advanced renal cell carcinomas, a type of cancer with very limited non-surgical treatment options. Although much less data support targeted therapy of other urologic malignancies, it is likely that new treatment options will become available in the years ahead. Besides single-agent regimens, the combination of anti-angiogenic drugs with conventional chemotherapy may be a field of possible future advances.

Acknowledgments

The authors thank Dr. Stefan Zastrow for providing the clinical images in figure 2 and Dr. Dag-Daniel Dittert and Prof. Gustavo Baretton for performing the immunohistochemical staining and providing the photomicrographs in figure 3.

References

- Sledge GW: What is targeted therapy? *J Clin Oncol* 2005;23:1614–1615.
- Patel PH, Chadalavada RS, Chaganti RS, Motzer RJ: Targeting von Hippel-Lindau pathway in renal cell carcinoma. *Clin Cancer Res* 2006;12:7215–7220.
- Arora A, Scholer EM: Role of tyrosine kinase inhibitors in cancer therapy. *J Pharmacol Exp Ther* 2005;315:971–979.
- Amato RJ, Jac J: Targeted anti-cancer therapies for renal cancer. *Drugs* 2006;66:2161–2171.
- Collins I, Workman P: New approaches to molecular cancer therapeutics. *Nat Chem Biol* 2006;2:689–700.
- Schultze JL: Voraussetzungen für die Entwicklung einer zielgerichteten, molekular definierten Therapie in der Onkologie. *Med Klin* 2006;101:617–623.
- Krause DS, Van Etten RA: Tyrosine kinases as targets for cancer therapy. *N Engl J Med* 2005;353:172–187.
- Rini BI, Small EJ: Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J Clin Oncol* 2005;23:1028–1043.
- Larkin JM, Eisen T: Kinase inhibitors in the treatment of renal cell carcinoma. *Crit Rev Oncol Hematol* 2006;60:216–226.
- Motzer RJ, Bukowski RM: Targeted therapy for metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:5601–5608.
- Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S: Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nat Rev Drug Discov* 2006;5:835–844.
- Ravaud A, Gardner J, Hawkins R, Von der Maase H, Zantl N, Harper P, Rolland F, Audhuy B, Machiels J, El-Hariry I, Tykier Renal Cell Cancer Study Group and GSK: Efficacy of lapatinib in patients with high tumor EGFR expression: results of a phase III trial in advanced renal cell carcinoma (RCC) (abstract). *J Clin Oncol* 2006;24(suppl):4502.
- Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI: Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:16–24.
- Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM, Figlin RA: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356:115–124.
- Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM; TARGET Study Group: Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125–134.
- Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, Steinberg SM, Chen HX, Rosenberg SA: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–434.
- Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, O'Toole T, Park Y, Moore L: A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC) (abstract). *J Clin Oncol* 2006;24(suppl):LBA4.
- Nagy V, Schneider H, Valansky L, Sokol L: Sarcomatous dedifferentiated renal cell carcinoma mimicking a severe purulent kidney infection. *Urol Int* 2006;76:77–81.
- Sosman JA, Puzanov I, Atkins MB: Opportunities and obstacles to combination targeted therapy in renal cell cancer. *Clin Cancer Res* 2007;13(2 Pt 2):764s–769s.
- Pantuck AJ, Belldegrun AS, Figlin RA: Cyto-reductive nephrectomy for metastatic renal cell carcinoma: is it still imperative in the era of targeted therapy? *Clin Cancer Res* 2007;13(2 Pt 2):693s–696s.
- Aus G, Abbou CC, Bolla M, Heidenreich A, Schmid HP, van Poppel H, Wolff J, Zattoni F; European Association of Urology: EAU guidelines on prostate cancer. *Eur Urol* 2005;48:546–551.

- 22 Dahut WL, Gulley JL, Arlen PM, Liu Y, Fedenko KM, Steinberg SM, Wright JJ, Parnes H, Chen CC, Jones E, Parker CE, Linehan WM, Figg WD: Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol* 2004;22:2532–2539.
- 23 Figg WD, Retter A, Steinberg SM, Dahut WL: In reply. *J Clin Oncol* 2005;23:2113–2114.
- 24 Dawson NA: New molecular targets in advanced prostate cancer. *Expert Rev Anticancer Ther* 2006;6:993–1002.
- 25 Beer TM, Ryan CW, Venner PM, Petrylak DP, Chatta G, Ruether JD, Henner WD, Chi KN, Cruickshank S; ASCENT Investigators' Interim Results from ASCENT: A double-blinded randomized study of DN-101 (high-dose calcitriol) plus docetaxel vs. placebo plus docetaxel in androgen-independent prostate cancer (AIPC) (abstract). *J Clin Oncol* 2005;23(suppl):4516.
- 26 Carducci MA, Jimeno A: Targeting bone metastasis in prostate cancer with endothelin receptor antagonists. *Clin Cancer Res* 2006;12(20 Pt 2):6296s–6300s.
- 27 Vogelzang NJ, Nelson JB, Schulman CC, Dearnaley DP, Saad F, Sleep DJ, Isaacson JD, Carducci MA: Meta-analysis of clinical trials of atrasentan 10 mg in metastatic hormone-refractory prostate cancer (abstract). *J Clin Oncol* 2005;23(suppl):4563.
- 28 Ziada A, Barqawi A, Glode LM, Varella-Garcia M, Crighton F, Majeski S, Rosenblum M, Kane M, Chen L, Crawford ED: The use of trastuzumab in the treatment of hormone refractory prostate cancer: phase II trial. *Prostate* 2004;60:332–337.
- 29 Lin AM, Rini BI, Weinberg V, Fong K, Ryan CJ, Rosenberg JE, Fong L, Small EJ: A phase II trial of imatinib mesylate in patients with biochemical relapse of prostate cancer after definitive local therapy. *BJU Int* 2006;98:763–769.
- 30 Steinbild S, Mross K, Morant D, Köberle D, Ditttrich C, Strumberg D, Hochhaus A, Hanauske A, Burkholder I, Scheulen ME: Phase II study of sorafenib (BAY 43-9006) in hormone-refractory patients with prostate cancer: a study of the Central European Society for Anticancer Drug Research – EWIV (CESAR) (abstract). *J Clin Oncol* 2006;24(Suppl):3094.
- 31 de Bono JS, Bellmunt J, Attard G, Droz JP, Miller K, Flechon A, Sternberg C, Parker C, Zugmaier G, Hersberger-Gimenez V, Cockey L, Mason M, Graham J: Open-label phase II study evaluating the efficacy and safety of two doses of pertuzumab in castrate chemotherapy-naïve patients with hormone-refractory prostate cancer. *J Clin Oncol* 2007;25:257–262.
- 32 Mitra AP, Datar RH, Cote RJ: Molecular pathways in invasive bladder cancer: new insights into mechanisms, progression, and target identification. *J Clin Oncol* 2006;24:5552–5564.
- 33 Philips G, Sanford B, Halabi S, Bajorin D, Small EJ: Phase II study of cisplatin (C), gemcitabine (G) and gefitinib for advanced urothelial carcinoma (UC): analysis of the second cohort of CALGB 90102 (abstract). *J Clin Oncol* 2006;24(suppl):4578.
- 34 Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pientkowski T, Jagiello-Grusfeld A, Crown J, Chan A, Kaufman B, Skarlos D, Campone M, Davidson N, Berger M, Oliva C, Rubin SD, Stein S, Cameron D: Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–2743.
- 35 Wülfing C, Machiels JP, Richel DJ, Grimm MO, Treiber U, De Groot MR, Beuzeboc P, Farrell J, Colman JR, El-Hariry IA: EGF20003: a single-arm, multicentre, open-label phase II study of orally administered lapatinib (GW572016) as single-agent, second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract: final analysis (abstract). *Ann Oncol* 2005;15(suppl 3):4160.
- 36 Kemmer K, Corless CL, Fletcher JA, McGreevey L, Haley A, Griffith D, Cummings OW, Wait C, Town A, Heinrich MC: KIT mutations are common in testicular seminomas. *Am J Pathol* 2004;164:305–313.
- 37 Einhorn LH, Brames MJ, Heinrich MC, Corless CL, Madani A: Phase II study of imatinib mesylate in chemotherapy refractory germ cell tumors expressing KIT. *Am J Clin Oncol* 2006;29:12–13.
- 38 Soule S, Baldrige L, Kirkpatrick K, Cheng L, Gilbert JL, Smith LR, Thurston VC, Vance GH, Einhorn LH, Miller K: HER-2/neu expression in germ cell tumours. *J Clin Pathol* 2002;55:656–658.
- 39 Kollmannsberger C, Pressler H, Mayer F, Kanz L, Bokemeyer C: Cisplatin-refractory, HER2/neu-expressing germ-cell cancer: induction of remission by the monoclonal antibody trastuzumab. *Ann Oncol* 1999;10:1393–1394.
- 40 Basciani S, Brama M, Mariani S, De Luca G, Arizzi M, Vesci L, Pisano C, Dolci S, Spera G, Gnessi L: Imatinib mesylate inhibits Leydig cell tumor growth: evidence for in vitro and in vivo activity. *Cancer Res* 2005;65:1897–1903.
- 41 Froehner M, Beuthien-Baumann B, Dittert DD, Schuler U, Wirth MP: Lack of efficacy of imatinib in a patient with metastatic Leydig cell tumor. *Cancer Chemother Pharmacol* 2006;58:716–718.
- 42 Kok VC, Yeh K, Chang W: Regression of chemotherapy-refractory metastatic tumor from CD117-negative prostate sarcoma with imatinib mesylate plus thalidomide (abstract). *J Clin Oncol* 2006;24(suppl):9557.
- 43 Kirschner LS: Emerging treatment strategies for adrenocortical carcinoma: a new hope. *J Clin Endocrinol Metab* 2006;91:14–21.