Dose individualization of sunitinib in mRCC: Toxicity-adjusted dose or Therapeutic drug monitoring

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ESMO/EAU treatment algorithm for mRCC therapy\textsuperscript{1,2}

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<th>Treatment-naïve*</th>
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<td>Sunitinib, Bevacizumab + IFN-α, Pazopanib</td>
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<td>Prior VEGFR-TKI</td>
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*Guidelines for clear cell mRCC

# First line Sunitinib in mRCC

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<th>Median PFS mths</th>
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<td>26.4</td>
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<td>9.5</td>
<td>29.3</td>
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Dose reductions common

• Recommended dose of Sunitinib
  – 50mg daily for 28 days then 14 day break

• Dose reductions in > 1/3 patients

• Expanded Access study (N = 4371 with dose info)
  – 50 mg  56%
  – 37.5 mg  33%
  – 25 mg  13%
  – 12.5 mg <1%

46% below recommended dose

Dose reduction vs no dose reduction of sunitinib
Khosravan et al ASCO GU 2012 Abst 363

Table 2. PFS in RCC patients in sunitinib 50 mg/day Schedule 4/2 arms of phase III and phase II trials, by dose-reduction status.

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<tr>
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<td>With dose reduction</td>
<td>Without dose reduction</td>
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<td>95</td>
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<td>Events, n ( % )</td>
<td>107 (55.2)</td>
<td>104 (57.5)</td>
<td>28 (54.9)</td>
<td>58 (61.1)</td>
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<td>Median PFS (months)</td>
<td>14.0</td>
<td>8.1</td>
<td>13.4</td>
<td>5.8</td>
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<td>95% CI (months)</td>
<td>13.1–16.2</td>
<td>6.3–10.6</td>
<td>9.8–19.8</td>
<td>3.9–8.5</td>
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</table>

Higher PFS in dose reduction patients
Dose individualization of sunitinib

Progression free survival

172 pts. Starting dose 50mg/d 28/14

Dose and schedule modified to keep Grade toxicity < 2
Sunitinib
Toxicity vs anticancer effect

**Hypertension**
- With HTN (n=442)
  - Median OS, 30.9 months
  - (95% CI: 27.9–33.7)
- Without (n=92)
  - Median OS, 7.2 months
  - (95% CI: 5.6–10.7)

*P < 0.0001*

**Neutropenia**
- Neutropenia Grade ≥2
  - Median OS 35.6m
  - (95% CI: 31.4–39.5)
- Neutropenia Grade < 2
  - Median OS 15.9m
  - (95% CI: 13.3–17.7)

*P < 0.001*

**Hand-foot syndrome**
- With HFS (n=179)
  - Median OS, 38.2 months
- Without HFS (n=591)
  - Median OS, 18.9 months

*P < 0.0001*

**Asthenia, fatigue**
- With A/F (n=583)
  - Median OS, 26.2 months
- Without A/F (n=187)
  - Median OS, 15.0 months

Donskov F, et al. ECCO-ESMO, 2011; Davis MP, et al. ECCO-ESMO, 2011*
TDM and Sunitinib disposition

- Metabolised by CYP3A4 to N-desethylsunitinib (Ndes)
  - equipotent
  - 30-50% of sunitinib level

- Half life
  - Sunitinib ~50hr (SS ~ 10 days)
  - Ndes ~100 hrs (SS ~ 20 days)

- Substantial Inter-patient variability

Faivre et al, JCO, 2006
Exposure and anti-cancer effect

- High sunitinib AUC correlates with improved OS in mRCC and GIST
- AUC correlates with toxicity (HTN, neutropenia, fatigue)
- Measuring AUC in clinical setting is impractical

Houk et al, Cancer Chemother Pharmacol, 2010
Trough Level Target

• Tumour xenograft
  – sunitinib inhibits TKI phosphorylation at 50-100 ng/mL

• Houk metaanalysis
  – high AUC = Su Trough level 35 ng/mL
  – Su + Ndes ~ 50ng/mL

? Target TTL = 50ng/mL

Background

Trough level acquisition relatively simple

BUT

Routine use requires:

1. Demonstration that \textit{intra}patient variation is LOW

2. Correlation of trough level with anticancer effect (PFS, OS)
CRESTO study
Metastatic renal cell cancer

**Sunitinib**
- 50mg/d (or 37.5mg)
  - 28/14
  - or
  - 14/7 schedule

- **Trough sample for sunitinib + Ndes**
- **Toxicity-adjusted dose**
- **‘Optimum dose’**

- **Treat until resistance**
- **Time-on-Treatment**

Could be on sunitinib before study entry
CRESTO study in mRCC

Toxicity-adjusted dosing regimen

Dose of sunitinib adjusted to ensure G1 or 2 toxicity for >10 days for each 42 day cycle

6 weekly review

- **No or minimal toxicity**
  - **INCREASE dose by 12.5/d**

- **Grade 1 or 2 for >10 days per 42d**
  - **NO change in dose**

- **Grade 3 for >10d or any Grade 4**
  - **DECREASE dose by 12.5mg/d**

"Optimum dose"

Gurney. J Clin Oncol. 1996 Sep;14(9):2590-611
Methods

• Bloods for Trough level collected every 6 weeks
  – 24 hr (± 2hr) after sunitinib dose
  – 28/14 schedule – On day 27, 28 or 29
  – 14/7 schedule – On day 13, 14 or 15

• Plasma concentrations of Sunitinib (Su) and N-desethydr Sunitinib (Ndes)
  – liquid chromatography/mass spectrometry
  – Total trough level = Su + Ndes
  – NOT used for dose adjustment
Questions

1. Is toxicity-adjusted dosing (TAD) feasible for sunitinib in mRCC?
   1. Does it allow does increase as well as dose reduction?

2. If Individualized dose is achieved by TAD
   1. Will interpatient variation in sunitinib level be reduced?
   2. Are sunitinib levels stable over time? (TDM)
   3. Do more patients have a potentially effective sunitinib level compared to standard dose schedule? (50ng/mL)
   4. Assessment of Time-on-Treatment as surrogate for PFS
Results

• 45 patients accrued at Westmead Hospital
  – June 2012 to March 2014

• 283 Sunitinib and NDES samples assayed
  – Number samples per patient
    • Median number = 5
    • Range 1 to 18
  – Sampling period
    • Median = 30 weeks
    • Range 6 to 108 weeks
<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>% of patients</th>
<th>Mean (range)</th>
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<tbody>
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<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td>62 (36-78)</td>
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<tr>
<td>Female</td>
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<td><strong>ECOG performance status</strong></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td></td>
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<tr>
<td>3, 4</td>
<td>5</td>
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<td><strong>Weight (kg)</strong></td>
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<td>83 (51 - 138)</td>
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<td><strong>Histology</strong></td>
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<td><strong>Heng risk score</strong></td>
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<tr>
<td>Favourable risk</td>
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<tr>
<td>Intermediate risk</td>
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<tr>
<td>Poor risk</td>
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<td><strong>Radical/partial nephrectomy</strong></td>
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Sunitinib levels according to schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Sunitinib level</th>
<th>NDES</th>
<th>TTL</th>
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<tbody>
<tr>
<td>14/7</td>
<td>50mg (13.0)</td>
<td>42.3 (19.0)</td>
<td>23.3 (16.8)</td>
<td>65.5 (30.1)</td>
</tr>
<tr>
<td>28/14</td>
<td>37.5mg (10.1)</td>
<td>32.0 (19.4)</td>
<td>18.4 (11.0)</td>
<td>58.0 (26.3)</td>
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<tr>
<td>p</td>
<td>0.005</td>
<td>0.014</td>
<td>0.007</td>
<td>0.003</td>
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Longer schedule had significantly lower Sunitinib dose and Su, NDES and TTL
### Baseline Optimal dose

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<th>Dose</th>
<th>N (%)</th>
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<tr>
<td>75</td>
<td>0</td>
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<tr>
<td>62.5</td>
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</tr>
<tr>
<td>50</td>
<td>30 (68%)</td>
</tr>
<tr>
<td>37.5</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>25</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>12.5</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

#### Dose Change

- 8 (20%)
- 23 (58%)
- 7 (18%)
- 2 (5%)

#### Dose variations

- **7% above recommended**
  - (20%)
- **43% below recommended**
  - (5%)

Dose range in adjustment period = 12.5 to 87.5mg/d
Summary 1

Is toxicity-adjusted dosing (TAD) feasible for sunitinib in mRCC?

- TAD is feasible
- At least 7% can have a long term dose increase with tolerable toxicity
- 3-fold range in dose (25 to 75mg/d)
<table>
<thead>
<tr>
<th>Dose</th>
<th>Baseline (range)</th>
<th>Optimum dose (range)</th>
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<tbody>
<tr>
<td>87.5</td>
<td>-- (--)</td>
<td>-- (--)</td>
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<tr>
<td>75</td>
<td>-- (--)</td>
<td>68.6 (33-123)</td>
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<tr>
<td>62.5</td>
<td>-- (--)</td>
<td>79.5 (15-190)</td>
</tr>
<tr>
<td>50</td>
<td>78.4 (21-158)</td>
<td>71.3 (15-190)</td>
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<tr>
<td>37.5</td>
<td>56.7 (24-122)</td>
<td>56.7 (19-127)</td>
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<td>25</td>
<td>55.9 (35-98)</td>
<td>63.0 (21-97)</td>
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<tr>
<td>12.5</td>
<td>28.6</td>
<td>-</td>
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</table>
TTL before and after dose adjustment

Md TTL ng/mL*

*Each point is median of multiple samples per patient
TTL and variation at Optimum dose

• Median TTL = 64.6ng/mL
  Mean TTL = 71.4ng/mL

• 38/45 (84.4%) had mean TTL >50ng/mL

• Inter-patient coefficient of variance = 33%
Median TTL interpatient variation

TTL

TTL ng/mL

Initial Dose
Optimum Dose
Clearsun study

CV

43%
33%
37%
Summary 2

Will inter-patient variation in sunitinib level be reduced with TAD?

Maybe—Interpatient variation in TTL is reduced but variation remains substantial
Low intra-patient variability at Optimum dose

No accumulation of Su or Ndes across dosing cycles
Intra-patient variability

• Using TAD-strategy
  – Mean intra-patient variation in TTL – 21%
  – 98% of TTL for all pts across measurement were within 2 SD of predicted TTL (standardised residuals)

• This indicates **low intra-patient variability even in early trough levels**
Summary 3

Are sunitinib levels stable over time on stable dose?

Yes— No significant intrapatient variation in TTL over repeated measures for up to 66 weeks
Time on treatment vs dose

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<th>Mean Time on treatment</th>
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<td>37.5mg</td>
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<td>&gt;50mg</td>
<td>14.7m</td>
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- No correlation between dose and time on treatment
- “Underdosed” patients - anticancer effect not compromised
Time on treatment using TAD

Median TTF: **25.0 months** (95% CI 12-39m: Range 2.9 - 91+m)
Mean TTF: 33.8 months

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**Median PFS**

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**Median OS**

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<td>29.3</td>
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* TFF not PFS
Time on treatment vs < or > 50ng/mL TTL

15% of patients
Mean TTL 37ng/mL

Mean TTL 77ng/mL
Summary 4

- Do more patients on TAD have a potentially effective sunitinib level compared to standard dose schedule?
  
  - ~85% had TTL over 50ng/mL on Optimum dose

- TTF of 25 months - comparable to other series
Conclusions 1 - TAD

• Toxicity adjusted dose (TAD) is feasible and allows safe escalation and dose decrease with 3-fold dose range (25-75mg/d)

• TAD associated with favourable Time-on-Treatment (median 25mnths)

• Even low doses (associated with toxicity) have
  – appropriate TTL (37.5mg cohort ?underdosed)
  – long Time-on-Treatment
Conclusions 2 – potential for TDM

• Sunitinib levels do not vary significantly in patients on stable dose
  – Single or limited blood sampling of trough levels may adequately define drug exposure

• TAD alone does not prevent low TTL
  – 15% <50ng/mL
  – Substantial inter-patient variation remains
  – ? some pts underdosed at 37.5mg/d
  – ? role for TDM for fine-tuning

• Definitive studies are required to determine whether sunitinib trough level correlate with anti-cancer effect
Planned phase 2 study
First-line, Clear cell RCC

- **Sunitinib**
  - 50mg/d
  - 14/7 schedule

1 or 2 Trough samples to fine-tune dose TTL >50ng/mL

‘Optimum dose’

Progression-free survival

- First-line
- Clear cell carcinoma
- N= 80
- End-point is PFS >12 months
- ?Phase 3 study