# High Dose (HD) IL-2 for Metastatic Renal Cell Carcinoma (mRCC) in the Targeted Therapy Era: Extension of OS Benefits Beyond Complete Response (CR) and Partial Response (PR)

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## ABSTRACT

BACKGROUND: In the pre-2006 NCI series of single agent HD IL-2 treatment, the overall response rate (ORR) for mRCC is 14-20% with a median overall survival (mOS) of 19 months (Klapper, 2008), at a time when few other therapies were available. The current study evaluates a multi-institutional registry experience of patients treated with HD IL-2 in the targeted therapy (TT) era.

RESULTS: Of 97 subjects, 39 patients were confirmed to be deceased, 58 were known to be alive, and none were lost to follow-up. The mOS was 50.9 months with a median follow-up of 37.1 months. Patients with complete response (CR), partial response (PR), and stable disease (SD) did not reach mOS. For patients with progressive disease (PD) median OS was 40.2 months. For those patients with no prior or prior TKI treatment the median OS was 61.8 months and 48 months, respectively. The ORR was 22% (8% CR and 14% PR). No deaths due to IL-2 related toxicity were reported in the retrospective cohort. We report summary findings including survival status as of April 2014 from a retrospective set of mRCC subjects (n=97, 11 sites).

## INTRODUCTION

For patients with metastatic renal cell carcinoma (mRCC), the prognosis is poor. Studies of HD IL-2 prior to the availability of TT describe mOS of around 19 months (Fyfe,1995; Klapper, 2008). Treatment with targeted therapies (TT), such as FDA-approved sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, everolimus, and temsirolimus must be continuously administered and rarely provide durable remissions. The International mRCC Database Consortium (IRDC) study of serial administration of TT showed a median survival of 18.8 months after initiation of TT therapy (Heng, 2013). The rapid adoption of these TT has largely replaced the previous standard of care treatments such as immunotherapy.

Several recent reports have studied the use of HD IL-2 during the TT era. A retrospective single site study of 88 mRCC patients treated between 2004-2011, showed a mOS of 35.5 month and a 2 yr OS rate of 60.6% (Hanzly, 2014). Another report of 186 patients from a single institution showed a 2 yr survival of 56% and an ORR of 24% (7% CR and 17% PR)(Payne, 2014). Birkhäuser et al., reported that 21 patients receiving TT after progressing on HD IL-2 experienced a significantly increased overall survival (median not reached) compared to 109 patients treated in the same institution with targeted therapy alone (30 months). These findings were further supported by Hanzly et al., which showed that 43 patients receiving HD IL-2 followed by TT to have the best median OS (40 mo). These data suggest that HD IL-2 should be considered in eligible patients, reserving palliative treatment with TT for salvage.

In an effort to confirm and extend the results of the HD IL-2 studies performed in 1992, a national HD IL-2 database, called PROCLAIM$^{SM}$, was initiated in 2011(Kaufman, 2014). The HD IL-2 observational database, currently with over 35 participating sites, consists of a retrospective cohort (treated between 2007 and 2012) informing an ongoing prospective cohort (>600 patients)(www.proclaimregistry.com). The registry is designed to establish a clinical database on patients diagnosed with metastatic renal cell carcinoma (mRCC) and metastatic melanoma (mM) who are treated with HD IL-2 immunotherapy. The retrospective PROCLAIM data set provides the basis for this poster.

## METHODS

Patient Selection

All patients identified as meeting the following criteria were included in the retrospective cohort: 18 years of age or older and treated for metastatic renal cell carcinoma with at least one dose of HD IL-2 between January, 2007 and February, 2012. Sites were instructed to enroll patients sequentially. Determination of clinical response was as reported by the patient's treating physicians.

Assessments

The data collected include eligibility, demographics, prior treatment, disease assessment, dosing, reasons for cycle conclusion, laboratory values, clinical response, cycle interval delays, progression, reasons for stopping HD IL-2 and survival. Data was uniformly collected for every cycle, at the standard tumor assessment (4-8 weeks) after each HD IL-2 course (2 cycles) and at a standard interval follow up (approximately every 6 months). The principal investigator determined tumor responses to HD-IL-2 are categorized using either WHO or RECIST criteria, depending on individual physician and site standards. Since the IRBs waived consent for collection of data on patients in the retrospective cohort, additional IRB approval was necessary to prospectively collect surival data. This presentation is based upon an April 2014 data sweep performed for the retrospective cohort.

## DEMOGRAPHICS

Table 1. Patient Demographics and Disease Characteristics

| Parameter | | Patients (n=97) No. | % |
|---|---|---|---|
| Gender | Male | 77 | 79.4 |
| | Female | 20 | 20.6 |
| Age(years) | Median | 56 | |
| | Range | 34-74 | |
| | ≥ 65 | 16 | 16.5 |
| | < 65 | 81 | 83.5 |
| Race | White | 90 | 92.8 |
| | Black | 1 | 1 |
| | Other | 4 | 4.1 |
| | Subject declined to give information | 2 | 2.1 |
| ECOG | 0 | 73 | 75.3 |
| | 1 | 22 | 22.7 |
| | 2 | 1 | 1 |
| Histology | Clear Cell | 95 | 97.9 |
| | Other | 2 | 2.1 |
| Site of Metastases | Skin, LNs, and/or Lung | 45 | 46.3 |
| | Other sites in addition to skin, LNs, or Lung | 49 | 51.0 |
| | Missing | 3 | 3.1 |
| Prior Treatment | Nephrectomy | 94 | |
| | Radiation | 11 | |
| | Immunotherapy | 1 | |
| | Targeted Therapy | 15 | |
| | Blinded Randomized Trial | 2 | |
| | Other | 1 | |
| | Previously Untreated | 2 | |

## CLINICAL RESPONSE

| | mRCC N=93 n(%) | ECOG 0 N=70 n(%) | ECOG 1 N=21 n(%) | LDH < 150 N=17 n(%) | LDH ≥ 150 N=38 n(%) |
|---|---|---|---|---|---|
| CR | 7(7.5) | 7(10) | 0(0) | 3(18) | 4(11) |
| PR | 13(14) | 12(17) | 0(0) | 5(29) | 5(13) |
| SD | 22(24) | 12(17) | 10(48) | 5(29) | 7 (18) |
| PD | 51(55) | 39(56) | 11(52) | 4(24) | 22(58) |

Table 2: Response Rates. Investigator determined overall response rate was collected at the last recorded, most current date. Data was available for 93 of 97 patients. Response rates were further stratified by performance status and LDH levels.

| | HD IL-2 registry, N=97 |
|---|---|
| ORR (CR+PR) | 21.5%* |
| CBR (CR+PR+SD) | 45.5% |
| Rate of drug-related deaths | 0% |

Table 3: Overall response rate (ORR), clinical benefit rate (CBR), and death rate. *Response rate was available for 93 of 97 patients.

## TIME ON THERAPY

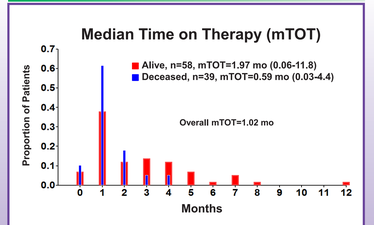


Figure 1: Time on HD IL-2 therapy. The median time on therapy (mTOT) was determined from the date of the first dose to the last dose of treatment. If the date of the last dose was not provided, the end of the study date was used. The median time on therapy is 1.02 months (0.03-11.8 range).

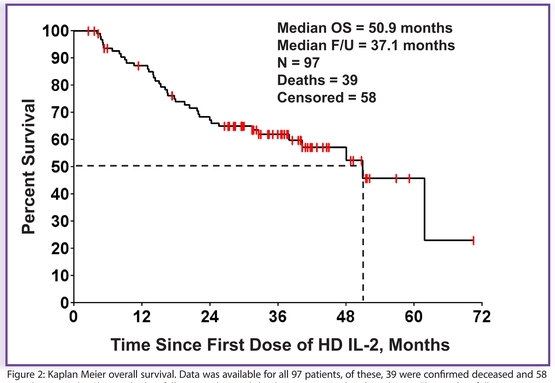


Figure 2: Kaplan Meier overall survival. Data was available for all 97 patients, of these, 39 were confirmed deceased and 58 were known to be alive at the last follow-up. Alive and dead status was updated April 2014. The median follow-up is 37.1 months. Red vertical bars represent censored subjects.

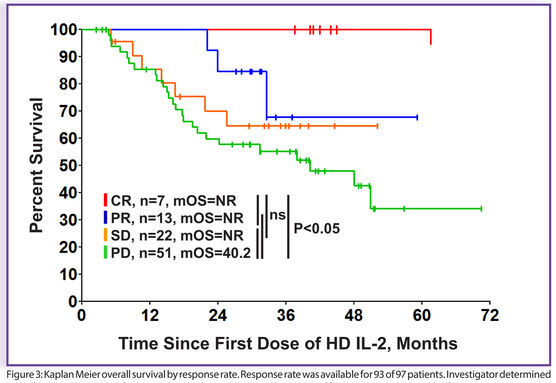


Figure 3: Kaplan Meier overall survival by response rate. Response rate was available for 93 of 97 patients. Investigator determined overall response rate was determined at the last assessment date. Vertical bars represent censored subjects.

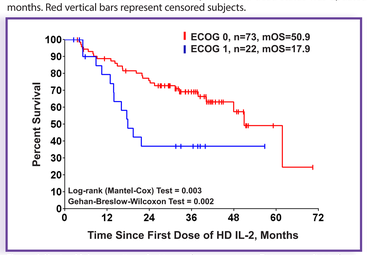


Figure 4: Kaplan Meier overall survival by performance status. Data was available for all 97 patients. There was 1 patient with ECOG status 2 that was not included in this analysis. Vertical bars represent censored subjects.

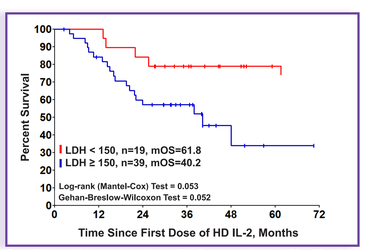


Figure 5: Kaplan Meier overall survival by LDH. Data was available for 58 of 97 patients. The pre-treatment LDH value was used when available, if not, a post cycle 1 or a pre cycle 2 value was used. Vertical bars represent censored subjects.

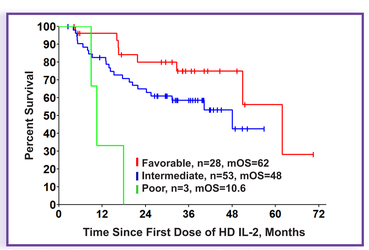


Figure 6: Kaplan Meier overall survival by risks factors. Six risk factors were considered using the International mRCC Database Consortium prognostic model, these include, ECOG ≥ 2, < 1 yr from initial diagnosis to treatment, Hgb concentration < LLN, Ca concentration > ULN, neutrophil count > ULN, platelet count > ULN (Heng, 2013). Favorable=0, intermediate=1-2, poor=3+ risk factors. Eighty four patients had complete data for all 6 prognostic factors and were included in the analysis. Vertical bars represent censored subjects.

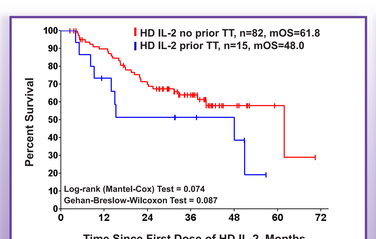


Figure 7: Kaplan Meier overall survival by prior therapy. Data was available for all 97 patients. The database captured the following prior treatments: nephrectomy, radiation, immunotherapy, targeted therapy, blinded randomized trial, or other. For this analysis, prior treatment included only targeted therapy (TT). Vertical bars represent censored subjects.

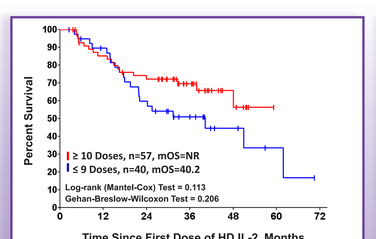


Figure 8: Kaplan Meier overall survival by the number of doses received in cycle 1. Data was available for all 97 patients. Vertical bars represent censored subjects.

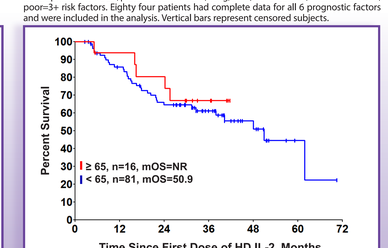


Figure 9: Kaplan Meier overall survival by age. Data was available for all 97 patients. Age was determine at the date of first dose of IL-2. Vertical bars represent censored subjects.

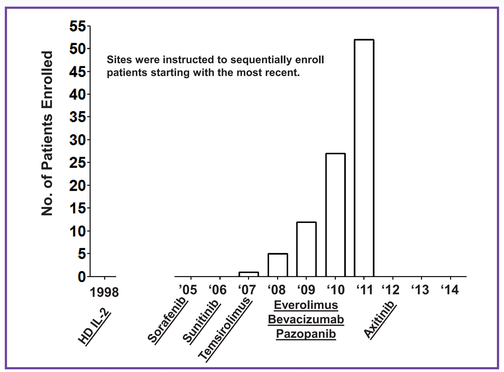


Figure 10: Timeline of drug approval by the number of patients enrolled in the HD IL-2 registry. There were 11 sites that participated.

## SUMMARY

- One, two, and three year survival rates were 86%, 66%, and 62%, respectively.
- Patients with progressive disease (PD) survive longer than expected (mOS=40.2 mo).
- HD IL-2 first line appears to have clinical benefit compared to patients with prior TKI treatment.
- ECOG and normal LDH continue to be helpful predictors in recommending IL-2.
- The majority of patients, 62%, are in the intermediate prognostic group, using the Heng prognostic model (Heng, 2013)
- Registry data show signifcant improvement in OS compared to pre-2006 NCI experience.

## CONCLUSIONS

Treatment options continue to increase for metastatic renal cell carcinoma (mRCC). Going forward it will be important to consider the long term goals of therapy, when considering deployment of the agents available. In patients where cure and longest survival are the goal, initial therapy with HD IL-2 or perhaps other immunotherapy would appear to be an important consideration. Drawing conclusions from the small numbers of patients in this study and the others cited, is difficult. A prospective randomized clinical trial (Rixe 2007 and 2013 ASCO abstract) showed PFS and OS benefit for both axitinib and sorafenib after HD IL-2. Validation of the first line use of HD IL-2 in the prospective cohort should be a priority.

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