Interleukin-2/interferon-α2a/13-retinoic acid-based chemoimmunotherapy in advanced renal cell carcinoma: results of a prospectively randomised trial of the German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN)

We performed a prospectively randomised clinical trial to compare the efficacy of four subcutaneous interleukin-2-(sc-IL-2) and sc interferon-α2a (sc-IFN-α2a)-based outpatient regimens in 379 patients with progressive metastatic renal cell carcinoma. Patients with lung metastases, an erythrocyte sedimentation rate ≤ 70 mm h⁻¹ and neutrophil counts ≤ 6000 µl⁻¹ (group I) were randomised to arm C: arm A plus intravenous 5-fluorouracil (iv-5-FU) (n = 78), or arm B: arm A plus inhaled-IL-2 (n = 65). All others (group II) were randomised to arm C: arm A plus intravenous 5-fluorouracil (iv-5-FU) (n = 116), or arm D: arm A plus po-Capecitabine (n = 120). Median overall survival (OS) was 22 months (arm A; 3-year OS: 29.7%) and 18 months (arm B; 3-year OS: 29.2%) in group I, and 18 months (arm C; 3-year OS: 25.7%) and 16 months (arm D; 3-year OS: 32.6%) in group II. There were no statistically significant differences in OS, progression-free survival, and objective response between arms A and B, and between arms C and D, respectively. Given the known therapeutic efficacy of sc-IL-2/sc-IFN-α2a/po-13cRA-based outpatient chemoimmunotherapies, our results did not establish survival advantages in favour of po-Capecitabine vs iv-5-FU, and in favour of short-term inhaled-IL-2 in patients with advanced renal cell carcinoma receiving systemic cytokines.

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The prognosis of metastatic renal carcinoma remains poor. Although this tumour is highly resistant to chemotherapy and hormone therapy, promising results have been reported with the use of molecular agents that is, recombinant cytokines, notably recombinant interleukin-2 (IL-2) and interferon-α (IFN-α), given intravenously, subcutaneously alone or in combination in outpatient regimes with objective response rates between 6 and 31% (Rosenberg et al, 1987; Atzpodien et al, 1990; Sleijfer et al, 1992; Jayson et al, 1998; Tourani et al, 2003).
When the present trial was planned, various studies focused on the combination of immunomodulator substances and chemotherapeutic agents to increase antitumour activity. In preliminary reports on oral 13-cis-retinoic acid (po-13cRA), a cell differentiation regulator, po-13cRA could enhance antitumour efficiency in IL-2/IFN-α or chemoimmunotherapy-treated metastatic renal cell carcinoma patients, with objective response rates between 17 and 42% (Atzpodien et al, 1995; Stadler et al, 1998). In the presence of pulmonary metastases, locoregional administration of inhaled IL-2 was reported to yield low toxicity combined with objective response rates of pulmonary disease of 2.5–21% (Lorenz et al, 1996; Merimsky et al, 2004). Other reports showed that the combination of cytokines with intravenous 5-fluorouracil (iv-5-FU) could increase objective response rates to between 12 and 39% (van Herpen et al, 2000; Atzpodien et al, 2001, 2004). Preliminary results of a phase II study combining IL-2/IFN-α with oral Capécitabine, which is converted to 5-FU in vivo, reported objective response rates of 34% (Oevermann et al, 2000).

Here, we prospectively compared the long-term therapeutic efficacy of four outpatient combination regimens: arm A (sc-IL2, sc-IFN-2α, po-13cRA) and arm B (arm A plus inhaled-IL-2) in patients with pulmonary disease, and arm C (arm A plus iv-5-FU) and arm D (arm A plus po-Capécitabine) in all others.

**PATIENTS AND METHODS**

**Patients**

Three hundred and seventy-nine patients with metastatic renal cell carcinoma were stratified into two groups (Figure 1). Group I patients (n = 143) were subsequently randomised to arm A (sc-IL-2, sc-IFN-2α, po-13cRA) or arm B (arm A plus inhaled-IL-2), whereas group II patients (all others; n = 236) were randomised to arm C (arm A plus iv-5-FU) or arm D (arm A plus po-Capécitabine). Median follow-up of these patients was 18 months (range 0–83 months). Patient pretreatment included radical tumour nephrectomy (n = 343), radiotherapy (n = 51), chemotherapy (n = 11), immunotherapy (n = 18), chemoimmunotherapy (n = 19), naturopathic therapy (n = 2), and others (n = 7) (Table 1).

Criteria for entry into the trial were as follows: histologically confirmed progressive and irremediable metastatic renal cell carcinoma; an expected survival duration of more than 3 months; Karnofsky performance status >80%; age between 18 and 80 years; white blood cell count >3500 µl⁻¹; platelet count >100000 µl⁻¹; haematocrit >30%; serum bilirubin, and creatinine <1.25 of the upper normal limit; no evidence of congestive heart failure, no severe coronary artery disease, no cardiac arrhythmias, no clinically symptomatic CNS disease or seizure disorders, no human immunodeficiency virus infection, no evidence of chronic active hepatitis, no concomitant corticosteroid therapy. In all patients treated, no chemotherapy or immunomodulatory treatment had been performed during the previous 4 weeks. Also, pregnant and lactating women were excluded.

Treatment was approved by the institutional review board, written informed consent was obtained from all patients before entry into the trial. Fifty-four participating centres entered a total of 379 eligible patients into this trial.

**Treatment design**

Patients were stratified into two groups according to the clinical characteristics adapted from Lopez-Hanninen et al (1996). Group I consisted of patients with lung metastases, an erythrocyte sedimentation rate ≤70 mm h⁻¹, and neutrophil counts ≤6000 µl⁻¹; group II included all other patients. As all treatment regimens were designed to be administered in the outpatient setting, this required selection of patients with good or fair performance status. Upon written receipt of patient pre-treatment evaluation, per centre block randomisation was performed to rule out centre-related statistical bias. Patients stratified to group I or II were randomised according to a per centre 1:1 randomisation. Group I patients received arm A (sc-IL2, sc-IFN-2α, po-13cRA) or arm B (arm A plus inhaled-IL-2), whereas group II patients received either arm C (arm A plus iv-5-FU) or arm D (arm A plus po-Capécitabine).

**Regimens**

Treatment arm A consisted of sc-IFN-2α (Roferon, Hoffmann-La Roche, Grenzach-Wyhlen, Germany) (5 × 10⁶ IU m⁻², day 1, weeks 1 + 4; days 1, 3, 5, weeks 2 – 3; 10 × 10⁶ IU m⁻², days 1, 3, 5, weeks 5 – 8), sc-IL-2 (Proleukin, Chiron, Emeryville) (10 × 10⁶ IU m⁻², twice daily, days 3 – 5, weeks 1 + 4; 5 × 10⁶ IU m⁻², days 1, 3, 5, weeks 2 + 3), and po-13cRA (20 mg 3 × daily) over 8 weeks. Treatment arm B consisted of treatment arm A combined with inhaled-IL-2 (Proleukin, Chiron, Emeryville) (9 × 10⁶ IU/2.5 ml basic solution, four times a day, days 1 – 5, weeks 2 + 3 and weeks 5 – 8); the IL-2 (2 × 18 × 10⁶ IU) was dissolved in 10 ml 5% glucose solution, out of which 2.5 ml (9 × 10⁶ IU IL-2 in solution) was taken for each of the four daily administrations; IL-2 was inhaled using a Salvia Lifetec Jetair inhalator (Kronberg, Germany) constantly providing 3 µm particles. Treatment arm C consisted of arm A plus iv-5-FU (1000 mg m⁻², day 1, weeks 5 – 8). Treatment arm D consisted of treatment arm A combined with po-Capécitabine (1000 mg m⁻² twice daily, days 1 – 5, weeks 5 – 8). Eight-week treatment cycles were repeated for up to three courses unless progression of disease occurred. Patients with an unchanged tumour response in cycle two did not receive a subsequent third treatment cycle.

Re-evaluation of the patients tumour status was performed between treatment cycles. Arm A, B, C, and D patients received a mean of 1.6, 1.6, 1.5, and 1.6 8-week cycles, respectively (range 1 – 6). Concomitant medication was given as needed to control adverse effects of chemoimmunotherapy. Sixty patients (15.8%) (arm A: 14%; arm B: 9.2%; arm C: 21.6%; arm D: 15%) did not complete cycle one owing to early disease progression before the first evaluation (2.9%), intolerance (8.7%), death during therapy (1.6%), patients’ wish (2.1%), and non-compliance (0.5%), respectively. Less than 4% of patients required in-patient care throughout treatment. All patients were seen at regular weekly or bi-weekly intervals by oncologic specialists; additional care was provided whenever needed.

**Assessment of response, survival, and toxicity**

Response to therapy was evaluated according to World Health Organization (WHO) criteria on an intent-to-treat basis. All responses were reviewed by Board-certified expert radiologists. In case of progression upon first re-evaluation after 8 weeks of treatment, progression-free survival (PFS) was calculated at 0 months. Survival was measured from start of therapy to date of death or to the last known date to be alive. All patients had to be followed up for survival for at least 3 years as cutoff. Systemic maximum toxicity was evaluated using a grading system adapted from the WHO.

**Statistical analysis**

The statistical end points in our analysis were (1) OS, (2) PFS, and (3) objective response of patients. The probability of OS and PFS was plotted over time according to the method of Kaplan and Meier (1958). Statistical significance was assessed using the log-rank test.
The 3-year survival rates were hypothesised to show a 20% advantage of arm B over arm A (40% vs 20%), and a 15% advantage of arm D over arm C (30% vs 15%). Using an \( \alpha \) of 0.05 (one-sided), a sample size of 64 patients each (arm A and arm B) and 95 patients each (arm C and arm D) was needed to have 80% power to statistically establish the assumed difference in 3-year survival rates. To meet these statistical end points, randomisation was performed 1:1 for groups I and II, respectively.

**RESULTS**

A total of 379 metastatic renal carcinoma patients were treated: 143 group I patients with pulmonary metastases (median OS: 21 months) were randomised to receive sc-IL-2, sc-IFN-\( \alpha \)2a, and po-13cRA (arm A); or arm A plus inhaled-IL-2 (arm B); 236 group II patients (median OS: 17 months) were randomised to receive arm A plus iv-5-FU (arm C); or arm A plus po-Capecitabine (arm D).

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*Initial stratification was performed according to clinical characteristics.

\( ^{sc-IL-2} \) = subcutaneous interleukin-2; \( ^{sc-IFN-\alpha} \) = subcutaneous interferon-\( \alpha \); \( ^{p.o.-13cRA} \) = peroral 13-cis-retinoic acid; \( ^{inhaled-IL-2} \) = inhaled interleukin-2; \( ^{i.v.-5-FU} \) = intravenous 5-fluorouracil; \( ^{p.o.-Capecit.} \) = peroral Capecitabine
Treatment response

Eight arm A (sc-IL-2/sc-IFN-α2a/po-13cRA) treated patients (10%) achieved a complete response and 15 patients (19%) had a partial remission (Table 2). The overall objective response rate was 29% (95% CI 19, 40). Twenty-eight patients (36%) showed disease stabilisation and 27 patients (35%) exhibited continuous disease progression despite therapy.

In arm B (arm A plus inhaled-IL-2), there were eight complete responders (12%) and 12 partial responders (19%), with an overall objective response rate of 31% (95% CI 20, 44). Seventeen patients (26%) had disease stabilisation, and in 28 patients (43%) a continuous disease progression was observed.

In arm C (arm A plus iv-5-FU), four patients (3%) achieved a complete response and 18 patients (16%) had a partial remission. The overall objective response rate was 19% (95% CI 13, 27). Thirty patients (26%) showed disease stabilisation and 64 patients (55%) exhibited continuous disease progression.

In arm D (arm A plus po-Capecitabine) treated patients (7%) achieved a complete response and 23 patients (19%) had a partial remission. The overall objective response rate was 26% (95% CI 19, 35). Thirty-two patients (27%) showed disease stabilisation, and in 56 patients (47%) a continuous disease progression was observed.

Progression-free survival

Seven patients (9%) in arm A (sc-IL-2/IFN-α2a/po-13cRA), six patients (9%) in arm B (arm A plus inhaled-IL-2), five patients (4%) in arm C (arm A plus iv-5-FU), and nine patients (8%) in arm D (arm A plus po-Capecitabine) remained progression-free at last follow-up. Patients reached a median PFS of 5 months in arm A (3-year PFS: 8.8%) and 4 months in arm B (3-year PFS: 10.8%). Median PFS was 0 months in arm C (3-year PFS: 7.8%) and 4 months in arm D (3-year PFS: 9.3%) (Figure 2). There was no statistically significant difference in PFS between arms A and B ($P = 0.9837$), and between arms C and D ($P = 0.3265$).

Overall survival

Seventeen patients (22%) in arm A (sc-IL-2/IFN-α2a/po-13cRA), 13 patients (20%) in arm B (arm A plus inhaled-IL-2), 16 patients (14%) in arm C (arm A plus iv-5-FU), and 22 patients (18%) in arm D (arm A plus po-Capecitabine) continued to be alive at last follow-up. Median OS was 22 months in arm A (3-year OS: 29.7%), 18 months in arm B (3-year OS: 29.2%), 18 months in arm C (3-year OS: 25.7%), and 16 months in arm D (3-year OS: 21 months).

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Table 1: Patients characteristics and pretreatment

| Characteristic          | Arm A | Arm B | Arm C | Arm D | All patients |
|-------------------------|-------|-------|-------|-------|--------------|
| Entered                 | 78    | 65    | 116   | 120   | 379          |
| Age (years)             |       |       |       |       |              |
| Median                  | 61    | 60    | 60    | 60    | 60           |
| Range                   | 28–79 | 42–75 | 32–78 | 35–75 | 28–79        |
| Sex                     |       |       |       |       |              |
| Male                    | 52    | 48    | 82    | 93    | 275          |
| Female                  | 26    | 17    | 34    | 27    | 104          |
| Pretreatment            |       |       |       |       |              |
| Radical tumour nephrectomy | 70   | 57    | 107   | 109   | 343          |
| Radiotherapy            | 7     | 6     | 19    | 19    | 51           |
| Chemotherapy            | 2     | 2     | 3     | 4     | 11           |
| Immunotherapy           | 2     | 3     | 4     | 9     | 18           |
| Chemoinmunotherapy      | 3     | 4     | 4     | 8     | 19           |
| Naturopathic            | 0     | 0     | 0     | 2     | 2            |
| Others                  | 1     | 1     | 5     | 0     | 7            |
| Metastatic sites        |       |       |       |       |              |
| Lung/pleural            | 78    | 65    | 57    | 70    | 270          |
| Lymph nodes             | 28    | 13    | 42    | 46    | 129          |
| Bone                    | 8     | 12    | 28    | 32    | 80           |
| Liver                   | 6     | 6     | 29    | 28    | 69           |
| Contralateral kidney    | 5     | 3     | 10    | 8     | 26           |
| Adrenals                | 3     | 2     | 5     | 7     | 17           |
| Soft tissue             | 2     | 0     | 10    | 11    | 23           |
| CNS                     | 0     | 0     | 4     | 1     | 5            |
| Othersb                 | 9     | 4     | 22    | 12    | 47           |

*Arm A (sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid); arm B (sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/inhaled-interleukin-2); arm C (sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/iv-5-fluorouracil); and arm D (sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/po-Capecitabine). *Including local relapse, thyroid, spleen, dermal, mammae.

Table 2: Response to therapy according to WHO criteria (intent to treat)

| Therapy                      | Complete response | Partial response | Stable disease | Progressive disease | Total |
|------------------------------|-------------------|------------------|----------------|---------------------|-------|
| Arm A                        |                   |                  |                |                     |       |
| sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid | n | 8 | 15 | 28 | 27 | 78 |
| Obj. Resp. (95% CI)           |                   |                  |                |                     |       |
|                             |                   | 10%              | 19%            | 36%                 | 35%   | 100% |
| Arm B                        |                   |                  |                |                     |       |
| sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/inhaled-interleukin-2 | n | 8 | 12 | 17 | 28 | 65 |
| Obj. Resp. (95% CI)           |                   |                  |                |                     |       |
|                             |                   | 12%              | 19%            | 26%                 | 43%   | 100% |
| Arm C                        |                   |                  |                |                     |       |
| sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/iv-5-fluorouracil | n | 4 | 18 | 30 | 64 | 116 |
| Obj. Resp. (95% CI)           |                   |                  |                |                     |       |
|                             |                   | 3%               | 16%            | 26%                 | 55%   | 100% |
| Arm D                        |                   |                  |                |                     |       |
| sc-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/po-Capecitabine | n | 9 | 23 | 32 | 56 | 120 |
| Obj. Resp. (95% CI)           |                   |                  |                |                     |       |
|                             |                   | 7%               | 19%            | 27%                 | 47%   | 100% |
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Table 3  Systemic maximum toxicity

| % Patients |
|-----------|
| Arm A | Arm B | Arm C | Arm D |
| I/II | III/IV | I/II | III/IV | I/II | III/IV | I/II | III/IV |
| Fever<sup>a</sup> | 76 | 2 | 67 | 4 | 77 | 4 | 74 | 9 |
| Chills | 69 | 5 | 61 | 4 | 68 | 9 | 67 | 7 |
| Malaise | 60 | 19 | 67 | 8 | 77 | 11 | 59 | 28 |
| Nausea/vomiting | 60 | 2 | 52 | 10 | 70 | 5 | 58 | 2 |
| Anorexia | 48 | 24 | 35 | 26 | 44 | 18 | 44 | 26 |
| Diarhoea | 33 | — | 29 | 5 | 38 | 4 | 38 | 2 |
| Respiratory distress | 41 | 7 | 48 | 4 | 41 | 7 | 39 | 4 |
| Mucositis | 52 | 2 | 48 | 4 | 46 | 2 | 45 | — |
| Hypotension | 38 | — | 19 | — | 23 | 2 | 23 | — |
| Alopecia | 3 | — | 36 | — | 23 | 2 | 28 | — |
| Anythia | 24 | 2 | 10 | — | 12 | 4 | 13 | 2 |
| CNS/disorientation | 26 | — | 19 | — | 22 | — | 26 | 2 |
| Paresthesias | 21 | — | 5 | — | 11 | — | 12 | — |
| Fluid retention/oedema | 12 | — | 14 | — | 5 | 2 | 13 | 2 |
| Leucocyte counts | 10 | 2 | 6 | 3 | 12 | — | 6 | 2 |
| Thrombocyte counts | 4 | — | — | — | 3 | — | 8 | 2 |
| Haemoglobin levels | 16 | 14 | 5 | 31 | 2 | 21 | 5 | 2 |

<sup>a</sup>Arm A (sci-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid); arm B (sci-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/inhaled-IL-2); arm C (sci-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/iv-5-fluorouracil); and arm D (sci-interleukin-2/sc-interferon-α2a/po-13-cis-retinoic acid/po-Capecitabine). All patients received a standard regimen of fever-reducing treatment employing p.o. paracetamol.

Treatment toxicity

All four sc-IL-2/sc-IFN-α2a/po-13-cis-RA-based therapies were moderately tolerated and could be administered in the outpatient setting. Most side effects were limited to WHO grades I and II, and no toxic deaths occurred. All toxicities reversed spontaneously following completion of chemioimmunotherapy.

Table 3 summarises all grade I/II and III/IV treatment-related adverse effects. More than 5% of patients experienced grade III or IV treatment-related anorexia (24% arm A, 26% arm B, 18% arm C, 26% arm D), malaise (19% arm A, 8% arm B, 11% arm C, 28% arm D), nausea/vomiting (10% arm B), chills (9% arm C, 7% arm D), fever (9% arm D), and respiratory distress (7% arm A, 7% arm C).

A total of 5% of arm A (sc-IL-2/IFN-α2a/po-13-cisRA), 8% of arm B (arm A plus inhaled-IL-2), 12% of arm C (arm A plus iv-5-FU), and 8% of arm D (arm A plus po-Capecitabine) patients discontinued treatment owing to toxicity.

DISCUSSION

In this prospectively randomised trial, we reported the results of 379 patients with progressive metastatic renal cell carcinoma who received (A) sc-IL-2, sc-IFN-α2a, po-13-cisRA, (B) arm A plus inhaled-IL-2, (C) arm A plus iv-5-FU, or (D) arm A plus po-Capecitabine.

We showed that patients with lung metastases, an erythrocyte sedimentation rate ≤70 mm h<sup>−1</sup>, and neutrophil counts ≤6000 μl<sup>−1</sup> (group I) achieved a median OS of 22 months (arm A) and 18 months (arm B), whereas all other patients (group II) reached a median OS of 18 months (arm C) and 16 months (arm D), with no statistically significant differences. Overall, other authors reported a median OS of 17 months (sc-IL-2/sc-IFN-α2a/po-13-cisRA) (Stadler et al., 1998), 19 months (sc-IL-2/sc-IFN-α2a/inhaled-IL-2) (Huland et al., 1994), and 11–27 months (sc-IL-2/sc-IFN-α2a/po-13cRA/iv-5-FU) (Soori et al., 2002; Atzpodien et al., 2004).

It should be noted that the primary end point of the current trial was not reached, given 3-year OS-rates of 29.7% (arm A) and 29.6% (arm C). There was no statistically significant difference in OS between arms A and B (P = 0.3387), and between arms C and D (P = 0.5652).
REFERENCES

Aass N, De Mulder PHM, Mickisch GH, van Oosterom AT, van Poppelt H, Fossa SD, de Prijck L, Sylvester TJ (2005) Randomized phase II/III trial of interferon alfa-2a with and without 13-cis-retinoic acid in patients with progressive metastatic renal cell carcinoma: The European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group (EORTC 30951). J Clin Oncol 23: 4172 – 4278

Atzpodien J, Kirchner H, Duensing S, Lopez Hanninen E, Franzke A, Buer J, Probst M, Anton P, Poliwoda H (1995) Biochemistry of advanced metastatic renal-cell carcinoma: results of the combination of interleukin-2, alpha-interferon, 5-fluorouracil, vinblastine, and 13-cis-retinoic acid. World J Urol 13: 174 – 177

Atzpodien J, Kirchner H, Illiger HJ, Metzner B, Ukena D, Schott H, Funke PJ, Gramatzki M, von Jürgenson S, Wandert T, Patzelt T, Reitz M (2001) IL-2 in combination with IFN-α and 5-FU vs tamoxifen in metastatic renal-cell carcinoma: Long-term results of a controlled randomized clinical trial. Br J Cancer 85(8): 1130 – 1136

Atzpodien J, Kirchner H, Jonas U, Bergmann S, Schott H, Heynemann H, Fornara P, Loening SA, Roigas J, Müller SC, Bodenstein H, Pomer S, Metzner B, Rebmann U, Oberneder R, Siebels TJ, Wandert T, Patzelt T, Reitz M, DGCIN-Group (2004) Interleukin-2- and interferon-alpha2a-based immunotherapy in advanced renal cell carcinoma: a prospectively randomized trial of The German Cooperative Renal Carcinoma Chemoimmunotherapy Group (DGCIN). J Clin Cancer Res 22(7): 1188 – 1194

Atzpodien J, Kofler A, Franks CR, Knuever-Hepp J, Lopez-Hanninen E, Fischer M, Mohr H, Dallmann I, Hadam M (1990) Home therapy with recombinant interleukin-2 and interferon-alpha 2b in advanced human malignancies. Lancet 335: 1509 – 1512

Huland E, Burger A, Fleischer J, Fornara P, Hatzmann E, Heidenreich A, Heinzler H, Heynemann H, Hoffmann L, Hofmann R, Huland H, Kämper J, Kindler M, Kirchner H, Möllhorn G, Mongiat TH, Rebmann U, Roigas J, Schneider TH, Schnoor D, Schmitz HJ, Wenisch R, Varga Z, Vinke J (2003) Efficacy and safety of inhaled recombinant interleukin-2 in high-risk renal cell cancer patients compared with systemically interleukin-2: an outcome study. Folia Biol (49(5): 183 – 190

Huland E, Heinzler H, Huland H (1994) Inhaled interleukin-2 in combination with low-dose interleukin-2 and interferon alpha in patients with pulmonary metastatic renal-cell carcinoma: effectiveness and toxicity of mainly local treatment. J Cancer Res Clin Oncol 120(4): 221 – 228

Jayson GC, Middleton M, Lee SM, Ashcroft L, Thatcher N (1998) A randomized phase II trial of interleukin 2 and interleukin 2-interferon alpha in advanced renal cancer. Br J Cancer 78: 366 – 369

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Ass 53: 457

Lopez-Hanninen EH, Kirchner H, Atzpodien J (1996) Interleukin-2 based home therapy of metastatic renal cell carcinoma: risks and benefits in 215 consecutive single institution patients. J Urol 155: 19 – 25

Lorenz J, Wilhelm K, Kessler M, Peschel C, Schwuler U, Lissner R, Strauß WG, Huland E, Huber C, Aulitzky WE (1996) Phase I trial of inhaled natural interleukin 2 for treatment of pulmonary malignancy: toxicity, pharmacokinetics, and biological effects. Clin Cancer Res 2: 1115 – 1122

Merimsky O, Gez E, Weiten R, Nehushtan H, Rubinov R, Hayat H, Peretz T, Ben-Shahar M, Biran H, Katsenelson R, Mermershtein V, Loven D, Karminsly N, Neumann A, Matejevsky D, Inbar M (2004) Targeting pulmonary metastases of renal cell carcinoma by inhalation of interleukin-2. Ann Oncol 15: 610 – 612

Motzer RJ, Murphy BA, Bacik J, Schwartz LH, Nanus DM, Mariotti T, Loehrer P, Wilding G, Fairclough DL, Cella D, Mazumdar M (2000) Phase III trial of interferon alpha-2a with or without 13-cis-retinoic acid for patients with advanced renal cell carcinoma. J Clin Oncol 18(6): 2972 – 2980

Oevermann K, Buer J, Hoffmann R, Franzke A, Schrader A, Patzelt T, Kirchner H, Atzpodien J (2000) Capecitabine in the treatment of metastatic renal cell carcinoma. Br J Cancer 83(5): 583 – 587

Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, Linehan WM, Robertson CN, Lee RE, Rubin JT (1987) A progress report on the treatment of 157 patients with advanced cancer using lymphokine activated killer cells and interleukin-2 or high-dose interleukin-2 alone. New Engl J Med 316: 889

Sleijfer DT, Janssen RA, Bouter J, de Vries EG, Willemsen PH, Mulder NH (1992) Phase II study of subcutaneous interleukin-2 in unselected patients with advanced renal cell cancer on an outpatient basis. J Clin Oncol 10: 1119 – 1123

Soori G, Dillman RO, Wiemmann MC, Stark JJ, Tai F, DePriest CB, Church CK, Schulof R (2002) Phase II trial of subcutaneous interleukin-2, subcutaneous interferon-alpha, 5-fluorouracil and cis-retinoic acid in the treatment of renal cell carcinoma: final results of cancer biotherapy research group 94-10. Cancer Biother Radiopharm 17(2): 165 – 173

Stadler WM, Kuzel T, Dumas M, Vogelzang NJ (1998) Multicenter phase II trial of interleukin-2, interferon-alpha, and 13-cis-retinoic acid in patients with metastatic renal-cell carcinoma. J Clin Oncol 6: 1820 – 1825
Tourani JM, Pfister C, Tubiana N, Ouldkaci M, Prevot G, Lucas V, Oudard S, Malet M, Cottu P, Ferrero JM, Mayeur D, Rixe O, Sun XS, Bernard O, Andre T, Tournigand C, Muracciole X, Guilhot J, Subcutaneous Administration Propeukin Program Cooperative Group (2003) Subcutaneous interleukin-2 and interferon alfa administration in patients with metastatic renal cell carcinoma: final results of SCAPP III, a large, multicenter, phase II, nonrandomized study with sequential analysis design – the Subcutaneous Administration Propeukin Program Cooperative Group. J Clin Oncol 21(21): 3987–3994

van Herpen CM, Jansen RL, Kruit WH, Hoekman K, Groenewegen G, Osanto S, De Mulder PH (2000) Immunchemotherapy with interleukin-2, interferon-alpha and 5-fluorouracil for progressive metastatic renal cell carcinoma: a multicenter phase II study. Dutch Immunotherapy Working Party. Br J Cancer 82: 772–776