Sorafenib
Side effects and dose adjustment
Adverse events: prevention and management as key

Patients should be informed to:

- Take preventive measures, where possible
- Be aware and report AEs as soon as possible

Patients alerted to possible AEs before beginning treatment:

- May be more accepting of these symptoms
- Are more likely to stay on treatment
Adverse events: prevention and management as key

**Early intervention and symptomatic treatment may:**

- Improve quality of life (QOL)
- Facilitate adherence to therapy, optimizing potential benefits of therapy

For non-life-threatening manageable events, the “take-home” message is:

- Symptoms can usually be alleviated with symptomatic treatment or dose modifications, and sorafenib treatment can continue $^{1-5}$
- Early intervention may reduce grade of toxicity / duration of AE
Possible side effects
## Side Effects: Protocol Overview

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common ( \geq 1/10 )</th>
<th>Common ( \geq 1/100, &lt;1/10 )</th>
<th>Uncommon ( \geq 1/1000, &lt;1/100 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic System Disorders</strong></td>
<td>Lymphopenia</td>
<td>Leucopenia Neutropenia Anemia Thrombocytopenia</td>
<td>Angioedema Anaphylactic reaction</td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td></td>
<td>Hypersensitivity reactions (incl. skin reactions and urticaria)</td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine Disorders</strong></td>
<td></td>
<td>Hypothyroidism Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td>Hypophosphatemia</td>
<td>Anorexia Hypocalcemia</td>
<td>Hyponatriemia, dehydration</td>
</tr>
<tr>
<td><strong>Ear and Labyrinth Disorders</strong></td>
<td></td>
<td>Tinnitus</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td>Myocardial ischemia and infarction*, congestive heart failure*</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Hemorrhage (incl. gastrointestinal*, respiratory tract* and cerebral hemorrhage*), hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, Thoracic and Mediastinal Disorders</strong></td>
<td></td>
<td>Hoarseness</td>
<td>Rhinorrhoea interstitial lung disease–like events (pneumonitis, radiation pneumonitis, acute respiratory distress, etc.)</td>
</tr>
</tbody>
</table>

* may have a life-threatening or fatal outcome

## Side Effects: Protocol Overview

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Diarrhea, nausea, vomiting</td>
<td>Constipation, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia</td>
<td>Gastro esophageal reflux disease, pancreatitis, gastritis, gastrointestinal perforations*</td>
</tr>
<tr>
<td><strong>Hepatobiliary Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Rash, alopecia, hand foot syndrome**, erythema, pruritus</td>
<td>Dry skin, dermatitis exfoliative, acne, skin desquamation</td>
<td>Eczema, erythema multiforme, minor keratocanthoma squamous cell cancer of the skin</td>
</tr>
<tr>
<td><strong>Musculoskeletal, Connective Tissue and Bone Disorders</strong></td>
<td>Arthalgia, myalgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td>Renal failure</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
<td>Erectile dysfunction</td>
<td>Gynaecomastia</td>
</tr>
<tr>
<td><strong>General conditions and Administration Site Conditions</strong></td>
<td>Fatigue, pain (including mouth, abdominal, bone, tumour pain and headache)</td>
<td>Asthenia, fever, influenza like illness</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Increased amylase, increased lipase</td>
<td>Weight decrease, transient increase in transaminases</td>
<td>Transient increase in blood alkaline phosphatase, INR abnormal, prothrombin level abnormal</td>
</tr>
</tbody>
</table>

* may have a life-threatening or fatal outcome  
** hand foot syndrome corresponds to palmar plantar erythrodysaesthesia syndrome in MedDRA
Dosing
## Dose Levels

<table>
<thead>
<tr>
<th>Dose Level 1</th>
<th>400mg bid (twice a day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level –1</td>
<td>400mg qd (every day)</td>
</tr>
<tr>
<td>Dose Level –2</td>
<td>400mg qod (every other day)</td>
</tr>
<tr>
<td>Dose Level 1b (re-escalation)</td>
<td>(400mg – 0 – 200mg ) qd (every day)</td>
</tr>
</tbody>
</table>

*
Dose Escalation

Day 0
- Primary interventional treatment (RFA / RE)

Day 3
- START Sorafenib: Dose level -1: 400mg qd

Day 10
- Dose level 1: 400mg bid
Dose–Adjustment
Dose De-escalation: General Comments

- 1st reduction to -1: 400mg qd
- 2nd reduction to -2: 400mg qod

CAVE: Withdrawal criteria!

- After toxicity resolution: step-wise re-escalation
- Documentation according to CTCAE 4.0
Dose Re-escalation – Overview

- **Treatment with decreased dose at level -1: 400mg qd**
  - Assessment after 28 days: Toxicity > grade 1?
    - **Yes**
      - Decrease / interrupt sorafenib according to the schemes in tables
    - **NO**
      - Re-escalate to level 1b: 400-0-200mg qd
        - Assessment after 28 days: Toxicity > grade 1?
          - **Yes**
            - Re-escalate to level 1: 400mg bid
              - Assessment after 28 days: Toxicity > grade 1?
                - **Yes**
                  - Decrease / interrupt sorafenib according to the schemes in tables

Aim: Maintain individual dose level with toxicity < grade 2. Discontinue treatment if not applicable.
Arterial Hypertension
• A disorder characterised by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mmHg
• Hypertension most commonly presents early
• Monitor blood pressure weekly during the first 6 weeks
• Thereafter, blood pressure check as needed
# Hypertension

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Prehypertension (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg)</td>
<td>Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic increase by &gt; 20 mmHg (diastolic) or to &gt; 140/90 mmHg if previously WNL; monotherapy indicated</td>
<td>Stage 2 hypertension (systolic BP ≥ 60 mmHg or diastolic BP ≥ 100 mm Hg) medical intervention indicated, more than one drug or more intensive therapy than previously used indicated</td>
<td>Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

CTCAE v4.0
Dose De-escalation: Hypertension (I)

**Grade 1**
- asymptomatic
- transient
- Consider increased BP-monitoring

**Grade 2**
- asymptomatic
- diastolic
- SBP 140–159 mmHg: and/or
  - DBP 90–99 mmHg
  - Begin antihypertensive therapy, continue sorafenib

SORAMIC
Grade 2
Symptomatic Persistent

Grade 3

Withhold until symptoms resolve + diastolic BP < 90 mmHG

When achieved, resume at dose level −1

If diastolic BP > 90 mmHG: de-escalation to level −2

Grade 4

Discontinuation

No re-escalation planned!
DP20  hiermit ist sicher der diastolische Druck gemeint? 
Falls ja würde ich das ggf. hinschreiben (obwohl es sich ggf. auch aus dem Zusammenhang erklärt) 
Dr. Joerg Pinkert; 24.06.2010

DP21  vor Grade 3 fehlt offensichtlich noch das "or" 
Dr. Joerg Pinkert; 24.06.2010
Nexavar® can raise blood pressure and your doctor will usually monitor your blood pressure.\textsuperscript{11,15,16}

Your doctor may prescribe medication to treat hypertension.\textsuperscript{11,15,16}
HFSR
Hand–Foot–Skin–Reaction
HFSR: Typical Presentation

- Painful, red, swollen, symmetrical, bilateral areas on palms/soles
  - Also on lateral sides of fingers and around the nail
- Thickening of skin (hyperkeratosis)
- Dry and/or cracked skin
- Callus-like blisters
- Preceded or accompanied by prickling, tingling or “creeping” sensation

HFSR: Onset and Course

- Onset usually within first 6 weeks of treatment with a Tyrosine Kinase Inhibitor (TKI)
  - Symptoms can begin as early as 1 to 2 weeks
  - Intensity of symptoms frequently decreases over time

- Preventative measures before treatment may minimize incidence and severity (reduce occurrence of Grade 3 events)

- If HFSR does occur
  - It must be recognized and treated promptly
  - Early symptoms may quickly resolve with adequate symptomatic treatment might prevent progression to higher grade

- Temporary treatment discontinuation often results in symptomatic improvement
  - Symptoms may be less severe when re-challenged at a dose reduction
Dose De-escalation: HFSR (I)

Grade 1
- Supportive measures & continue at same dose level

Grade 2
- Supportive measures and decrease to level -1 (28 days)
  - If toxicity < °1, re-escalate
  - If toxicity > °1, interrupt for 7 days
    - If no toxicity > °1, resume at level -1 (28 days)
      - If toxicity < °1, re-escalation possible

Hand-Foot-Skin reaction

400mg qod
400mg qd
400mg bid
(400-0-200mg ) qd

SORAMIC
**Dose De-escalation: HFSR (II)**

**Grade 2**

**2nd occurrence**
- Interrupt for 7 days
- If no toxicity > °1, resume at level -1 (28 days)
- If no toxicity > °1, re-escalation possible
  - Maximum level at which toxicity was not exceeding °1

**3rd occurrence**
- Interrupt for 7 days
- If no toxicity > °1, resume at level -1 indefinitely

**4th occurrence**
- Interrupt for 7 days
- If toxicity > °1, de-escalation to -2 or discontinuation
Dose De-escalation: HFSR (III)

Grade 3

1st occurrence

Interrupt for 7 days / until tox. \leq \textdegree 1

If no toxicity \geq \textdegree 1, resume at level -1 (28 days)

If no toxicity \geq \textdegree 1, re-escalation possible

2nd occurrence

Interrupt for 7 days / until tox. \leq \textdegree 1

Decrease indefinitely to level with toxicity \leq \textdegree 1

3rd occurrence

Interrupt for 7 days / until tox. \leq \textdegree 1

If toxicity \geq \textdegree 1, de-escalation to -2 or discontinuation
Hematologic side effects
<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>LLN – 3000/mm³</td>
<td>&lt;3000– 2000/mm³</td>
<td>&lt;2000– 1000/mm³</td>
<td>&lt;1000/mm³</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>LLN – 3.0 x 10⁹/L</td>
<td>&lt;3.0 – 2.0 x 10⁹/L</td>
<td>&lt;2.0 – 1.0 x 10⁹/L</td>
<td>&lt;1.0 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>LLN – 1500/mm³</td>
<td>&lt;1500– 1000/mm³</td>
<td>&lt;1000– 500/mm³</td>
<td>&lt;500/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LLN – 1.5 x 10⁹/L</td>
<td>&lt;1.5 – 1.0 x 10⁹/L</td>
<td>&lt;1.0 – 0.5 x 10⁹/L</td>
<td>&lt;0.5 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>LLN – 75,000/mm³</td>
<td>&lt;75,000– 50,000/mm³</td>
<td>&lt;50,000– 25,000/mm³</td>
<td>&lt;25,000/mm³</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LLN – 75.0 x 10⁹/L</td>
<td>&lt;75.0 – 50.0 x 10⁹/L</td>
<td>&lt;50.0 – 25.0 x 10⁹/L</td>
<td>&lt;25.0 x 10⁹/L</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>Hgb &lt; LLN – 6.2 mmol/l</td>
<td>Hgb &lt; 6.2 – 4.9 mmol/l</td>
<td>Hgb &lt; 4.9 – 4.0, transfusion indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>death</td>
</tr>
</tbody>
</table>

CTCAE v4.0

SORAMIC
Dose De-escalation: Haematologic (I)

Grade 1 / 2
- Continue at same dose level

Grade 3
- Withhold until toxicity is $\leq ^1$
  - then resume at same dose level

  - In case of 2nd $^3$ toxicity
    - Withhold until toxicity is $\leq ^2$, resume at dose level $-1$

  - Treatment at this level for 28 days

  - If no toxicity $> ^1$, re-escalation possible

  - If toxicity $> ^1$, de-escalation to $-2$ or discontinuation

SORAMIC
Dose De-escalation: Haematologic (II)

Grade 4 ➡️ Withhold until toxicity is ≤ °2, resume at dose level −1

Discontinuation at the investigator’s discretion
Discussion with study sponsor

If toxicity > °1, de-escalation to −2 or discontinuation

Haematopoetic reactions

SORAMIC
Diarrhea
Common GI Symptoms: Description

<table>
<thead>
<tr>
<th></th>
<th>HCC (n = 297)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55</td>
</tr>
<tr>
<td>Nausea</td>
<td>24²</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15²</td>
</tr>
</tbody>
</table>

- Can occur at any time during the course of treatment and include:
  - Diarrhea: usually presents as loose/more frequent stools rather than watery diarrhea
  - Nausea
  - Vomiting
  - Abdominal cramps and bloating
- GI symptoms are usually Grade 1 or 2

2. NEXAVAR® (sorafenib tablets) [summary of product characteristics]. Bayer Healthcare; 2012.
Dose De-escalation: Non-Haematologic (I)

Grade 1 / 2
Continue at same dose level
Supportive treatment

Grade 3
Withhold until toxicity is ≤°1
then resume at same dose level

In case of 2nd °3 toxicity
Withhold until toxicity is ≤°1, resume at dose level −1

Treatment at this level for 28 days

If no toxicity > °1, re-escalation possible

If toxicity > °1, de-escalation to −2 or discontinuation

SORAMIC
Dose De-escalation: Non-Haematologic (II)

- Grade 4
  - Withhold until toxicity is ≤ °1, resume at dose level −1
  - Discontinuation at discretion of investigator
    - Discussion with study sponsor
  - If toxicity > °1, de-escalation to −2 or discontinuation

- Dosage levels:
  - 400mg qod
  - 400mg qd
  - 400mg bid
  - (400–0–200mg) qd
Fatigue
Fatigue: grading of severity

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
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<th>2</th>
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<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation:</strong></td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest; limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting self care ADL</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Characterized by a state of general weakness with a pronounced inability to summon sufficient energy to accomplish daily activities
Fatigue: Management

Fatigue related to other diseases should be excluded:
- Hypothyroidism
- Anemia
- Depression (organic cause)

Symptoms of fatigue may be relieved by:
- Setting priorities so patients can complete their most important tasks
- Saving demanding activities for when they have the most energy
- Avoiding long naps that will keep them awake at night
- Distracting themselves with games, music, books, etc.
- Staying as active as they can during the day
- Exercising regularly: advise them to talk to their doctor before starting an exercise program
- Avoiding caffeine after midday

No standard treatment exists for cancer- or cancer treatment related fatigue

National Comprehensive Cancer Network.