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**The latest developments from US FDA drug and biologic advisory committee meetings.**

# Today's Headline: Unanimous Support for Pfizer's Inlyta for Advanced Renal Cell Carcinoma

**December 7, 2011**
**Meeting Begin Time:** 7:59 a.m. | **End Time:** 11.33 a.m.

***IN THIS ISSUE***



**Subject:** New drug application (NDA) 202324, proposed trade name Inlyta (axitinib) tablets, Pfizer, Inc, proposed for the treatment of patients with advanced renal cell carcinoma.

**Announced in the Federal Register**
October 24, 2011 (IDRAC 133088)
(Volume 76, Number 205)

## Decision / Voting

The Oncologic Drugs Advisory Committee (IDRAC 118092) (ODAC) offered unanimous support for the benefit/risk ratio of Inlyta (axitinib) tablets to treat advanced renal cell carcinoma (RCC), also called metastatic (mRCC). Proposed by Pfizer, Inc, the new molecular entity is intended for patients who have previously failed first-line systemic therapy. Committee members based their support on the results of a single phase 3 trial. While some members stated they had cast their favorable vote reluctantly, they also asserted that axitinib represents a needed treatment alternative and that the sponsor had met regulatory requirements for approval.

| FDA Questions to the Committee | Vote | | Comments |
|---|---|---|---|
| | Yes | No | |
| Is the benefit/risk evaluation favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy? | **13** | 0 | |

There was committee discussion about the efficacy of axitinib versus currently approved tyrosine kinase inhibitors used to treat RCC. In response, the FDA reminded committee members that axitinib is being reviewed for "regular" approval, not accelerated. Regulations governing the regular approval process demand only that drugs demonstrate safety and efficacy; there is no requirement that comparative safety and efficacy be demonstrated. ODAC members agreed, and some noted that axitinib is the first RCC drug that has been compared in pre-approval clinical trials against an approved agent. In the phase 3 trial presented, axitinib demonstrated a better hazard ratio (HR) than the comparator [sorafenib (IDRAC 128887) (Nexavar, Bayer HealthCare)], albeit only marginally better. In that regard, the axitinib sponsor exceeded regulatory requirements for approval.

ODAC members also discussed the toxicity profile of axitinib, noting that overall toxicity is at a level similar to that of currently approved drugs. While the degree of toxicity is similar, the axitinib toxicity profile is different; this was considered advantageous. Different patients will respond differently to various toxicities, so it is useful to have a variety of drugs approved and

available to them. The advantages of adding an RCC drug with a different toxicity profile was also mentioned when members discussed the FDA conclusion that axitinib is unlikely to raise overall survival (OS) rates.

## Background Information

At the morning session of this meeting of the Oncologic Drugs Advisory Committee (IDRAC 118092) (ODAC), the committee reviewed new drug application (NDA) 202324 for Pfizer, Inc's Inlyta (axitinib) tablets as a treatment for patients with advanced renal cell carcinoma (RCC). A new molecular entity, axitinib is a small molecule tyrosine kinase inhibitor. It selectively inhibits vascular endothelial growth factor (VEGF) receptors 1, 2 and 3, which can influence tumor growth, vascular angiogenesis, and cancer progression. It also inhibits platelet-derived growth factor (PDGF) and colony-stimulating factor-1 (CSF-1) receptor tyrosine kinases.

Men are approximately twice as likely as women to develop kidney cancer, according to the American Cancer Society (ACS). Of all kidney cancer cases, approximately 90% are RCC; the remainder are transitional cell cancer (TCC). There were an estimated 58,240 new cases of RCC in 2010 and 13,040 RCC deaths, according to statistics presented by the FDA. The ACS considers RCC to be "relatively rare" overall, representing about 3% of all adult cancers. RCC is the seventh most common type of cancer in men and the eighth most common in women, according to the FDA. RCC progresses to become advanced (metastatic) cancer in about 30% of adult patients diagnosed with the disease, according to the National Kidney Foundation (NKF).

While the cause of kidney cancer is unknown, risk factors have been linked to the disease, according to the NKF. These include smoking, obesity, blood pressure, and family history of kidney cancer. People with advanced chronic kidney disease (CKD) that requires dialysis are also at heightened risk. Typical treatments for kidney cancer involve a combination of nephrectomy, radiation therapy, immunotherapy, chemotherapy, and hormone therapy.

***Proposed Indication***

- *Inlyta (axitinib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).*

***Proposed Dose***

- *Axitinib tablets, oral, 5 mg starting dose, twice daily (BID).*

***Regulatory History***

| | |
|---|---|
| December 2001 | Initiation of investigational new drug (IND) application 63662 for axitinib. |
| May 2007 | The FDA and sponsor held an end-of-phase 2 meeting. The FDA recommended overall survival (OS) as a primary endpoint and discouraged interim analyses for efficacy based on PFS. |
| January 2008 | The FDA denied a special protocol assessment (SPA) based on 1) PFS as primary endpoint; 2) potential interim efficacy analyses by the data monitoring committee (DMC); 3) inadequate case report forms; 4) inadequate safety monitoring during the trial; and 5) continued treatment despite documented disease progression. |
| April 2008 | The FDA granted SPA with caveat that improvements in the primary endpoint of PFS must be both clinically and statistically significant. |
| August 2009 | The sponsor began a phase 3 trial in the first-line RCC setting. |
| January 2010 | A pre-NDA meeting was held. The sponsor proposed "advanced RCC" for the indication, and the FDA noted that the indication will reflect the population studied. The sponsor also indicated that a second ongoing Phase 3 trial in second-line advanced RCC may be amended to include treatment-naïve patients. The FDA suggested that the trial be powered to detect a realistic improvement in OS. |
| February 2011 | Axitinib was granted orphan status (IDRAC 26135) in Europe for RCC. |
| April 2011 | The FDA designated the axitinib filing for standard review. |
| June 2011 | The sponsor filed a marketing authorization application (IDRAC 14888) (MAA) in the European Union (EU) for use of axitinib in the treatment of patients with advanced RCC after failure of prior systemic treatment; it was accepted for review. |

| | |
|---|---|
| February/March 2011 | Target PDUFA action date timeframe. |

In the afternoon session of this meeting, the ODAC will review NDA 202799 from Affymax, Inc, for peginesatide injection, proposed as a treatment for anemia associated with chronic renal failure in adult patients on dialysis.

## Regulatory Issues

The phase 3 trial of axitinib presented in support of this NDA used progression-free survival (PFS) as the primary endpoint. PFS is defined as the time from randomization until objective tumor progression or death, according to the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May-2007 (IDRAC 70060) [Guidance Bulletin (IDRAC 52959)]. As noted in the Briefing Information (IDRAC 135614) for this meeting, PFS has been used as the primary endpoint in the "vast majority" of trials for drug approvals to treat patients with advanced RCC.

The 2007 guidance notes that formal validation of PFS as a surrogate for survival can be difficult for a variety of reasons. Some of those reasons include:

- Typically, data are inadequate for a robust interpretation of the correlation between effects on survival.
- Cancer trials frequently are small. The proven survival benefits for existing drugs are "modest."
- The role of PFS as an endpoint to support licensing approval varies among different cancer settings.
- The ability of improved PFS to represent direct clinical benefit or to act as a surrogate for clinical benefit depends on 1) the magnitude of the effect and 2) the risk-benefit ratio of the new treatment versus available therapies.

The guidance cites other disadvantages to using PFS as an endpoint, including lack of standardized definitions. PFS is imprecisely measured, and particularly subject to assessment bias in open-label studies. It also requires frequent radiological or other assessments, as well as balanced timing of assessments across treatment arms.

The 2007 guidance also addresses issues related to other potential endpoints in clinical trials for cancer indications. These include overall survival (OS), symptom endpoints (patient reported outcomes [PROs]), disease-free survival (DFS), objective response rate (ORR), time-to-treatment failure (TTF), and complete response.

In terms of clinical trial design, there are no standard regulatory criteria for defining progression, according to the guidance. Historically, applicants have used various criteria, including the Response Evaluation Criteria in Solid Tumors (RECIST). Studies should be blinded when possible. At a minimum, assessments should be subjected to a blinded independent adjudication team, generally consisting of radiologists and clinicians, according to the FDA [See the IDRAC Expert Report, Clinical Research: Initiation and Conduct of Clinical Trials (IDRAC 34592)].

EU guidelines recommend using OS as a secondary endpoint when PFS is used as the primary endpoint [Committee for Medicinal Products for Human Use (CHMP) Guideline CPMP/EWP/205/95 Rev 3, Corr.: Evaluation of Anticancer Medicinal Products in Man, 14-December-2005 (IDRAC 54541)]. Likewise, if OS is the primary endpoint, PFS should be the secondary. (OS is defined the time from randomization to death from any cause.) When there is a large effect on PFS, a long expected survival after progression, or a clearly favorable safety profile, precise estimates of OS may not be required for approval, according to the CHMP.

## Clinical Issues

Efficacy and safety of axitinib as a second-line therapy for metastatic RCC were assessed in a single phase 3 clinical trial (A4061032), the AXIS trial. AXIS included 723 subjects who had experienced failure of one previous RCC therapy. The controlled, open-label, multicenter trial randomized subjects to receive either a 5 mg oral dose twice daily (BID) of axitinib or a 400 mg oral dose BID of sorafenib (IDRAC 128887) (Nexavar, Bayer HealthCare). The primary efficacy endpoint was PFS, as assessed by an independent review committee (IRC) consisting

of 2 blinded radiologists. Secondary endpoints included OS, ORR, duration of response, and investigator-assessed PFS.

In the majority of patients in AXIS, the prior treatment received was sunitinib (IDRAC 121623) (Sutent; Pfizer, Inc) (53.7% of axitinib patients; 53.9% of sorafenib patients). A significant number of patients had received cytokine (34.9% of axitinib patients; 34.5% of sorafenib). The other drugs received previously were bevacizumab (IDRAC 131721) (Avastin; Genentech, Inc) (8% of axitinib patients and 8.3% of sorafenib) and temsirolimus (IDRAC 127426) (Torisel; Pfizer) (3.3% of axitinib patients, 3.3% of sorafenib). AXIS subjects received treatment until the development of progressive disease, unacceptable toxicity, protocol deviation, and/or consent withdrawal.

As stated previously, the FDA's Briefing Information (IDRAC 135614) notes that PFS was the primary efficacy endpoint in the "vast majority" of trials for approval of drugs to treat advanced RCC. The appropriate endpoint for drugs in the second-line setting is "unclear." Given the shorter expected duration of OS in the second-line setting, the FDA has suggested that use of OS as the primary endpoint could be considered.

***Safety***

The safety analysis was performed primarily on the 714 patients who received one or more dose of axitinib or sorafenib. In terms of the types of adverse events (AEs), the FDA states that the axitinib safety profile is comparable to that of other drugs in the same class of small molecule inhibitors of the VEGF pathway. Common AEs included diarrhea, nausea, fatigue, asthenia, hypertension, and dermatologic events.

Less common serious adverse events (SAEs) included arterial and venous thrombotic events, gastrointestinal (GI) perforation, bleeding events, hypothyroidism, dysphonia, proteinuria and reversible posterior leukoencephalopathy syndrome. Nonfatal SAEs occurred in 34.8% of patients on the axitinib arm and 32.7% on the sorafenib arm.

There were 113 total deaths on the axitinib arm, and 109 on the sorafenib arm. More deaths on the axitinib arm were associated with treatment-emergent adverse events (TEAEs) than on the sorafenib arm (2.5% versus 1.1%). On the axitinib arm, 9.7% of deaths occurred within 28 days of last drug dose; 6.5% of deaths on the sorafenib arm occurred within 28 days of the last drug dose.

***Efficacy***

The efficacy analysis was based primarily on the intent-to-treat (ITT) population of 723 patients. At the time of the final analysis, 402 patients had experienced a PFS event. The median PFS was 6.7 months (95% CI 6.3-8.4) for axitinib and 4.7 months (95% CI 4.6-5.6) for sorafenib, with a hazard ratio of 0.67 (95% CI 0.55-0.81; p-value <0.0001).

The FDA identified 2 issues of concern. First, the observed PFS benefit was driven by the subset of patients who were treated with cytokines as first-line systemic treatment, according to the agency. In North America and in Europe, patients were almost twice as likely to receive sunitinib as prior treatment versus cytokines, leading the agency to question whether PFS benefit was driven by a subset of patients that is likely to be scarce in the US.

Overall, the difference in median PFS was approximately 2 months. However, the difference in median PFS for patients previously treated with cytokines was 5.6 months (HR 0.47; 95% CI: 0.32-0.68); the difference in patients previously treated with sunitinib was 1.4 months (HR 0.74; 95% CI: 0.57-0.96). (The numbers of patients who received prior bevacizumab or temsirolimus treatment were too small for reliable analysis.) The FDA stated that the PFS benefit is not apt to translate to an OS benefit: with more than half the events needed for the final analysis, the hazard ratio was 1.009 (95% CI: 0.77-1.31).

No sorafenib patients were crossed over to axitinib after progression. The response rate is 19.5% on the axitinib arm, compared to 9.4% on the sorafenib arm. Although more than half of subjects had received sunitinib and slightly more than one-third had received cytokines, there were more responses on the axitinib arm in patients previously treated with cytokines than patients previously treated with sunitinib.

The FDA's second stated concern pertains to the benefit/risk ratio. The agency has asked the ODAC to consider whether the benefit/risk ratio is favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy. The committee was asked to vote on a benefit/risk question at this meeting.

## Medical Issues

The prognosis for RCC patients with locally advanced or metastatic disease is poor, according to the FDA's Briefing Information (IDRAC 135614) for this meeting. While surgical treatment of localized RCC is associated with excellent potential for long-term survival, surgery and traditional chemotherapy have not been shown to affect survival in patients with advanced RCC. Cytokines (e.g., interferon-α [IFN-α] and interleukin-2 [IL-2] have response rates ranging from 7% to 23%, according to the FDA. High-dose IL-2 has been shown to induce durable complete responses in approximately 5% of treated patients. The toxicity associated with these agents has diminished their use, however. Treatment options for patients with advanced RCC have increased over the last 6 years from IFN-α and IL-2 to 6 new agents with 2 different modes of actions (see *Market Issues*).

RCC subtypes vary in aggressiveness and treatment response. When determining patient prognosis, it can be as important to identify the RCC subtype or cell type as it is to identify the RCC stage or grade, according to the Kidney Cancer Association (KCA). The ACS notes several subtypes of RCC, including:

- Clear cell (conventional) RCC is the most common form of RCC, representing approximately 70% of all cases.
- Papillary RCC is the second most common form of RCC, representing approximately 10% of all cases. Papillary tumors feature "finger-like projections" called *papillae*.
- Chromophobe RCC represents approximately 5% of all RCC cases.
- Collecting duct carcinoma typically is metastatic when diagnosed, according to the KCA More common among younger patients, collecting duct carcinoma is very aggressive and represents less than 1% of all kidney cancers.
- Unclassified RCCs comprise less than 1% of all RCCs, according to the KCA. The structure and genetic features of unclassified RCC cells are unlike those of other RCC subtypes; tumors tend to be very aggressive.

## Pharmacology Issues

As noted previously, axitinib is an oral inhibitor of the VEGF, PDGF and CSF-1 receptor tyrosine kinases. It suppresses angiogenesis and has demonstrated inhibition of VEGF-stimulated endothelial cell proliferation and survival at subnanomolar concentrations. Axitinib is chemically designated as N-methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-400 6-ylsulfanyl]-benzamide. The molecular formula is C22H18N4OS, and the molecular weight is 386.47 Daltons.

## Market Issues

The Oncologic Drugs Advisory Committee (IDRAC 118092) (ODAC) met to discuss an NDA by Pfizer, Inc, for Inlyta (axitinib) tablets, as a treatment for advanced RCC. The FDA approved 6 drugs for RCC between December 2005 and October 2009, according to an agency press release (IDRAC 96190). Table 2 lists the treatments currently available for advanced RCC. One of the 6, everolimus (IDRAC 127831) is indicated as a second-line treatment of advanced RCC, following failure of treatment with sunitinib (IDRAC 121623) or sorafenib (IDRAC 128887). The other 5 drugs have the broad indication of treatment for advanced RCC.

**Table 2. FDA-Approved Treatments for Advanced RCC (ATC: L01X)**

| Trade Name | Generic Name | Company |
|---|---|---|
| Afinitor (IDRAC 127831) | everolimus | Novartis Pharmaceuticals Corp |
| Avastin (IDRAC 131721) | bevacizumab | Genentech, Inc |
| Nexavar (IDRAC 128887) | sorafenib | Bayer HealthCare Pharmaceuticals, Inc |
| Sutent (IDRAC 121623) | sunitinib | Pfizer, Inc |
| Torisel (IDRAC 127426) | Temsirolimus | Pfizer, Inc |
| Votrient (IDRAC 133144) | pazopanib | GlaxoSmithKline |

The 6 agents listed have 2 different modes of action. Sorafenib, sunitinib, and pazopanib are vascular endothelial growth factor receptor (VEGF-R) inhibitors, and bevacizumab is a VEGF antibody. Temsirolimus and everolimus are rapamycin (mTOR) inhibitors.

Current phase 3 trials of products for RCC indications include a study by Immatics Biotechnologies GmbH to investigate whether a multipeptide cancer vaccine, IMA901, can prolong overall survival in patients with metastatic and/or locally advanced RCC when added to standard first-line therapy with sunitinib. Secondary objectives for the trial include a subgroup analysis of OS in patients defined by a certain biomarker signature, and investigations of PFS, best tumor response, safety, and immunological parameters. The study began in December 2010 and is still recruiting subjects; completion is anticipated for April 2014.

An ongoing phase 3 trial by AVEO Pharmaceuticals, Inc, is comparing the PFS of subjects with advanced RCC randomized to treatment with either sorafenib or tivozanib, a novel oral VEGF receptor tyrosine kinase inhibitor. Secondary outcome measures include comparisons of OS, ORR, duration of response (DR), safety and tolerability, and kidney-specific symptoms and health outcome measurements. The trial began in December 2009 and expected to be completed in December 2011.

Active Biotech AB began a phase 2/3 trial in January 2007 comparing the safety and efficacy (assessed by tumor status and survival) of ABR-217620 when combined with standard therapy interferon-alpha versus interferon-alpha alone in patients with advanced RCC. ABR-217620 is describes as a fusion of 2 proteins: one recognizes tumor cells, the other activates white blood cells to trigger an attack on the tumor cells. The primary outcome for the study is time to death; secondary outcomes include PFS, ORR best overall response, and DR. The final data collection date for the primary outcome is June 2012.

An axitinib "fact sheet" published by the sponsor notes ongoing development of the drug as a treatment for hepatocellular carcinoma (HCC). The axitinib sponsor began a phase 2 trial in January 2011 for patients with unresectable HCC. Other sponsors are conducting trials with axitinib as well, and axitinib activity has been shown in various phase 2 trials in a variety of cancers, including thyroid, pancreatic, lung, renal, breast and colorectal cancers, and in melanoma. Some of the other indications currently investigated in phase 2 trials include prostate cancer, non-small cell lung cancer, adrenocortical cancer, malignant melanoma, and nasopharyngeal carcinoma.

## Additional *IDRAC* Resources Briefing Information

Agenda and Questions (IDRAC 135611)
Briefing Information (IDRAC 135614)
Conflict of Interest Statements
Minutes
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## Future *AdComm Bulletin* and *FDA Workshop Bulletin* Coverage Schedule*

Click here for: AdComm Bulletin and FDA Workshop Bulletin Schedule Updates (IDRAC 23827)

**December**

December 7, 2011 (Afternoon): Oncologic Drugs Advisory Committee (IDRAC 118092)

December 8, 2011: Joint meeting of the Advisory Committee for Reproductive Health



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Drugs (IDRAC 23062) and the Drug Safety and Risk Management Advisory Committee (IDRAC 59127)

December 9, 2011: Joint meeting of the Advisory Committee for Reproductive Health Drugs (IDRAC 23062) and the Drug Safety and Risk Management Advisory Committee (IDRAC 59127)

December 12, 2011: Psychopharmacologic Drugs Advisory Committee (IDRAC 60610)

December 14-15, 2011: Antiviral Drugs Advisory Committee (IDRAC 121100)

**January**

January 6, 2012: Science Board to the FDA (IDRAC 70615)

January 10-11, 2012: FDA Workshop (IDRAC 117996): Development and Evaluation of Human Cytomegalovirus Vaccines

January 20, 2012: Advisory Committee for Reproductive Health Drugs (IDRAC 23062)

**February**

February 27, 2012: Dermatologic and Ophthalmic Drugs Advisory Committee (IDRAC 23046)

**April**

April 12, 2012: FDA Workshop (IDRAC 117996): Role of Naloxone in Opioid Overdose Fatality Prevention

*Subject to change pending the FDA schedule.
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