Efficacy and Safety of Testosterone in Metastatic Renal Cell Carcinoma Patients with Fatigue: Multicenter Randomized Phase 2 Study (FARETES)

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Fatigue is a frequent symptom of metastatic renal cell carcinoma (mRCC), and most common adverse event of treatment with tyrosine kinase inhibitors and checkpoint inhibitors.

<table>
<thead>
<tr>
<th>Compound / Study</th>
<th>All grades</th>
<th>3-4 grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib + Everolimus</td>
<td>59%</td>
<td>14%</td>
</tr>
<tr>
<td>Motzer et al. Lancet Oncol. 2015</td>
<td></td>
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<tr>
<td>Cabozantinib</td>
<td>56%</td>
<td>9%</td>
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<tr>
<td>Choueiri et al. NEJM 2015</td>
<td></td>
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<tr>
<td>Sunitinib</td>
<td>54%</td>
<td>11%</td>
</tr>
<tr>
<td>Motzer et al. JCO 2009</td>
<td></td>
<td></td>
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<tr>
<td>Axitinib</td>
<td>37%</td>
<td>10%</td>
</tr>
<tr>
<td>Motzer et al. Lancet Oncol. 2013</td>
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<tr>
<td>Nivolumab + Ipilimumab</td>
<td>37%</td>
<td>4%</td>
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<tr>
<td>Motzer et al. NEJM 2018</td>
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<tr>
<td>Nivolumab</td>
<td>33%</td>
<td>2%</td>
</tr>
<tr>
<td>Motzer et al. NEJM 2015</td>
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<tr>
<td>Everolimus</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>Motzer et al. Cancer 2010</td>
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<tr>
<td>Pazopanib</td>
<td>20%</td>
<td>2%</td>
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<td>Sternberg et al. EJC 2013</td>
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The aim of this multicenter randomized phase 2 study was to determine efficacy and safety of testosterone undecanoate in mRCC patients with fatigue developed during targeted therapy.
• multicenter randomized phase 2 study FARETES, N=60

**Male patient with:**
- clear cell mRCC
- normal PSA level
- low testosterone level (<12.1 nmol/L)
- no evidence of hypothyroidism
- fatigue as side effect of first-line sunitinib or pazopanib

*TESTOSTERONE UNDECANOATE* + TARGETED THERAPY

TARGETED THERAPY

*Nebido®, 1,000 mg, was injected intramuscular deeply on Day 1 of a new treatment cycle*
Primary endpoint:
difference in mean change of fatigue according to Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

Secondary endpoints:
safety
FKSI-19 score,
testosterone serum concentrations,
red blood cells count
hemoglobin level

Exploratory endpoints:
Duration of TT, ORR, PFS, OS

Assessments:
The assessments were performed at baseline and Day 28 of a treatment cycle
RESULTS (1): PATIENT CHARACTERISTICS & TOXICITY

- Rate of hypogonadism was 75.6% (62 from 82 screened patients)

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>T group, N=30</th>
<th>Control group, N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (range)</td>
<td>52 (33-71)</td>
<td>55 (42-69)</td>
</tr>
<tr>
<td>Sunitinib, N (%)</td>
<td>28 (93)</td>
<td>28 (93)</td>
</tr>
<tr>
<td>Pazopanib, N (%)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>IMDC poor risk factors, 0-2, N (%)</td>
<td>21 (70)</td>
<td>22 (73)</td>
</tr>
<tr>
<td>Previous nephrectomy, N (%)</td>
<td>30 (100)</td>
<td>30 (100)</td>
</tr>
</tbody>
</table>

- Testosterone was well tolerated in mRCC patients
- No unexpected and grade 2-4 toxicity was observed
RESULTS (2): FACIT-F

- Change from baseline in the fatigue score on the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) questionnaire

Scoring is based on a scale from 0 to 52, with lower scores indicating less fatigue.

The current study did achieve its primary endpoint based on the significant differences favored Testosterone over targeted therapy alone regarding fatigue (P=0.012).
RESULTS (3): NCCN-FACT FKSI-19

- Change from baseline in the fatigue score on the NCCN/Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index 19 (NCCN-FACT FKSI-19) questionnaire (Ver. 2)
  Scoring is based on a scale from 0 to 76, with lower scores indicating less fatigue.

The health-related quality-of-life scores in the Testosterone group were better than those in the control group ($P = 0.01$)
RESULTS (4): TESTOSTERONE, RBC, HB

- Testosterone serum concentration was significantly higher on the Day 28 (P = 0.029)
- There was non-significant positive trend in RBC count and hemoglobin level between 2 groups
At data cutoff (June 20, 2018), median (range) follow-up was 11.2 (7.8 -14.6) mo

**Objective response rate:**
- 46.7% (14/30) including 1 CR and 13 PRs in the Testosterone arm
- 33.3% (10/30) including all PRs in the Control arm (P=0.3)

**Median duration of targeted therapy (from the start of first-line):**
- was not reached for Testosterone
- was 8.3 (95% CI 7-9.6) mo for Targeted therapy alone

**Discontinuation** due to SU/PAZ-related adverse events was occurred in 3% (1/30) of patients in the Testosterone group and in 17% (5/30) of patients in the Control group

**Median PFS and OS** has not been reached in both arms
CONCLUSIONS

- Male patients with mRCC receiving targeted therapy had significantly less fatigue and better symptom control with Testosterone

- Testosterone therapy was safe

- Testosterone can prolong the duration of targeted therapy

- PFS and OS will be reported