Table 1 – Objective response rates in RCC studies as assessed by core laboratory

Best overall response rate (ORR) *n*(%)	Pivotal trial (*N* = 106)	Supportive trial (*N* = 63)
Complete response (CR)	0	0
Partial response (PR)	27 (26)	16 (25)
Stable disease (⩾6 weeks)	65 (61)	–
Progressive disease	14 (13)	–
ORR (CR+PR), % (95% confidence interval)	26 (18–35)	25 (15–38)

CONDITIONAL APPROVAL OF SUNITINIB

Laurie Strawn. *Regulatory Affairs, Pfizer Inc., 10646 Science Centre Dr., 92121 San Diego, CA 92121, USA*

E-mail address: laurie.strawn@pfizer.com

Sunitinib malate (Sutent) is a small molecule ATP site-directed competitive inhibitor. It inhibits multiple processes necessary for tumour growth, including tumour cell proliferation and angiogenesis, through its action on multiple receptor tyrosine kinases.[1]

The initial development strategy for this anticancer agent was to pursue approval for treating gastrointestinal stromal tumour (GIST) and renal cell carcinoma (RCC) in parallel based on the scientific rationale that GIST progression is characterised by KIT or platelet-derived growth factor receptor (PDGFR) mutations and that RCC is highly vascular and expresses vascular endothelial growth factor receptor (VEGFR) as well as PDGFR. Preliminary efficacy data on sunitinib from phase I studies demonstrated that sunitinib had activity across tumour types, including GIST and RCC.

For RCC, the manufacturer's initial strategy was to seek accelerated approval in United States based on two phase II studies in cytokine-refractory patients using a primary endpoint of objective response rate. As shown in Table 1, the resulting response rates were much higher than historical data for any other treatment. A subsequent phase III study in treatment-naïve patients would be the basis for full approval in the United States, the European Union, and the rest of the world. The primary endpoint would be progression-free survival (PFS) as a means of demonstrating clinical benefit.

Scientific advice was sought about the possibility of registering sunitinib in the European Union based on the phase II RCC studies. The feedback indicated that response-rate studies from two phase II studies would be unlikely to provide sufficient evidence for registration. Nevertheless, the company decided to seek approval in the European Union because of the unmet need for RCC patients and the compelling and consistent study results. In addition, interim data from a randomised Phase III study comparing sunitinib and interferon-α in treatment-naïve RCC patients were expected to be available during the review period. The marketing authorisation application (MAA) would also include randomised GIST data showing safety in 202 additional patients and efficacy in a second tumour type. Additionally, the company could withdraw the RCC indication from the MAA if members of the Committee for Medicinal Products for Human Use (CHMP) objected. Ultimately, sunitinib received an Orphan Drug Designation.

In its assessment report, the CHMP requested better justification of clinical benefit from the phase II RCC data. Members of the Scientific Advisory Group Oncology met in March 2006 and concluded that the high response rate was likely to translate into a clinically relevant effect on PFS and overall survival in RCC patients. The supporting data were deemed to be of high quality with radiologic confirmation of progressive disease on cytokine therapy at recruitment and responses to sunitinib on study. The group considered drug toxicity to be manageble. Additionally, the interim analysis of the phase III study showed an ORR of 26% for sunitinib and 7% for interferon-α. The conclusion was that the benefit–risk ratio was positive.

Nevertheless, several CHMP members thought the data were inadequate for a normal marketing authorisation. Therefore, conditional approval was granted in April 2006 with a specific obligation for subsequent normal approval to submit PFS data from the phase III randomised study in treatment-naïve RCC patients. The specific obligation applied to both RCC and GIST because they were included in the same MAA.

The interim results of the phase III study showed that PFS was significantly longer for patients treated with sunitinib than with interferon-α. Pfizer submitted these data and requested accelerated review (60 days instead of 90). CHMP adopted a positive opinion for a new indication for advanced and/or metastatic RCC. A normal marketing authorisation was granted for both indications 6 months after conditional authorisation.

RCC patients benefited by having earlier access to an effective new therapy than would have been the case if phase III data were required. This was made possible because Pfizer chose to include RCC in the initial MAA despite scientific advice that the phase II RCC data were probably not sufficient for approval. However, the company had a contingency plan (i.e. to withdraw RCC indication if objections were encountered). CHMP was willing to grant conditional marketing authorisation although the legislation was only recently put in place.

Dr. Bob Milsted congratulated Dr. Strawn on the first conditional approval granted in the European Union.

CONFLICT OF INTEREST STATEMENT: Dr. Laurie Strawn Ph.D. the author of this report is a full time employee of Pfizer Inc., she can confirm that there is no conflict of interest involved with any matters presented in this paper.

Reference:

1. Sun L et al. Discovery of 5-[5-fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide, a novel tyrosine kinase inhibitor targeting vascular endothelial and platelet-derived growth factor receptor tyrosine kinase. *J Med Chem* 2003;**46**:1116–9.

doi:10.1016/j.ejcsup.2007.09.041