Regional Insights Into a Patient’s Treatment for Advanced RCC

Pfizer convened a panel of physicians from the Midwest to provide insights on their clinical experience in treatment planning and management for advanced renal cell carcinoma (RCC). The attendees for this panel have received a fee from Pfizer for their participation.

The panelists reviewed and discussed an adapted case study of an actual patient with advanced RCC who was treated with SUTENT® (sunitinib malate) as first-line therapy and INLYTA® (axitinib) as second-line therapy. Please note that individual patient results may vary.

SUTENT® is indicated for the treatment of advanced RCC.

**SUTENT**® (sunitinib malate) Selected Safety Information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.

Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

INLYTA is indicated for the treatment of advanced RCC after failure of one prior systemic therapy.

**INLYTA**® (axitinib) Selected Safety Information

Hypertension including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.
INDICATION
SUTENT® (sunitinib malate) is indicated for the treatment of advanced renal cell carcinoma (RCC).

IMPORTANT SAFETY INFORMATION
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. Given the potential for serious adverse reactions (ARs) in nursing infants, a decision should be made whether to discontinue nursing or SUTENT.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported. Use SUTENT with caution in patients who are at risk for, or who have a history of, these events. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsades de Pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

There have been (<1%) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS).

Hemorrhagic events, including tumor-related hemorrhage such as pulmonary hemorrhage, have occurred. Some of these events were fatal. Perform serial complete blood counts (CBCs) and physical examinations.

Cases of tumor lysis syndrome (TLS) have been reported primarily in patients with high tumor burden. Monitor these patients closely and treat as clinically indicated.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, has been reported in patients who received SUTENT as monotherapy and in combination with bevacizumab. Discontinue SUTENT in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Perform baseline and periodic urinalysis during treatment, with follow-up measurement of 24-hour urine protein as clinically indicated. Interrupt SUTENT and dose-reduce if 24-hour urine protein is ≥3 g; discontinue SUTENT in cases of nephrotic syndrome or repeat episodes of urine protein ≥3 g despite dose reductions.

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN are present, SUTENT treatment should be discontinued. If a diagnosis of SJS or TEN is suspected, treatment must not be re-started. Necrotizing fasciitis, including fatal cases, has been reported, including of the perineum and secondary to fistula formation. Discontinue SUTENT in patients who develop necrotizing fasciitis.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.

SUTENT has been associated with symptomatic hypoglycemia, which may result in loss of consciousness or require hospitalization. Reductions in blood glucose levels may be worse in patients with diabetes. Check blood glucose levels regularly during and after discontinuation of SUTENT. Assess whether antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the jaw (ONJ) has been reported. Consider preventive dentistry prior to treatment with SUTENT. If possible, avoid invasive dental procedures, particularly in patients receiving bisphosphonates.

Cases of impaired wound healing have been reported. Temporary interruption of therapy with SUTENT is recommended in patients undergoing major surgical procedures.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

Dose adjustments are recommended when SUTENT is administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John’s Wort.

The most common ARs occurring in ≥20% of patients receiving SUTENT for treatment-naive metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The most common grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

The most common grade 3/4 lab abnormalities (occurring in ≥5% of patients with RCC receiving SUTENT vs IFNα) included lymphocytosis (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytosis (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).
INDICATION
INLYTA is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

IMPORTANT SAFETY INFORMATION

Hypertension including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

Arterial and venous thrombotic events have been observed and can be fatal. Use with caution in patients who are at increased risk or who have a history of these events.

Hemorrhagic events, including fatal events, have been reported. INLYTA has not been studied in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the INLYTA dose.

Cardiac failure has been observed and can be fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with INLYTA. Management of cardiac failure may require permanent discontinuation of INLYTA.

Gastrointestinal perforation and fistula, including death, have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment.

Hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

No formal studies of the effect of INLYTA on wound healing have been conducted. Stop INLYTA at least 24 hours prior to scheduled surgery.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been observed. If signs or symptoms occur, permanently discontinue treatment.

Monitor for proteinuria before initiation of, and periodically throughout, treatment. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment.

Liver enzyme elevation has been observed during treatment with INLYTA. Monitor ALT, AST, and bilirubin before initiation of, and periodically throughout, treatment.

For patients with moderate hepatic impairment, the starting dose should be decreased. INLYTA has not been studied in patients with severe hepatic impairment.

Women of childbearing potential should be advised of potential hazard to the fetus and to avoid becoming pregnant while receiving INLYTA.

Avoid strong CYP3A4/5 inhibitors. If unavoidable, reduce the dose. Grapefruit or grapefruit juice may also increase INLYTA plasma concentrations and should be avoided.

Avoid strong CYP3A4/5 inducers and, if possible, avoid moderate CYP3A4/5 inducers.

The most common (≥20%) adverse events (AEs) occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The most common (≥10%) grade 3/4 AEs occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

The most common (≥20%) lab abnormalities occurring in patients receiving INLYTA (all grades, vs sorafenib) included increased creatinine (55% vs 41%), decreased bicarbonate (44% vs 43%), hypocalcemia (39% vs 59%), decreased hemoglobin (35% vs 52%), decreased lymphocytes (absolute) (33% vs 36%), increased ALP (30% vs 34%), hyperglycemia (28% vs 23%), increased lipase (27% vs 46%), increased amylase (25% vs 33%), increased ALT (22% vs 22%), and increased AST (20% vs 25%).
Supporting Clinical Trial Design and Data

### SUTENT® (sunitinib malate) Clinical Trial

**Phase 3, multicenter, randomized trial of SUTENT vs interferon-alfa (IFN-α)** in patients with metastatic renal cell carcinoma (mRCC; N=750)

- Randomization was stratified according to baseline levels of lactate dehydrogenase (LDH; >1.5 upper limit of normal [ULN] vs ≤1.5x ULN), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS; 0 vs 1), and prior nephrectomy (yes vs no)
- Patients were treated with either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off or 9 MIU of IFN-α 3 times per week until disease progression or study withdrawal
- Primary endpoint was progression-free survival (PFS); secondary endpoints included objective response rate (ORR), overall survival (OS), and safety and tolerability

<table>
<thead>
<tr>
<th>Prognostic risk*</th>
<th>SUTENT, % (n)</th>
<th>IFN-α, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable (0 risk factors)</td>
<td>38% (143)</td>
<td>34% (121)</td>
</tr>
<tr>
<td>Intermediate (1-2 risk factors)</td>
<td>56% (209)</td>
<td>59% (212)</td>
</tr>
<tr>
<td>Poor (≥3 risk factors)</td>
<td>6% (23)</td>
<td>7% (25)</td>
</tr>
</tbody>
</table>

*Prognostic factor modeling using risk factors based on published Memorial Sloan Kettering Cancer Center data.

In the Phase 3 trial comparing SUTENT with IFN-α, SUTENT (N=750):

- Median PFS with SUTENT (n=375) was 11 months vs 5 months with IFN-α; demonstrated superior PFS vs IFN-α (primary endpoint)

**ORR (secondary endpoint)**:

- For the first analysis (November 2005), ORR for SUTENT was 28% (95% CI: 23.0, 32.3) vs 5% for IFN-α (95% CI: 3.3, 8.1); P<.0001
- 90 patients’ scans had not been read at the time of analysis
- For the final analysis (March 2010), ORR for SUTENT was 39% (95% CI: 33.7, 43.8) vs 8% for IFN-α (95% CI: 5.2, 10.9); P<.001

**OS (secondary endpoint)**:

- Median OS with SUTENT was 26.4 months (95% CI: 23.0, 32.9) vs 21.8 months with IFN-α (95% CI: 17.9, 26.9)
- Unstratified HR=0.818 (95% CI: 0.669, 0.999); P=0.49 (log-rank test)
- Stratified HR=0.818 (95% CI: 0.669, 0.999); P=0.49 (log-rank test)

### INLYTA® (axitinib) AXIS Clinical Trial

**Phase 3, multicenter, open-label, head-to-head trial of INLYTA vs sorafenib in patients with mRCC (N=723)**

- Patients with mRCC after failure of one prior systemic therapy (sunitinib-, temsirolimus-, bevacizumab-, or cytokine-containing regimen) were randomized (N=723) to receive either INLYTA (5 mg twice daily) or sorafenib (400 mg twice daily), with dose adjustments allowed in both groups
- Primary endpoint was PFS; secondary endpoints included ORR, OS, and safety and tolerability

**Prior systemic therapy**

<table>
<thead>
<tr>
<th>INLYTA, % (n)</th>
<th>Sorafenib, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>54% (194)</td>
</tr>
<tr>
<td>Cytokine(s)</td>
<td>35% (126)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>8% (29)</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>3% (12)</td>
</tr>
</tbody>
</table>

In the Phase 3, head-to-head AXIS trial, INLYTA (N=723):

- Demonstrated superior PFS vs sorafenib (primary endpoint)
  - Median PFS with INLYTA (n=361) was 6.7 months vs 4.7 months with sorafenib (n=362)
    - 95% CI: 6.3, 8.6 and 4.6, 5.6, respectively
    - HR=0.67 (95% CI: 0.54, 0.81); P<.0001

In prespecified subset analyses, INLYTA:

- Nearly doubled median PFS after progression on cytokine therapy
  - Median PFS with INLYTA (n=126) was 12.1 months vs 6.5 months with sorafenib (n=125)
    - 95% CI: 10.1, 13.9 and 6.3, 8.3, respectively
    - HR=0.46 (95% CI: 0.32, 0.68); the P value is not included because it was not adjusted for multiple testing
- Prolonged median PFS after progression on sunitinib
  - Median PFS with INLYTA (n=194) was 4.8 months vs 3.4 months with sorafenib (n=195)
    - 95% CI: 4.5, 6.4 and 2.8, 4.7, respectively
    - HR=0.74 (95% CI: 0.57, 0.96); the P value is not included because it was not adjusted for multiple testing

In the Phase 3 AXIS trial (N=723):

- ORR (secondary endpoint):
  - 19.4% for INLYTA (95% CI: 15.4, 23.9) vs 9.4% for sorafenib (95% CI: 6.6, 12.9)
    - Risk ratio=2.06 (95% CI: 1.4, 3.0); the P value is not included because it was not adjusted for multiple testing
    - All responses were partial responses per RECIST

**OS (secondary endpoint):**

- Median OS with INLYTA (n=361) was 20.1 months (95% CI: 16.7, 23.4) vs 19.2 months with sorafenib (n=362) (95% CI: 17.5, 22.3)
  - HR=0.97 (95% CI: 0.80, 1.17); P=not significant
  - The difference between the treatment arms was not statistically significant

The most common adverse reactions (ARs) occurring in ≥20% of patients receiving SUTENT for treatment-naïve mRCC (all grades, vs IFN-α) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspnea (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 21%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%). The most common Grade 3/4 ARs (occurring in ≥5% of patients with RCC receiving SUTENT vs IFN-α) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diabetes (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

The most common adverse events (AEs) occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29), nausea (32% vs 22%), dyspnea (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The most common (≥20%) adverse events (AEs) occurring in patients receiving INLYTA (all grades, vs sorafenib) were hypertension (16% vs 11%), diabetes (11% vs 7%), and fatigue (11% vs 5%).

Please see Important Safety Information for SUTENT and INLYTA on pages 2 to 3 and full Prescribing Information for each agent, including BOXED WARNING for SUTENT, in the pocket.
**ADAPTED CLINICAL CASE STUDY:**

First-Line Followed by Second-Line Therapy for Advanced RCC

This case study was adapted from an actual patient; individual patient results may vary.

A 69-year-old male patient presented with a medical history of abdominal pain and hematuria. A physical exam and computed tomography (CT) scan detected a large, right-side renal mass. Bilateral adrenal lesions as well as low-density hepatic lesions of unclear etiology were also detected. A nephrectomy and right adrenalectomy were performed, and histology showed a Fuhrman grade 3 clear-cell RCC with renal vein involvement, inferior vena caval thrombus, and adrenal metastasis. The tumor stage was determined to be pT3bNxM1.

A subset of the patient’s laboratory test results is shown in Table 1. The patient’s performance status was determined to be ECOG grade 1. Risk factors according to published Memorial Sloan Kettering Cancer Center risk stratification data placed the patient in the intermediate-risk category based on a short time from initial diagnosis to systemic treatment (~4 months) as well as a high LDH laboratory value.2

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>300 U/L (H)</td>
<td>45-90 U/L</td>
</tr>
<tr>
<td>Serum hemoglobin</td>
<td>12.5 mg/dL</td>
<td>10-14 mg/dL</td>
</tr>
<tr>
<td>Corrected serum calcium</td>
<td>9.3 mg/dL</td>
<td>8.5-10 mg/dL</td>
</tr>
</tbody>
</table>

First-line treatment with SUTENT was initiated. The dosage was 50-mg SUTENT once daily on Schedule 4/2 (4 weeks on, 2 weeks off therapy). At the time of treatment initiation, the patient was counseled on ARs associated with SUTENT therapy and on strategies to help manage certain ARs.

A follow-up visit was scheduled for 15 days following the initiation of SUTENT therapy. At this visit, the patient reported ARs of grade 1 fatigue and grade 1 diarrhea. Strategies to help manage fatigue and diarrhea were reviewed with the patient. Another follow-up visit was scheduled for 28 days following the initiation of first-line therapy. At this visit, the patient reported ARs of grade 2 fatigue, grade 2 diarrhea, and grade 1 nausea. To help manage the treatment, an antidiarrheal medication was prescribed. At the end of his first cycle of SUTENT, the patient was seen for another follow-up visit, 6 weeks after initiation of therapy. At this visit, the patient reported grade 2 fatigue and grade 1 diarrhea. A second cycle of SUTENT was started, keeping the dosage at 50 mg once daily on Schedule 4/2.

**SUTENT® (sunitinib malate) Selected Safety Information**

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported.

Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Women of childbearing potential should be advised to use effective contraception during SUTENT therapy and for 1 month after treatment is stopped. SUTENT should be administered with CYP3A4 inhibitors or inducers. During treatment with SUTENT, patients should not drink grapefruit juice, eat grapefruit, or take St John’s Wort.

Please see Important Safety Information for SUTENT and INLYTA on pages 2 to 3 and full Prescribing Information for each agent, including BOXED WARNING for SUTENT, in the pocket.

---

**COMMENTARY**

Staff in the clinic who interact with a new patient

Dr Haluschak: In addition to the physician, a new patient in our clinic would see the financial counselors, who find information about co-pays and co-pay assistance, as it differs in different circumstances. We have our own pharmacy, so they interact with the patient, too.

Dr Karim: The nurse and nurse practitioner help so much with processing the medication and insurance.

Dr Chandana: We also have a clinical nurse coordinator—who is educating these patients and following them for side effects.

**SUTENT® (sunitinib malate) Recommended Dose**

The recommended dose of SUTENT for advanced RCC is 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off.

Dosage interruption and/or dosage modification in 12.5-mg increments or decrements is recommended based on individual safety and tolerability.

**National Comprehensive Cancer Network (NCCN®) Category 1 Recommendation**

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer have included sunitinib malate (SUTENT) as a category 1 recommendation for first-line therapy in patients with advanced clear-cell RCC since 2008.

---
SUTENT® (sunitinib malate) Selected Safety Information

**Thyroid dysfunction** may occur. Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, and treat per standard medical practice.

**Hypertension** may occur. Monitor blood pressure and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

INLYTA® (axitinib) Dosing

The starting dose is 5 mg orally twice daily. Administer INLYTA dose approximately 12 hours apart with or without food.

Dose increase or reduction is recommended based on individual safety and tolerability.

For a strong CYP3A4/5 inhibitor is required, decrease the INLYTA dose by approximately half.

For patients with moderate hepatic impairment, decrease the starting dose by approximately half.

Criteria for increasing the dosage of INLYTA to 7 mg twice daily are:

- Patient tolerates INLYTA for at least 2 consecutive weeks with no AEs > grade 2 for 2 consecutive weeks
- Patient is normotensive
- Patient is not on antihypertensive medication

If a dosage reduction from the starting dosage is required:

- Reduce dosage to 3 mg twice daily
- Reduce dosage to 2 mg twice daily if additional dosage reduction is required

NCCN Category 1 Recommendation

The NCCN Guidelines® for Kidney Cancer include axitinib (INLYTA) as a category 1 recommendation in patients with advanced predominately clear-cell RCC who have failed one prior systemic therapy.

INLYTA® (axitinib) Selected Safety Information

**Hypothyroidism** requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

**Hypertension** including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.

**SUTENT® (sunitinib malate) Selected Safety Information**

**Thyroid dysfunction**

- Monitor thyroid function in patients with signs and/or symptoms of thyroid dysfunction.
- Treat per standard medical practice.

**Hypertension**

- Monitor blood pressure and treat as needed.
- Temporarily suspend SUTENT if hypertension is not controlled.

**Hypothyroidism, Hyperthyroidism, and Thyroiditis**

- Monitor thyroid function before initiation and periodically.

**INLYTA® (axitinib) Dosing**

- Starting dose: 5 mg orally twice daily.
- Adjustments based on safety and tolerability.

**NCCN Category 1 Recommendation**

- Category 1 for patients with advanced clear-cell RCC who have failed one prior systemic therapy.

**COMMENTARY**

**Medication compliance**

**Dr Chandana:** In our center, we monitor compliance by giving patients a drug diary. Every time they come in, they have to bring it in. They have to mark on the sheet every day when they take their medication, and they have to write down any side effects.

**Dr Manges:** I check in with patients frequently at the start of treatment to make sure they understand how to take their medication. Also, the pharmacies will call if patients are not filling their medication.

**In the Phase 3 trial comparing SUTENT with IFN-α, SUTENT (N=750)**

- *Demonstrated superior PFS vs IFN-α (primary endpoint)*
  - Median PFS with SUTENT (n=750) was 11 months vs 5 months with IFN-α (n=375)
    - 95% CI: 9.8, 11.7 and 3.8, 5.5, respectively
    - HR=0.42 (95% CI: 0.32, 0.54); P <.00001

**In the phase 3 trial comparing SUTENT with IFN-α (N=750)**

- *ORR (secondary endpoint)*
  - For the first analysis (November 2005), ORR for SUTENT was 28% (95% CI: 23.0, 32.3) vs 5% for IFN-α (95% CI: 3.3, 8.1); P <.001
  - For the final analysis (March 2010), ORR for SUTENT was 39% (95% CI: 33.7, 43.8) vs 8% for IFN-α (95% CI: 5.2, 10.9); P <.001
  - All responses assessed by blinded core review at 2 different time points were partial responses per RECIST

**A physical exam prior to the initiation of second-line therapy found that the patient’s ECOG PS was 1.** The physical exam revealed no significant findings, other than weight loss. The patient’s laboratory values were normal. Second-line treatment with INLYTA at a dosage of 5 mg twice daily was initiated. At the initiation visit, the patient was counseled on AEs associated with INLYTA therapy and on strategies to help manage certain AEs.

**Dr Haluschak:** Our practice is trying to develop a standard timing for testing thyroid levels.

**Dr Ward:** We check it early, at their first visit, then periodically, with any concerning symptoms, or at least every 3 months or so.

**Dr Chandana:** I do the same, 3 months in, or at least every 3 months or so.

**Dr Stadler:** We tend to check it about every 6 weeks in these patients.

**COMMENTARY**

**Testing thyroid levels**

**Dr Haluschak:** We tend to check it about every 6 weeks in these patients.

**Dr Manges:** We check in with patients frequently at the start of treatment to make sure they understand how to take their medication. Also, the pharmacies will call if patients are not filling their medication.

**Dr Ward:** We check it early, at their first visit, then periodically, with any concerning symptoms, or at least every 3 months or so.

**Dr Chandana:** I do the same, 3 months in, or at least every 3 months or so.

**Dr Stadler:** We tend to check it about every 6 weeks in these patients.

**At the end of his second cycle of SUTENT, 12 weeks after the initiation of first-line therapy, the patient was seen for a follow-up visit.** The patient reported ARs of grade 3 fatigue, grade 2 anorexia, grade 2 nausea, and grade 1 mucositis. The patient reported that his diarrhea was controlled by the antiarrheal medication. A follow-up CT scan for disease assessment revealed a partial response in the adrenal nodule. A laboratory workup revealed hypothyroidism. In response to this follow-up, the dosage of SUTENT was reduced to 37.5 mg daily on Schedule 4/2 for his third cycle of SUTENT. Supportive therapy was initiated to treat hypothyroidism and nausea.

**INLYTA® (axitinib) Dosing**

- Starting dose: 5 mg orally twice daily.
- Administer INLYTA dose approximately 12 hours apart with or without food.
- Adjustments based on safety and tolerability.
- For a strong CYP3A4/5 inhibitor is required, decrease the INLYTA dose by approximately half.
- For patients with moderate hepatic impairment, decrease the starting dose by approximately half.
- Criteria for increasing the dosage of INLYTA to 7 mg twice daily are:
  - Patient tolerates INLYTA for at least 2 consecutive weeks with no AEs > grade 2 for 2 consecutive weeks
  - Patient is normotensive
  - Patient is not on antihypertensive medication
- If a dosage reduction from the starting dosage is required:
  - Reduce dosage to 3 mg twice daily
  - Reduce dosage to 2 mg twice daily if additional dosage reduction is required

**NCCN Category 1 Recommendation**

- Category 1 recommendation in patients with advanced predominately clear-cell RCC who have failed one prior systemic therapy.

**INLYTA® (axitinib) Selected Safety Information**

**Hypothyroidism** requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment.

**Hypertension** including hypertensive crisis has been observed. Blood pressure should be well controlled prior to initiating INLYTA. Monitor for hypertension and treat as needed. For persistent hypertension, despite use of antihypertensive medications, reduce the dose. Discontinue INLYTA if hypertension is severe and persistent despite use of antihypertensive therapy and dose reduction of INLYTA, and discontinuation should be considered if there is evidence of hypertensive crisis.
A follow-up phone call was scheduled for 2 weeks following the initiation of second-line therapy. During this phone call, the patient reported grade 1 fatigue. A follow-up visit was scheduled for 2 weeks later, 1 month following the initiation of INLYTA second-line therapy. During this follow-up visit, the patient reported AEs of grade 1 fatigue and grade 2 nausea. Grade 1 hypertension (blood pressure [BP] of 135/88) was detected upon physical exam. An antiemetic was initiated. The dosage of INLYTA was titrated to 7 mg twice daily.

A follow-up visit was scheduled for 2 months after initiation of INLYTA. At this visit, the patient reported AEs of grade 2 diarrhea, grade 2 fatigue, and grade 1 nausea. The patient was found to have grade 3 hypertension (BP of 180/105) upon physical exam. A follow-up CT scan indicated no progression of disease. Supportive treatments were started for diarrhea and hypertension. The antiemetic was continued. INLYTA was maintained at a dosage of 7 mg twice daily.

A month later, the patient was seen for another follow-up visit, 3 months following the initiation of second-line INLYTA therapy. The patient reported AEs of grade 2 fatigue and grade 2 diarrhea. The patient was found to have grade 2 hypertension (BP of 150/95) upon physical exam. The supportive treatments for diarrhea, hypertension, and nausea were continued. The patient’s antihypertensive medication was adjusted. The dosage of INLYTA was reduced to 5 mg twice daily.

The patient remained on INLYTA 5 mg twice daily for 2 more months, with continued follow-up and monthly monitoring. The patient developed proteinuria and showed progression by follow-up CT scan approximately 5 months after second-line treatment initiation. INLYTA was discontinued.

References

OVERALL THOUGHTS ON TREATMENT DECISION MAKING AND MANAGEMENT IN ADVANCED RCC
Throughout the case study presentation, common themes emerged regarding considerations for treatment decision making and management in first-line followed by second-line therapy for advanced RCC. In selecting appropriate therapies for first- and second-line treatment of advanced RCC, the advisors agreed that they consider both the perceived efficacy of the therapy, based on both clinical data and their own experiences, as well as the safety profile of the therapy. Management of AEs was a focal topic throughout the meeting. The advisors discussed their considerations for using dose modification to help manage AEs, when possible. They also described their techniques to help manage AEs by using patient education, suggesting lifestyle modification, and using supportive medications. As Dr Chandana stated, “The art of medicine is in reading the patient with the goal of helping them live as well as possible on therapy.” The advisors also discussed how several members of their practice work together in providing patients with tips to help manage AEs. As Dr Stadler explained, “It’s a team sport.” The advisors all commented that nurses and advanced practitioners in their practice play key roles in counseling patients on helping to manage their AEs while on therapy. They also discussed the role that pharmacists play in helping to get access to the drugs, educating on side effects, and monitoring for compliance.

INLYTA® (axitinib) Selected Safety Information
The most common (≥20%) adverse events (AEs) occurring in patients receiving INLYTA (all grades, vs sorafenib) were diarrhea (55% vs 53%), hypertension (40% vs 29%), fatigue (39% vs 32%), decreased appetite (34% vs 29%), nausea (32% vs 22%), dysphonia (31% vs 14%), hand-foot syndrome (27% vs 51%), weight decreased (25% vs 21%), vomiting (24% vs 17%), asthenia (21% vs 14%), and constipation (20% vs 20%).

The most common (≥10%) grade 3/4 AEs occurring in patients receiving INLYTA (vs sorafenib) were hypertension (16% vs 11%), diarrhea (11% vs 7%), and fatigue (11% vs 5%).

Please see Important Safety Information for SUTENT and INLYTA on pages 2 to 3 and full Prescribing Information for each agent, including BOXED WARNING for SUTENT, in the pocket.