Current Treatment in Advanced Renal Cell Carcinoma (RCC): Impact of Targeted Therapies in the Management of RCC

Joaquim Bellmunt*
University Hospital del Mar, Barcelona, Spain

Abstract
Renal cell carcinoma (RCC) is a highly resistant tumour for which there are currently no therapies that are effective across all patient subgroups. Recently, there has been an increased understanding of the molecular pathophysiology underlying RCC. The von Hippel–Lindau/hypoxia–inducible factor pathway has been strongly implicated in RCC. Several key molecules of this signalling pathway, including vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor, and the mammalian target of rapamycin have been identified. The recognition that these molecules play a pivotal role in tumour angiogenesis and tumour cell proliferation has led to the development of novel targeted agents for therapeutic intervention. This article discusses the efficacy of standard treatments for RCC and describes targeted agents that are currently being evaluated in clinical trials. Whilst the results from trials of epidermal growth factor receptor inhibitors have generally been disappointing, bevacizumab, sorafenib, sunitinib, and temsirolimus have shown potential in clinical trials. To date, both sorafenib and sunitinib are well tolerated and have demonstrated activity in phase 3 trials in patients with advanced or metastatic RCC, whilst temsirolimus has shown activity in a subgroup of poor-prognosis patients with advanced RCC.

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* Medical Oncology Service, University Hospital del Mar, Passeig Maritim 25–29, Barcelona 08003, Spain. Tel. +34 93 248 3137; Fax: +34 93 248 3366.
E-mail address: jbellmunt@imas.imim.es.

1. RCC and current treatment options
Renal cell carcinoma (RCC), which accounts for 80–85% of all malignant kidney tumours, is the most aggressive of the urologic cancers [1]. Prognosis of patients with advanced RCC is extremely poor, with a median time to tumour progression (TTP) of 2.4 mo and median overall survival (OS) from time of metastasis of 10.2 mo reported in one study [2] of patients enrolled in a range of clinical trials.

In the past, treatment options for RCC have been extremely limited. RCC is highly resistant to chemotherapy, and single-agent chemotherapy with a variety of drugs has failed to produce response rates (RR) higher than 10% [3,4]. Likewise, only modest activity has been achieved with combination
regimens [5,6]. The cytokines, interferon-α (IFN-α) and interleukin-2 (IL-2) are the current standard therapies for patients with advanced RCC. However, like cytotoxic therapies, RR are low (5–15%) with these agents [7].

Until recently, high-dose IL-2 was the only agent approved by the US Food and Drug Administration for the treatment of advanced RCC. Despite being the sole approved treatment, high-dose IL-2 produces clinical benefit and long-term survival in only a small minority of patients, and, to date, no controlled clinical trials have been able to demonstrate a survival benefit for IL-2 over placebo or non-IL-2 therapies [8,9]. Furthermore, the significant and sometimes serious toxicity associated with IL-2 limits its widespread use, because special facilities are required for its administration and subsequent intensive patient monitoring. IFN-α, on the other hand, has achieved modest improvements in survival compared with noncytokine therapies. However, the responses are not durable [10–12] and, like IL-2, IFN-α is poorly tolerated, with many patients developing flu-like symptoms whilst receiving the drug [13].

Prognostic studies in patients with advanced RCC have shown that the benefits of cytokine therapies are restricted to a highly selected subset of patients with low-risk (good prognosis) disease. In addition, a recent study [14] indicated that patients with papillary RCC are unlikely to respond to treatment with cytokines. Furthermore, because of tolerability and safety issues, these therapies are contraindicated in many patients, including those with pulmonary, cardiac, and autoimmune disease. Consequently, cytokine therapy is not suitable for a large proportion of patients (80% or more) with advanced RCC, and currently there is no proven effective therapy for patients who do not respond to, or relapse after, cytokine-based treatment [15]. In light of the poor prognosis of patients with advanced RCC and the limited available treatment options, there is an urgent need to pursue new approaches for the treatment of advanced RCC. The development of new agents has been facilitated by considerable advances in molecular biology and the recent identification of promising new therapeutic targets.

2. Molecular targets for the treatment of RCC

The von Hippel–Lindau (VHL) pathway plays a critical role in RCC. The VHL gene encodes a cytoplasmic protein that acts as an oxygen sensor. In conditions of normoxia and normal VHL function, VHL forms a multiprotein complex that binds to the transcription factor hypoxia-inducible factor (HIF)1-α, tagging it for degradation [16]. Under hypoxic conditions, the VHL protein complex is disrupted and HIF1-α is protected from degradation. The consequent accumulation of HIF1-α results in the overexpression of genes encoding vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-α (TGF-α) [17]: pivotal events for the initiation of angiogenesis.

VHL disease is an autosomal dominant syndrome caused by germline mutations in the VHL gene [18]. Whilst this hereditary syndrome is rare, it was subsequently discovered that complete inactivation of the VHL gene, due to mutation or methylation, occurs in up to 76% of sporadic cases of clear cell RCC [19]. The inactivation of VHL causes HIF1-α accumulation during normoxic conditions, which in turn leads to the inappropriate overexpression of proangiogenic factors, and the promotion of tumour cell proliferation and angiogenesis.

VEGF is well established as having a central role in angiogenesis, PDGF is believed to play a role in endothelial stabilisation [20], and TGF-α is thought to be critical for autocrine growth stimulation [21] and can enhance signalling via the epidermal growth factor receptor (EGFR) [22], which is overexpressed in 50–90% of RCCs [23]. Activation of EGFR and the VEGF receptor (VEGFR) initiates a downstream signalling cascade involving the Raf/MEK/ERK pathway. Raf kinase, a key molecular component of this signalling pathway, has been shown to mediate cell survival and prevent apoptosis, and is, therefore, another important therapeutic target in RCC [24].

![Fig. 1 – Molecular targets for renal cell carcinoma (RCC).](Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Cancer 2002;2:673–82, copyright (2002).)
Components of other signalling cascades have also emerged as promising targets in RCC. One of these, the mammalian target of rapamycin (mTOR), is a 289-kDa serine-threonine kinase of the phosphoinositide kinase-related protein kinase family. Evidence suggests that mTOR plays an important role in the regulation of cell growth and proliferation. mTOR activation has also been shown to increase HIF1-α gene expression and, consequently, angiogenesis. Therefore, on the basis of all these observations, there is a sound rationale for targeted inhibition of these molecules in the treatment of RCC (Fig. 1) [25,26].

3. Targeted agents in development for the treatment of RCC

Recently, several agents that target components of the VHL pathway have shown activity as single agents in metastatic RCC (Table 1). Recent data from clinical trials involving these agents are described below.

### 3.1. Targeting proliferation

Several clinical studies have been conducted to evaluate the efficacy of EGFR inhibitors. Cetuximab (Erbitux®; Imclone Systems, New York, NY, USA), an anti-EGFR antibody, was evaluated in a single-arm, phase 2 trial [27] in patients with metastatic RCC. In this trial, patients (n = 55) were treated with cetuximab (intravenous [i.v.] infusion) at a loading dose of 400 or 500 mg/m², followed by a weekly maintenance dose of 250 mg/m². However, no objective responses (ORs) were observed and the median TTP was 57 d. No further studies are planned with cetuximab as a single agent for the treatment of metastatic RCC.

In another phase 2 trial [28], the safety and efficacy of ABX-EGF (panitumumab; Abgenix Inc and Amgen Inc, Thousand Oaks, CA, USA), a high-affinity human monoclonal EGFR antibody, was investigated in a single-arm study in patients who had failed or were unable to receive IL-2 or IFN-α. Thirty-one patients received ABX-EGF (1.0, 1.5, or 2.0 mg/kg) for 8 wk. Data revealed that only two ORs

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Target(s)</th>
<th>Description</th>
<th>Clinical development stage in RCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Chimeric mouse/human monoclonal anti-EGFR antibody</td>
<td>No further single-agent studies planned following disappointing phase 2 results</td>
</tr>
<tr>
<td>Panitumumab (ABX-EGF)</td>
<td>EGFR</td>
<td>High-affinity human monoclonal EGFR antibody</td>
<td>Phase 2 (advanced RCC)</td>
</tr>
<tr>
<td>Laptinib (GW572016)</td>
<td>EGFR</td>
<td>Inhibitor of EGFR and ErbB2 tyrosine kinases</td>
<td>Phase 3 (advanced RCC)</td>
</tr>
<tr>
<td>Gefitinib (ZD1839)</td>
<td>EGFR</td>
<td>Small-molecule EGFR tyrosine kinase inhibitor</td>
<td>No further single-agent studies planned following disappointing phase 2 results</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Recombinant humanised monoclonal antibody</td>
<td>Phase 2 (single agent) and phase 3 (in combination with IFN-α) in advanced RCC</td>
</tr>
<tr>
<td>Pazopanib (GW786034)</td>
<td>VEGFR, PDGFR, c-KIT</td>
<td>Tyrosine kinase inhibitor</td>
<td>Phase 3 (advanced RCC)</td>
</tr>
<tr>
<td>Sunitinib (SU11248)</td>
<td>VEGFR, PDGFR, c-KIT, FR-3</td>
<td>Small-molecule tyrosine kinase inhibitor</td>
<td>Approved in the USA for treatment of advanced RCC</td>
</tr>
<tr>
<td>Temsirolimus (CCI-779)</td>
<td>mTOR</td>
<td>Rapamycin ester inhibitor of mTOR</td>
<td>Approved in the EU for treatment of advanced and/or metastatic RCC after failure of IFN-α or IL-2 therapy—now extended to include first-line use</td>
</tr>
<tr>
<td>Everolimus (RAD001)</td>
<td>mTOR</td>
<td>Serine/threonine kinase inhibitor of mTOR</td>
<td>Phase 3 (adjunct)</td>
</tr>
<tr>
<td>Sorafenib (BAY 43-9006)</td>
<td>Raf-1, VEGF-2, VEGF-3, PDGFR, RET, Fgf-3, c-KIT</td>
<td>Dual-action multikinase inhibitor</td>
<td>Approved in the USA for treatment of advanced RCC</td>
</tr>
</tbody>
</table>

EGFR = epidermal growth factor receptor; RCC = renal cell carcinoma; mTOR = mammalian target of rapamycin; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; PDGFR = platelet-derived growth factor receptor; FR-3 = fms-like tyrosine kinase-3; IFN-α = interferon-α; IL-2 = interleukin-2.
were achieved: one each for the 1.0 and 1.5 mg/kg dose.

Lapatinib (Tykerb®; GlaxoSmithKline plc, Research Triangle Park, NC, USA) [29] is an orally active inhibitor of EGFR and ErbB2 tyrosine kinases. A phase 3 trial [30] comparing lapatinib with standard hormone therapy in patients with advanced RCC who had failed first-line cytokine therapy has been completed. The main study endpoints were TTP and OS. At the time of the latest analysis, 417 patients were randomised, and 298 TTP events were reported. The median TTP was similar between treatment groups (15.3 wk for the lapatinib group and 15.4 wk for the hormone therapy group, hazard ratio [HR] = 0.94; p = 0.60). In a subgroup of 241 patients with tumours that overexpressed EGFR (a score of 3+ by immunohistochemistry staining), lapatinib showed a trend towards improved TTP compared with hormone therapy (15.1 vs. 10.9 wk, HR = 0.76; p = 0.06). In addition, lapatinib significantly improved median OS compared with hormone therapy (46.0 vs. 37.9 wk, HR = 0.69; p = 0.02). However, no studies appear to be pursuing the use of lapatinib in RCC.

The antitumour activity of a small-molecule EGFR tyrosine kinase inhibitor, gefitinib (Iressa®; AstraZeneca, Macclesfield, UK), was compared with IFN-α in a small phase 2 study [31] in 18 patients with advanced RCC. In this study, treatment with gefitinib resulted in no complete responses or PRs, and 13 patients (81%) had progressive disease within 4 mo of starting therapy. No further studies with this agent in patients with RCC are currently planned.

Although there is strong biologic rationale for targeting EGFR for the treatment of RCC, clinical trials to date have yielded disappointing results. Few clinical responses have been reported, and TTP has not been prolonged compared with historical data from studies evaluating the efficacy of cytokines. This lack of antitumour activity does not support EGFR-targeted molecules as single agents for the treatment of patients with advanced RCC.

3.2 Targeting angiogenesis

3.2.1 Bevacizumab

Bevacizumab (Avastin®; Genentech Inc, South San Francisco, CA, USA), a recombinant humanised monoclonal antibody, binds to human VEGF and inhibits its biologic activity in both in vitro and in vivo assay systems [32]. Bevacizumab, in combination with carboplatin and paclitaxel, is currently approved by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the treatment of unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. It is also approved, in combination with intravenous 5-fluorouracil-based chemotherapy, for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum [33].

Bevacizumab was evaluated in a randomised, placebo-controlled, phase 2 trial [34] in patients with advanced RCC. Patients (n = 116) were randomised to receive two different dose levels of bevacizumab (1.5 mg/kg [n = 39] or 5 mg/kg [n = 37]) per week i.v. infusion, given every 2 wk at a dose of 3 mg/kg or 10 mg/kg) or placebo (n = 40). The primary endpoints were RR and TTP. Four patients in the high-dose bevacizumab group had a PR, giving a RR of 10% (95% confidence interval [CI], 2.9%–24.2%). High-dose bevacizumab significantly prolonged TTP compared with placebo (4.8 vs. 2.5 mo; HR = 2.55, p < 0.001). TTP was also improved in the low-dose bevacizumab group (3 mo) compared with placebo, but this difference was not statistically significant (HR = 1.26, p < 0.053). No significant differences were observed in survival between groups, possibly because patients in the placebo group, whose disease had progressed, were allowed to cross over to the bevacizumab treatment arm because survival was not a primary endpoint in this trial.

Two phase 3 studies of bevacizumab in combination with IFN-α immunotherapy in patients with clear cell RCC have completed patient accrual in the European Union (EU) and the United States [35]. Results are expected in 2007.

3.2.2 Tyrosine kinase inhibitors

Two tyrosine kinase inhibitors, sunitinib (Sutent®; Pfizer Inc, New York, NY, USA) and pazopanib (GlaxoSmithKline plc, Research Triangle Park, NC, USA), are currently in clinical development for the treatment of advanced RCC. Sunitinib is a small-molecule tyrosine kinase inhibitor that is currently approved as a single-agent therapy in both the United States and the EU for patients with advanced RCC [36]. Early clinical data suggest that the tyrosine kinase inhibitor pazopanib is also active as a single agent in advanced RCC.

Sunitinib is an orally bioavailable inhibitor of the receptor tyrosine kinases VEGFR and PDGFR, which play pivotal roles in angiogenesis, as well as the oncogenic receptor tyrosine kinases c-KIT and RET. Sunitinib was investigated in two sequentially conducted, single-arm, multicentre, phase 2 trials in patients with advanced RCC who had failed initial cytokine therapy (Study 014 [37] and Study 1006 [38]). In these studies, sunitinib was administered in 6-wk...
cycles (50 mg orally, daily): 4 wk on treatment, followed by 2 wk off. The primary endpoint of both studies was overall RR; duration of response was assessed as a secondary endpoint.

Of the 63 evaluable patients in Study 014, 25 (40%) had a PR, with no complete responses. Seventeen patients (27%) demonstrated stable disease (SD) ≥3 mo. Median TTP was 8.7 mo. The most common ≥grade 3 treatment-related adverse events (AEs) were neutropenia (13%), fatigue (11%), diarrhoea (3%), nausea (3%), and stomatitis (2%). In the second study (1006), investigator assessment of 105 evaluable patients found that one patient (1%) had a complete response and 45 patients (43%) had a PR, giving a RR of 44%. However, independent assessment revealed a lower RR of only 34%. In this study, 23 patients (22%) demonstrated SD ≥3 mo. Treatment-related toxicities (≥grade 3) included neutropenia (16%), fatigue (11%), hand-foot skin reaction (7%), hypertension (6%), stomatitis (5%), diarrhoea (3%), and a ≥20% nonreversible decline from baseline in left ventricular ejection fraction (5%).

A phase 3 study [39] compared sunitinib with IFN-α as a first-line treatment in 750 patients with advanced RCC. Sunitinib significantly improved progression-free survival (PFS) compared with IFN-α (47.3 vs. 24.9 wk; HR = 0.394; p < 0.000001). The OR was 35.7% in the sunitinib group and 8.8% in the IFN group (p < 0.000001). Independent assessment revealed a PR in 103 patients (31%) receiving sunitinib compared with 20 patients (6%) receiving IFN-α. SD was observed in 160 patients (48%) receiving sunitinib and 160 patients (49%) receiving IFN-α. In all, 8% of patients in the sunitinib group and 13% of patients in the IFN-α group withdrew from the study because of AEs.

A number of additional studies with sunitinib are in progress, including a phase 2 study investigating continuous dosing of sunitinib in patients with metastatic RCC, a phase 2 study in bevacizumab-refractory patients with metastatic RCC, and an expanded access trial. Sunitinib is also being investigated in combination with immunotherapy and other targeted treatments.

Pazopanib is a potent oral tyrosine kinase inhibitor that targets VEGFR-1, VEGFR-2, and VEGFR-3 to inhibit tumour angiogenesis [40]. The only clinical data available so far for pazopanib came from an open-label, nonrandomised, phase 1, dose-escalation study [41] of 43 patients with relapsed/refractory solid tumours. In this study, pazopanib showed clinical benefit (tumour reduction or SD) in all five patients with advanced RCC when given at doses ≥300 mg twice daily (b.i.d.). The most commonly reported AEs with pazopanib were hypertension and fatigue. Hair depigmentation was also reported at doses ≥800 mg/d.

A phase 2, multicentre, two-stage trial [42] of pazopanib, utilising a randomised discontinuation design, has since been initiated in patients with locally recurrent or metastatic clear cell RCC. The results of this trial are expected in mid-2007. Enrolment has also recently opened for a phase 3 trial [43] of single-agent pazopanib 800 mg once daily versus placebo in patients with locally advanced and/or metastatic RCC.

### 3.3. Targeting both proliferation and angiogenesis

#### 3.3.1. Inhibitors of mTOR

Temsirolimus (Wyeth, Madison, NJ, USA), an inhibitor of mTOR, has been evaluated in a phase 3 trial [44] comparing temsirolimus (25 mg i.v. weekly), IFN-α (up to 18 million units [MU] subcutaneously three times weekly) and temsirolimus (15 mg i.v. weekly) plus IFN-α (6 MU three times weekly) as first-line therapy in poor-prognosis patients with advanced RCC. This study included 626 poor-prognosis patients with advanced RCC and at least three of six poor-risk features. An interim analysis, performed in March 2006 after 442 deaths, showed that temsirolimus alone improved median OS by 49% versus IFN alone (10.9 vs. 7.3 mo; p = 0.0069). The combination of temsirolimus plus IFN-α did not improve OS compared with IFN-α alone. Temsirolimus was also better tolerated than IFN alone, with a reduction of 16% in the proportion of patients with grade ≥3 AEs. The most common AEs were ≥grade 3 asthenia, anaemia, and dyspnoea.

A phase 2 study [45] has recently been reported with RAD001 (everolimus; Novartis International AG, Basel, Switzerland), an oral serine-threonine kinase inhibitor of mTOR. RAD001 was well tolerated with RAD001 (everolimus; Novartis International AG, Basel, Switzerland), an oral serine-threonine kinase inhibitor of mTOR. RAD001 was well tolerated at doses up to 10 mg orally daily and demonstrated promising antitumour activity, with 33% of patients achieving a PR and a median TTP of >3 mo in 86% of patients.

#### 3.3.2. Sorafenib

Sorafenib (Nexavar®; Bayer Healthcare, West Haven, CT, USA) is a multikinase inhibitor that simultaneously targets upstream receptor tyrosine kinases (VEGFR-2, VEGFR-3, PDGF-β, RET, fms-like tyrosine kinase-3, and c-KIT) and downstream serine/threonine kinases (C-Raf, B-Raf) in both the tumour cell and the tumour vasculature. Sorafenib is currently approved in the United States for the treatment of advanced RCC [46] and in the EU for the treatment of advanced RCC [46].
treatment of RCC in patients who have failed prior IFN-α or IL-2–based therapy or are considered unsuitable for such therapy [47].

Sorafenib has been evaluated in a phase 2, randomised discontinuation trial [48] in patients with metastatic RCC. In this study, patients received sorafenib (400 mg orally, b.i.d.) for a 12-wk run-in period, followed by randomisation of potential responders (patients with tumour shrinkage/growth of <25%) to continue sorafenib or placebo. Continued treatment with sorafenib significantly prolonged PFS (24 vs. 6 wk for placebo, p = 0.087; Fig. 2). Moreover, 70% of patients receiving sorafenib had tumour shrinkage or disease stabilisation following the 12-wk run-in period. A subgroup analysis of data from 32 patients with RCC from this study who had received no prior systemic therapy revealed a median PFS of 40 wk [49]. Six patients (18.8%) achieved a PR, 8 patients (25%) achieved a minor response, and 10 patients (31.3%) had SD, yielding a disease control rate of 75%. In addition, among these 32 patients, sorafenib demonstrated a favourable toxicity profile and did not impair quality of life.

The potential of sorafenib as a first-line treatment for RCC is currently being investigated and compared with IFN-α 2a in a phase 2 clinical trial [50]. The primary endpoint of the study is PFS, with secondary endpoints of disease control rate and health-related quality of life. Initially, patients (n = 188) were randomised to receive sorafenib (400 mg b.i.d. orally) or IFN-α 2a (9 MU three times weekly). On disease progression, sorafenib-treated patients receive a higher dose of sorafenib (600 mg b.i.d.); patients treated with IFN-α 2a receive sorafenib (400 mg b.i.d.). Preliminary safety data were presented at the 2006 American Society of Clinical Oncology (ASCO) meeting. In all, 8.2% of patients treated with sorafenib experienced an AE of grade 3 or higher compared with 11% of patients treated with IFN-α 2a. The most common ≥grade 3 AEs with sorafenib were diarrhoea (24.7%), fatigue (14.4%), hypertension (13.4%), nausea (5.2%), and hand–foot skin reaction (6.2%). The most common ≥grade 3 AEs experienced by patients treated with IFN were diarrhoea (5.5%), fatigue (20.9%), fever (18.7%), nausea (13.2%), and flu-like syndrome (6.6%). PFS data are expected to be presented in 2007.

Sorafenib has been evaluated in a phase 3, second-line trial [51]: the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET). TARGET is the largest, randomised, placebo-controlled trial ever conducted in patients with advanced RCC (described in the article by Dr Escudier in this supplement). Sorafenib demonstrated a favourable safety profile, with the rate of discontinuations due to AEs similar between sorafenib (10%) and placebo (8%). There was also a statistically and clinically significant improvement in PFS and clinical benefit compared with placebo. The promising efficacy in phase 2 and phase 3 studies has prompted the initiation of clinical trials of sorafenib in combination with immunotherapy and other targeted agents.

4. Conclusions and future directions for targeted therapies for RCC

The development of molecular-targeted therapies during the past decade is expected to revolutionise the treatment of RCC. Recent data from clinical trials have shown that EGFR inhibitors, when used alone, do not demonstrate clinical benefit. In contrast, responses have been reported in patients treated with the anti-VEGF agent bevacizumab, although no survival data have yet been reported. Clinically meaningful benefit in terms of PFS in the first-line setting has been shown with the tyrosine kinase inhibitor sunitinib, with 8% of patients discontinuing therapy because of AEs. To date, in the second-line setting, the multikinase inhibitor sorafenib is the only targeted treatment that has demonstrated clinical benefit with limited impact on patient tolerability in a large, randomised, phase 3 trial in advanced RCC. The long-term impact of these treatments on OS still needs to be demonstrated. Efficacy of these agents in different clinical settings and of combinations of targeted therapies are currently under investigation; preliminary results are promising.
Conflicts of interest

Joaquim Bellmunt has received consulting and lecture fees from Bayer, Pfizer, and Wyeth, and lecture fees from Novartis.

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References


