Impact of Sequencing Targeted Therapies With High-dose Interleukin-2 Immunotherapy: An Analysis of Outcome and Survival of Patients With Metastatic Renal Cell Carcinoma From an On-going Observational IL-2 Clinical Trial: PROCLAIMSM

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Abstract

Proleukin[R] Observational Study to Evaluate the Treatment Patterns and Clinical Response in Malignancy (PROCLAIM[SM]) is the largest observational clinical database of high-dose

interleukin-2 (HD IL-2)-treated patients in the US. Herein, the survival and outcome for patients with renal cell carcinoma receiving HD IL-2 in sequence with targeted therapy are described. HD IL-2 has an acceptable efficacy and safety profile in current clinical practice and remains a valuable therapy for patients with renal cell carcinoma.

Background: This analysis describes the outcome for patients who received targeted therapy (TT) prior to or following high-dose interleukin-2 (HD IL-2).

Patients and Methods: Patients with renal cell carcinoma (n = 352) receiving HD IL-2 were enrolled in Proleukin[R] Observational Study to Evaluate the Treatment Patterns and Clinical Response in Malignancy (PROCLAIM[SM]) beginning in 2011. Statistical analyses were performed using datasets as of September 24, 2015.

Results: Overall, there were 4% complete response (CR), 13% partial response (PR), 39% stable disease (SD), and 43% progressive disease (PD) with HD IL-2. The median overall survival (mOS) was not reached in patients with CR, PR, or SD, and was 15.5 months in patients with PD (median follow-up, 21 months). Sixty-one patients had prior TT before HD IL-2 with an overall response rate (ORR) to HD IL-2 of 19% (1 CR, 9 PR) and an mOS of 22.1 months. One hundred forty-nine patients received TT only after HD IL-2 with an mOS of 35.5 months. One hundred forty-two patients had no TT before or after HD IL-2, and mOS was not reached. The mOS was 8.5 months in PD patients who received HD IL-2 without follow-on TT and 29.7 months in PD patients who received follow-on TT after HD IL-2.

Conclusions: HD IL-2 as sole front-line therapy, in the absence of added TT, shows extended clinical benefit (CR, PR, and SD). Patients with PD after HD IL-2 appear to benefit from follow-on TT. Patients who progressed on TT and received follow-on HD IL-2 experienced major clinical benefit. HD IL-2 therapy should be considered in eligible patients.

Introduction

Nearly 64,000 new cases of renal cell carcinoma (RCC) were diagnosed and over 13,000 deaths occurred in the United States in 2014.[1] Although surgical resection of localized RCC can be curative, 20% to 40% of patients with RCC develop metastases after primary nephrectomy.[2] Prior to the advent of targeted therapy, metastatic RCC (mRCC) had an historical 5-year survival rate of 5% to 10% and median overall survival (mOS) of 13 months.[3] The US Food and Drug Administration approval of novel targeted therapies (TT), including inhibitors of the vascular endothelial growth factor (VEGF) pathway (axitinib, bevacizumab, pazopanib, sorafenib, sunitinib) and inhibitors of the mammalian target of rapamycin (mTOR) pathway (temsirolimus and everolimus),[4–7] in the past decade has led to prolongation of mOS to about 28 months in 2012.[6] More recent approval of cabozantinib (2016), nivolumab (2015), and the combination of lenvatinib with everolimus (2016) have added to the treatment landscape of mRCC for second-line.[8–10] Despite the success of TT, the optimal management of mRCC remains a therapeutic challenge as complete durable responses are rare, and alternative therapy options often need to be considered.

Prior to the availability and adoption of TTs, immunotherapy with high-dose interleukin-2 (HD IL-2) was a well-established therapeutic approach to mRCC.[11] The safety and efficacy data that led to the approval of HD IL-2 in 1992 was based on 255 treated patients derived from a pool of 7 nonrandomized phase II clinical trials.[12,13] These earlier studies revealed the overall response rate (ORR) to be 15% with an mOS of 16.3 months, and the treatment-related death rate to be 4%.[2] Recent data for the use of HD IL-2 in mRCC shows an improved profile of overall safety and efficacy. In a study of 88 patients diagnosed with mRCC treated at Roswell Park between 2004 and 2011, the observed mOS was 35.5 months.[14] A retrospective analysis performed at Providence Portland Cancer Center involving 186 patients with mRCC treated with HD IL-2 revealed an ORR of 24% and a 3-year survival rate of 44%, and the reported IL-2-related death rate among 500 treated patients was less than 1%.[15] A prospective multicenter Cytokine Working Group study of 120 patients with mRCC treated between 2006 and 2009, reported an ORR of 25% and an mOS of 42.8 months.[16] Taken together, these reports of patients treated with HD IL-2 during 2004 to 2011, perhaps with improved patient selection, but also clearly in the era of TT, suggest longer survival for patients receiving HD IL-2 than in the earlier HD IL-2 reports. [14–16]

This has led us to evaluate the outcome of HD IL-2 treatment in patients who may have had sequential therapies for metastatic RCC. Proleukin[R] Observational Study to Evaluate the Treatment Patterns and Clinical Response in Malignancy (PROCLAIM[SM]) registry (NCT01415167), a national observational database, was established in 2011 to document and study the current treatment outcomes with HD IL-2.[17] The registry is designed to create a clinical database of patients diagnosed with mRCC or metastatic melanoma who are treated with HD IL-2 alone or HD IL-2 in combination or sequence with other therapies. At the time of this report, there are 44 sites participating in the PROCLAIM[SM] registry, with over 1300 patients enrolled to date. Follow-up data at the time of this analysis are available for 1280 patients, including both retrospectively and prospectively collected data (www.proclaimregistry.com). In the prospectively enrolled cohort, there are currently 385 patients with melanoma and 496 patients with mRCC with confirmed disease classification. Herein, we report the survival outcome of patients with mRCC treated with HD IL-2 within the TT era based on findings from patients enrolled prospectively in the PROCLAIM[SM] database (2011 to 2014). This consists of 352 patients with follow-up survival data as of a data cutoff of September 24, 2015, and having had their last dose of HD IL-2 before January 1, 2015.

Patients and Methods

Patients

Data from the 352 prospectively enrolled patients with a diagnosis of mRCC were analyzed for this report. Data collection began in 2011 and is ongoing. Patients receiving their last dose of HD IL-2 before January 1, 2015 were included in this analysis. All patients identified as meeting the following criteria were included in the prospective cohort analysis: 18 years of age or older, diagnosed with mRCC, treated with at least 1 dose of HD IL-2, and with a posttreatment scan. All patients signed informed consent for data collection.

Enrolling sites agreed to enroll consecutive patients receiving at least 1 dose of HD IL-2. Available baseline data from enrolled patients included demographics (gender, age, and race) and clinical characteristics (Eastern Cooperative Oncology Group [ECOG] performance status, clear cell or non-clear cell histology, sites of metastasis, and prior treatment). Patients could have received multiple prior treatments which included, but were not limited to, surgery, chemotherapy, radiation, immunotherapy, TT, or other (Table 1). Patient eligibility at each site was confirmed by a study coordinator, and an Electronic Data Capture system was used to record the data. All data were subject to routine quality control procedures.

HD IL-2 Therapy

Physicians managed and treated patients with HD IL-2 (proleukin) per institutional standard of care and their own clinical judgment. HD IL-2 was generally administered intravenously at a dose of 600,000 IU/kg or 720,000 IU/kg over 15 minutes every 8 hours up to 14 consecutive doses over 5 days (1 cycle of therapy). The majority of patients received a second cycle of HD IL-2 after approximately a 9-day rest period, per the discretion of the investigator. Two cycles of HD IL-2 treatment constituted 1 standard course of HD IL-2 therapy. Additional courses were administered per the discretion of the treating physician. Sites were asked to enter the top 3 most affected organ systems during cycle dosing that lead to cycle conclusion, which included cardiac, renal, neurologic, metabolic, gastrointestinal, pulmonary, hematologic, vascular, hepatic, and cutaneous.

Study Design and Treatment

Patients were separated into groups based on when, if any, TT was administered (See Supplemental Figure 1 in the online version): patients who received no TT before or after HD IL-2 ("No TT" group), patients who received TT before HD IL-2 and could also have received TT after HD IL-2 ("Prior TT" group), and patients who received TT after HD IL-2 and did not receive prior TT ("Post TT Only" group). In the "Prior TT" group there were 27 patients who also received TT after HD IL-2 treatment. Specific TT agent data was collected, but not response to prior or post TT.

Toxicity data collection for the registry was designed to identify the reasons for holding doses or stopping treatment with IL-2. Therefore, investigators were asked to list the 3 organ systems affected that led to holding or stopping IL-2. These toxicities were not graded as per the common toxicity criteria, as these are inherent and expected in the management of patients receiving HD IL-2.

Response Evaluation to HD IL-2

The investigator, using either the World Health Organization criteria or Response Evaluation Criteria in Solid Tumors, depending on the individual physician preference and site standards, determined response to HD IL-2. Response was documented after each HD IL-2 treatment course (2 cycles). Information on follow-up treatments after HD IL-2 therapy was collected approximately every 6 months after completion of HD IL-2 dosing until the final cutoff date for this analysis (September 24, 2015) or until patient death (whichever occurred

first). ORR was calculated as the summation of patients with complete response (CR) and partial response (PR) divided by all patients of the given group.

Statistical Analyses

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Patient characteristics, tumor response, and survival status were determined using data as of September 24, 2015. Frequency counts and measures of central tendency were performed to provide descriptive statistics. Kaplan-Meier curves with 95% confidence intervals (CIs) were used to estimate mOS (the primary outcome), with the log-rank test to determine significance ($P < .05$). Overall survival time was calculated from the date of the first dose of HD IL-2 to the date of death or the date of the most recent follow-up. One-, 2-, and 3-year survival probabilities were obtained using the Kaplan-Meier product limit method, and corresponding CIs were obtained using the Greenwood formula. Patients were followed until the date of death or until the last day of follow-up.

Results

Baseline Characteristics on HD IL-2 Therapy

Patient characteristics and demographics are listed in Table 1. The median age was 57 years (range, 25–83 years), but 20% of patients were 65 years of age or older. The majority of patients had an ECOG performance status (PS) of 0 (n = 237; 70%), whereas 97 (29%) patients had an ECOG PS of 1. Ninety-three percent of patients had clear cell histology and had a nephrectomy prior to HD IL-2 therapy. Non-clear cell histology was not further characterized in the registry and reflects only 23 patients (Table 1). Data on sites of and numbers of metastases was collected (Table 1) (See Supplemental Table 1 in the online version).

Response Data

Of 352 patients who were treated with HD IL-2, tumor response data was available for 328 (93%) patients. There were 57 (17%) objective responses, which included 14 (4%) CRs and 43 (13%) PRs. There were 129 (39%) additional patients who experienced stable disease (SD), and 142 (43%) had progressive disease (PD). In patients with CR (71%), PR (86%), or SD (88%), the majority of responses were determined after course 2 of therapy, whereas PD was diagnosed in 79% of patients after course 1 (See Supplemental Table 2 in the online version).

HD IL-2 Treatment

The number of IL-2 doses received in the Prior TT group compared with the No Prior TT group was similar for both groups. In the Prior TT group, the median number of doses received in cycle 1 and 2 was 9 and 8, respectively. For patients that did not receive prior TT, the median number of doses received was 9 and 7 for cycles 1 and 2, respectively.

The duration of HD IL-2 drug administration was assessed from the start of the first dose of HD IL-2 to the end of the last dose of HD IL-2, and included rest periods in between cycles and courses. For patients still alive at the time of analysis (n = 236), the median duration of

HD IL-2 drug administration was 2.5 months (range, 0.10–18.3 months) (See Supplemental Table 3 in the online version). For all patients (n = 352), the median duration of HD IL-2 drug administration was 0.90 months (range, 0.03–18.3 months).

Survival Data

Survival estimates were calculated from the date of first dose of HD IL-2. The mOS was not reached for all patients based on the median follow-up of 21 months (Figure 1A). The 1-, 2-, and 3-year survival rates were 78%, 61%, and 52%, respectively. The mOS was not reached for patients who experienced CR (n = 14), PR (n = 43), or SD (n = 129), whereas patients who progressed (n = 142) had an mOS of 15.5 months (95% CI, 12.2–24.5 months). There was a statistically significant relationship between tumor response including SD and survival (*P* < .0001) (Figure 1B). The 2.5-year survival rate for patients with CR, PR, SD, and PD was 100%, 75%, 78%, and 39%, respectively.

Survival by Heng Criteria

To determine overall survival based on externally validated prognostic risk factors for mRCC, patients were separated into risk groups using the International mRCC Database Consortium model, also known as the Heng criteria.[18] A series of 6 clinical factors were used to stratify patients into 3 prognostic groups. Patients were stratified into favorable (no factors), intermediate (1–2 factors), and poor (more than 3 factors) risk groups (Figure 2). These factors include: ECOG PS greater than or equal to 2, duration of less than 1 year from initial diagnosis to treatment, hemoglobin less than the lower limit of normal, serum-corrected calcium greater than the upper limit of normal (ULN), absolute neutrophil count greater than ULN, and platelets greater than ULN.[18] There were 271 patients (77%) who had complete data for all 6 parameters, of whom 50 patients (18%) stratified into the favorable-risk group, 196 patients (72%) into the intermediate-risk group, and 25 patients (9%) into the poor-risk group (Figure 2). The mOS for patients in the favorable-risk group was not reached, whereas the mOS for patients in the intermediate- and poor-risk groups was 35.5 (95% CI, 22.7-not estimable [NE]) and 12.6 (95% CI, 5.3–14.1) months, respectively.

Prior TT

There were 61 patients in the database who received TT prior to HD IL-2 treatment (Table 2), referred to as the "Prior TT" group. Fifty-one patients (84%) received TT as their last treatment before starting HD IL-2. Forty-one patients (67%) had only 1 TT, and 20 patients (33%) had 2 or more TTs prior to HD IL-2. The most commonly prescribed TT was sunitinib, followed by pazopanib. In the Prior TT group, 55 (90.16%) of patients had clear cell histology. Sites of metastases are described in Supplemental Table 1 (in the online version). To determine whether patients with prior TT exposure benefited from HD IL-2 therapy, response to HD IL-2 was assessed. Data were available for 53 (87%) of the 61 Prior TT patients. The ORR in this set of patients was 19%. One patient achieved CR, and 9 patients achieved a PR at final tumor assessment after completing HD IL-2 therapy. Fourteen patients (26%) achieved SD, and 29 patients (55%) experienced PD as their final tumor response to HD IL-2. The mOS across all Prior TT patients, calculated from the time of HD IL-2 treatment, was 22.1 months (95% CI, 13.08- NE) (Figure 3A). The mOS was not

reached in patients attaining CR, PR, or SD, and there was no statistically significant differences in mOS across these 3 subgroups (Figure 3B). There was statistical significance in comparing each of the aforementioned groups with the mOS of PD patients, which was 13.1 months (95% CI, 7.7–16.6 months). The 2.5-year survival rate for CR, PR, SD, and PD was 100%, 100%, 68%, and 20%, respectively (Figure 3B). Among the 61 patients in the Prior TT group, 27 patients received subsequent treatment with TT after HD IL-2.

IL-2 Only (No TT) and Post-IL-2 TT Groups

There were 142 patients in the database who received no TT before or after HD IL-2 treatment, referred to here as the "No TT" group. There were 149 patients who received TT after completing HD IL-2 therapy and did not receive prior TT, referred to here as the "Post TT Only" group. The number of metastases and sites of metastases are described in Supplemental Table 1 (in the online version). The mOS for the No TT group was not reached (95% CI, NE-NE), and for the Post TT only group was 35.5 months (95% CI, 24.4-NE) (Figure 4A). There was no statistically significant difference in mOS between the Post TT Only group and the No TT group ($P > .05$). Survival estimates were stratified by tumor response to HD IL-2 for both groups (Figures 4B and 4C). Response data was available for 143 (96%) patients in the Post TT Only group and 132 (93%) patients in the No TT group. For patients in the Post TT Only group, the mOS for patients with CR (n = 3), PR (n = 9), or SD (n = 50) was not reached, whereas the mOS for patients with PD (n = 81) was 29.7 months (95% CI, 17.0-NE) (Figure 4B). The 2.5-year survival rate for patients with CR, PR, SD, and PD was 100%, 55%, 68%, and 51%, respectively. For the No TT group, the mOS for patients with CR (n = 10), PR (n = 25), or SD (n = 65) was not reached, whereas the mOS for patients with PD (n = 32) was 8.5 months (95% CI, 5.6–12.6 months) (Figure 4C). The 2.5-year survival rate for patients attaining CR, PR, SD, and PD was 100%, 79%, 92%, and 20%, respectively.

Safety

There were 5 reported deaths related to HD IL-2 drug administration in 352 patients, translating to a drug-related death rate of 1.4%. One patient with a history of hypertension and hypercholesterolemia discontinued cycle dosing because of acute kidney injury and hypotension, and eventually expired owing to ischemic bowel. One patient who experienced hypotension and shortness of breath experienced progressive renal failure prior to death. Another patient required intubation after stopping cycle dosing for anion gap acidosis and worsening hypotension, became asystolic, and died. A single patient with metastases to the lung and brain experienced expected HD IL-2-related toxicity that resolved with medical management during cycle 1; however, following 11 of 14 doses during cycle 2, this patient experienced bradycardia, became unresponsive, and died. Only 1 of the 5 patients that expired because of toxicities related to IL-2 drug treatment had received prior TT, and that agent was bevacizumab. This patient received 11 doses of HD IL-2 during cycle 1. The cause of death was attributed to respiratory failure with increased pulmonary infiltrates.

For cycle 1 dosing, in both the Prior TT and No TT groups, the top 3 most affected organ systems were cardiac, renal, and neurologic. The most common reported cardiac toxicities were hypotension followed by arrhythmia for both groups. There were no differences in

rates or expected toxicities for HD IL-2 between groups. Specifically there were no unexpected cardiac toxicities noted for the Prior TT group. A summary of toxicities by organ system leading to holding or stopping HD IL-2 for the first 4 cycles of HD IL-2 is described in Supplemental Table 4 (in the online version). Of note, these are all expected toxicities and characteristic of HD IL-2 treatment.

Discussion

TTs are the most commonly used first-line therapy for mRCC, yet HD IL-2 remains the only agent that has shown durable responses in selected patients. The optimal sequencing of these agents towards maximizing benefit remains uncertain. HD IL-2 has significant clinical benefit and should be considered an option for selected patients with appropriate performance status. In this analysis, patients who progressed on or after TT and were eligible for HD IL-2 had an objective response rate of 19% with no unexpected toxicities noted.

Another key observation that emerged from this analysis in PROCLAIM[SM] was that patients who did not receive targeted therapies before HD IL-2 or require TT soon after HD IL-2 treatment experienced prolonged clinical benefit (Figure 1B), again confirming durable benefit from HD IL-2 based on this "real world" data. This finding was also noted most recently in the IL-2 "select" trial, and was demonstrated in long-term follow-up reports of patients receiving IL-2 therapy.[12,13,16]

A third important finding from this analysis of PROCLAIM[SM] is that patients with SD experienced similar survival outcomes as did patients with PRs, and that this translates into meaningful clinical benefit (Figures 1B, 3B, 4B, 4C). This was observed in the overall group as well as in the subgroups related to timing of TT. As shown in Figure 1B, overall, 129 patients achieved SD, and the mOS for these patients was not reached. For patients with prior TT, 14 (26%) achieved SD, and likewise, the mOS was not reached (Figure 3B). Until recently, SD had not been considered a relevant statistical endpoint, but recent appreciation and understanding of the mechanism of action of TTs and newer immunotherapies is shifting this view. Given the delayed kinetics necessary to mediate immune-based tumor rejection, patients with SD may be able to achieve long-term survival benefit, making objective response rates an incomplete and/or insufficient assessment of clinical benefit in response to immunotherapy agents.

Several single-institution reports are consistent with these prospectively collected multi-center "real world" data from the PROCLAIM[SM] registry. A recent retrospective report by Lam et al showed an ORR of 13% in patients treated with HD IL-2 following an anti-VEGF tyrosine kinase inhibitor (TKI), including CRs.[19] The authors concluded that administration of HD IL-2 could be safe and effective following TKI therapy, and recommended a TKI to HD IL-2 interval of at least 2 months.[19] The efficacy of HD IL-2 in patients with prior VEGF TTs was also reported by Evans et al.[20] In this report, 23% of VEGF treatment-naive patients achieved complete responses compared with 19% among patients pretreated with anti-VEGF agents. Both groups consisted of approximately 88% with "favorable" histology.

In these analyses, mOS was not reached in patients attaining CR, PR, or SD with HD IL-2, demonstrating that HD IL-2 was active in patients who have received prior TTs.

Additionally, a recent publication from Roswell Park by Hanzly et al reported that the mOS for patients initially treated with TT and followed by HD IL-2 was 5 months compared with an mOS of 40 months for patients treated initially with HD IL-2 and then TT. There were no treatment-related deaths in this report.[14] Because this was a retrospective observational report as well, it is uncertain whether these differences are because of patient selection, lead-time bias of pretreated patients, or to follow-on treatment of other therapies. Nevertheless, clinical benefit was observed with institution of subsequent TT in patients experiencing PD after HD IL-2, resulting in an mOS of 29.7 months compared with 8.6 months in patients who did not receive TT.

These observations suggest that access to newer TTs may be one reason for enhanced survival benefit among patients with RCC treated initially with HD IL-2. Birkhauser et al from UCLA have reported similar results, with a median disease-specific survival of 83 months in 51 patients who received TT after progressing on HD IL-2, versus 30 months in 233 patients treated in the same institution with TT alone.[21]

Addressing the possibility of pre-selection as a basis for survival improvement in contemporary HD IL-2 treatment reports, we applied the International Metastatic RCC Database Consortium prognostic model (Heng criteria) for mRCC.[18] When applied to the PROCLAIM[SM] registry, a large majority of patients who received HD IL-2 were found to stratify into the intermediate-prognosis group (72%) and not the favorable-risk group (18%). This suggests that the observed improved OS is less likely attributable to a favorable risk group pre-selection bias.

For patients with mRCC, 2006 marked the beginning of availability of TT options such as sorafenib, sunitinib, bevacizumab, pazopanib, axitinib, everolimus, temsirolimus, cabozantinib, nivolumab, and the combination of lenvatinib with everolimus that has resulted in a shift away from HD IL-2 use.[11] The ability to apply these agents to greater numbers of patients with mRCC might in part explain the improved overall survival in the modern era of HD IL-2 therapy, compared with historical experience. Better patient screening and improved patient management may also be factors. The ability to receive HD IL-2 early in the course of mRCC may delay the need for subsequent therapy, and with the durable SD noted in this study, add time off-treatment for these patients.

The recent introduction of T cell checkpoint blockade with antibodies directed against the programmed cell death receptor-1 (nivolumab and pembrolizumab),[22,23] is also changing the treatment landscape for a range of solid tumors, including mRCC.[9,24,25] As newer TTs and immune therapies continue to be introduced, it will be critical to understand the safety and efficacy of these agents when used serially or concomitantly. PROCLAIM[SM] represents the largest collection of clinical data involving HD IL-2-treated patients in the US, and is useful in hypothesis generation regarding the safety and efficacy of serially applied or combined therapies as it relates to HD IL-2.

Limitations

Data extracted from clinical registries are susceptible to uncontrolled sources of bias (eg, differences in cancer treatments across groups being compared). Clinicians could apply variable methodologies to determine progression on the basis of clinical and radiographic data; for example, response to HD IL-2 was determined by the investigator using either the World Health Organization criteria or Response Evaluation Criteria in Solid Tumors, depending on the individual physician preference and site standards. Although PROCLAIM[SM] investigators were asked to enter consecutive patients into the registry, the actual inclusion of patients occurred at the investigators' discretion and patients' willingness to consent to study participation. Data from this registry is not representative of all patients with mRCC, owing to differences in eligibility criteria for HD IL-2 therapy across centers.

Conclusions

Data from this observational clinical trial (PROCLAIM[SM]) provide real-world clinical data on safety and efficacy of sequential TTs used with HD IL-2 for patients with mRCC. The data presented here suggest that HD IL-2 should be considered as an initial option before TT in eligible patients. Additionally, we report that HD IL-2 can be safe and effective in patients who were pretreated with anti-VEGF TTs. The survival benefit appears to extend to patients achieving SD, and is quite durable. The current treatment-related death rate is lower than historical experience and is likely owing to improved treatment practices and better patient selection criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- HD IL-2 is an immunotherapy with curative potential for mRCC.

- There are few clinical studies performed to assess the potential benefits of sequencing HD IL-2 with TT.

- PROCLAIM[SM] registry data suggest that the highest survivals were attained by patients who received initial HD IL-2 followed by subsequent TT. HD IL-2 should hence be considered a first-line therapy option in eligible patients.

- HD IL-2 can be active and administered safely in patients who have failed prior treatments with TT and still meet HD IL-2 eligibility criteria.

- HD IL-2 has an acceptable efficacy and safety profile in the current clinical practice and remains a valuable therapy for eligible patients with mRCC.
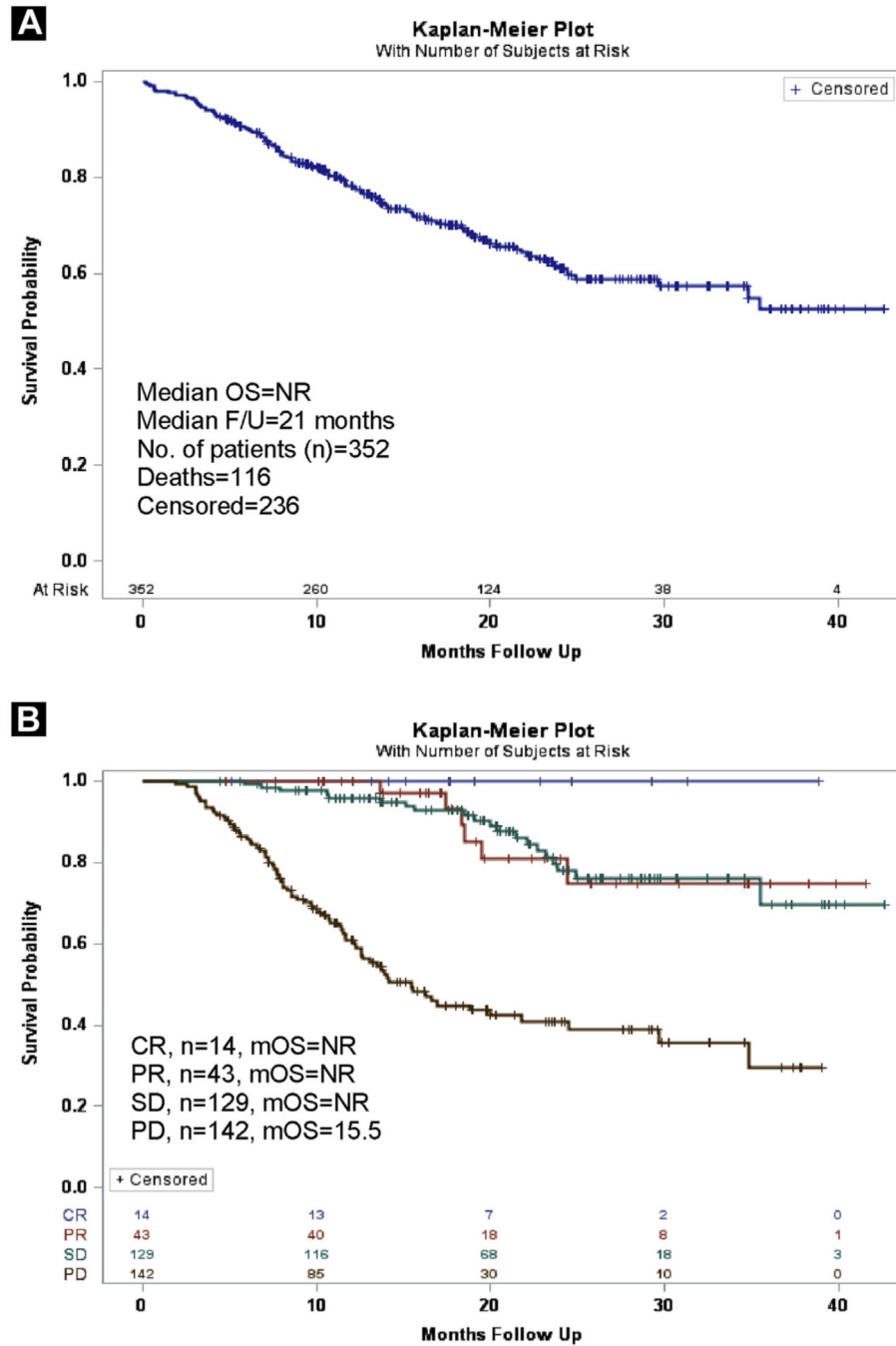
Figure 1.

Overall Survival. A, Analysis Population, n [352. Data Was Available for All 352 Patients; of These, 116 Were Confirmed Deceased and 236 Were Known to Be Alive at the Last Follow-up Date of September 24, 2015. The Overall Survival Data (Not Reached [NR]) Was Calculated From the Time of Starting High-dose Interleukin-2 (HD IL-2) Therapy. The Median Follow-up Was 21 Months. Vertical Bars Represent Censored Subjects. B, Overall Survival by Response to HD IL-2. Response Rate Was Available for 328 of 352 Patients. The Median Overall Survival (mOS) for Patients With Complete Response (CR), Partial

Response (PR), and Stable Disease (SD) Was Not Reached. One Hundred Forty-Two Patients With Progressive Disease (PD) After HD IL-2 Experienced an mOS of 15.5 Months. Vertical Bars Represent Censored Subjects
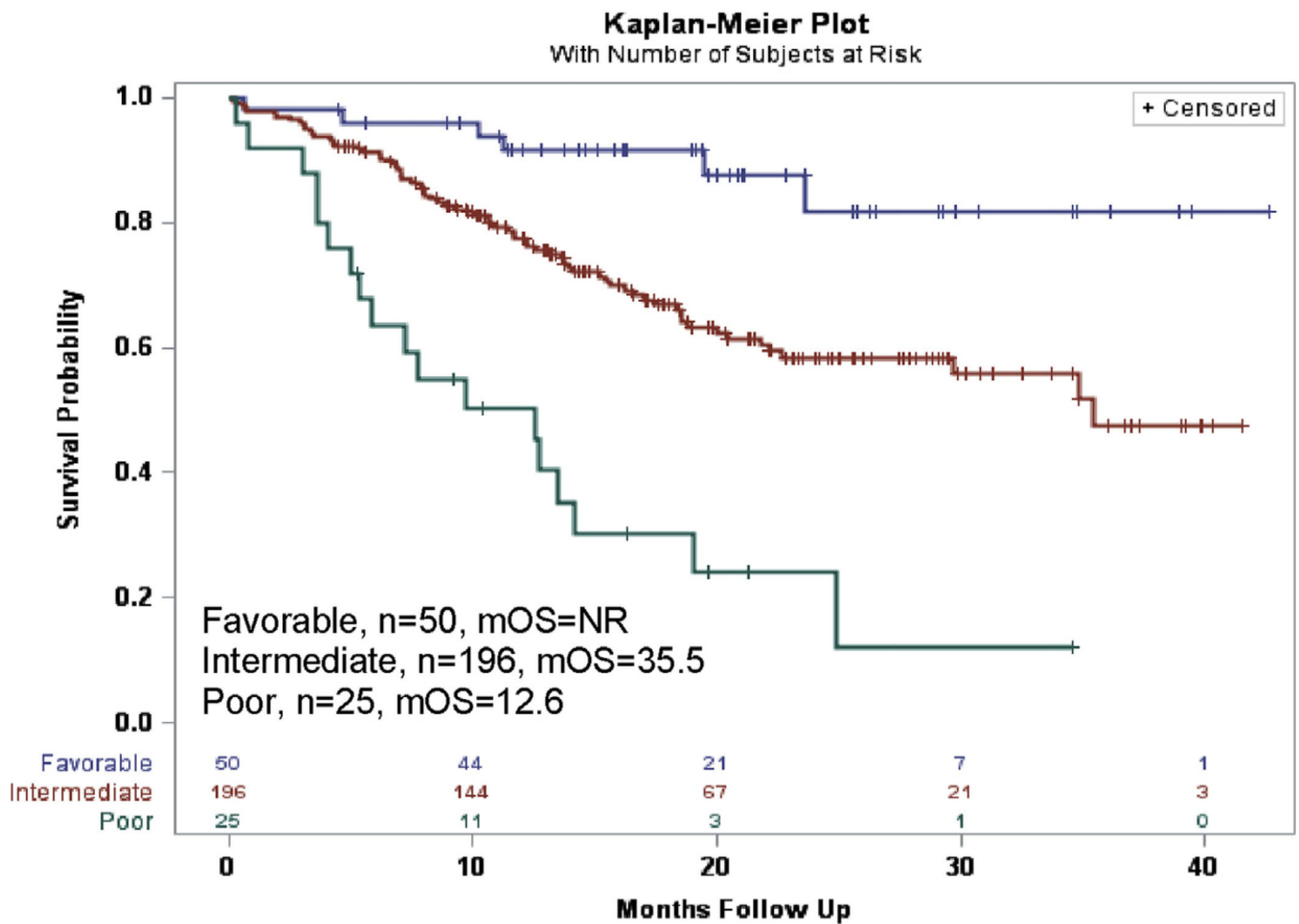
Figure 2.
Kaplan-Meier Overall Survival by the International mRCC Database Consortium Risk
Factors. Six Risk Factors Were Considered Using the International mRCC Database
Consortium Prognostic Model. Patients Were Grouped Into 3 Categories: Favorable [0,
Intermediate [1–2, Poor [3 D Risk Factors. Two Hundred Seventy-One Patients had
Complete Data for All 6 Prognostic Factors and Were Included in the Analysis. Fifty
Patients Were in the Favorable Group, 196 Were in the Intermediate Group, and 25 Were in
the Poor Group. Vertical Bars Represent Censored Subjects
Abbreviations: mOS = median overall survival; mRCC = metastatic renal cell carcinoma;
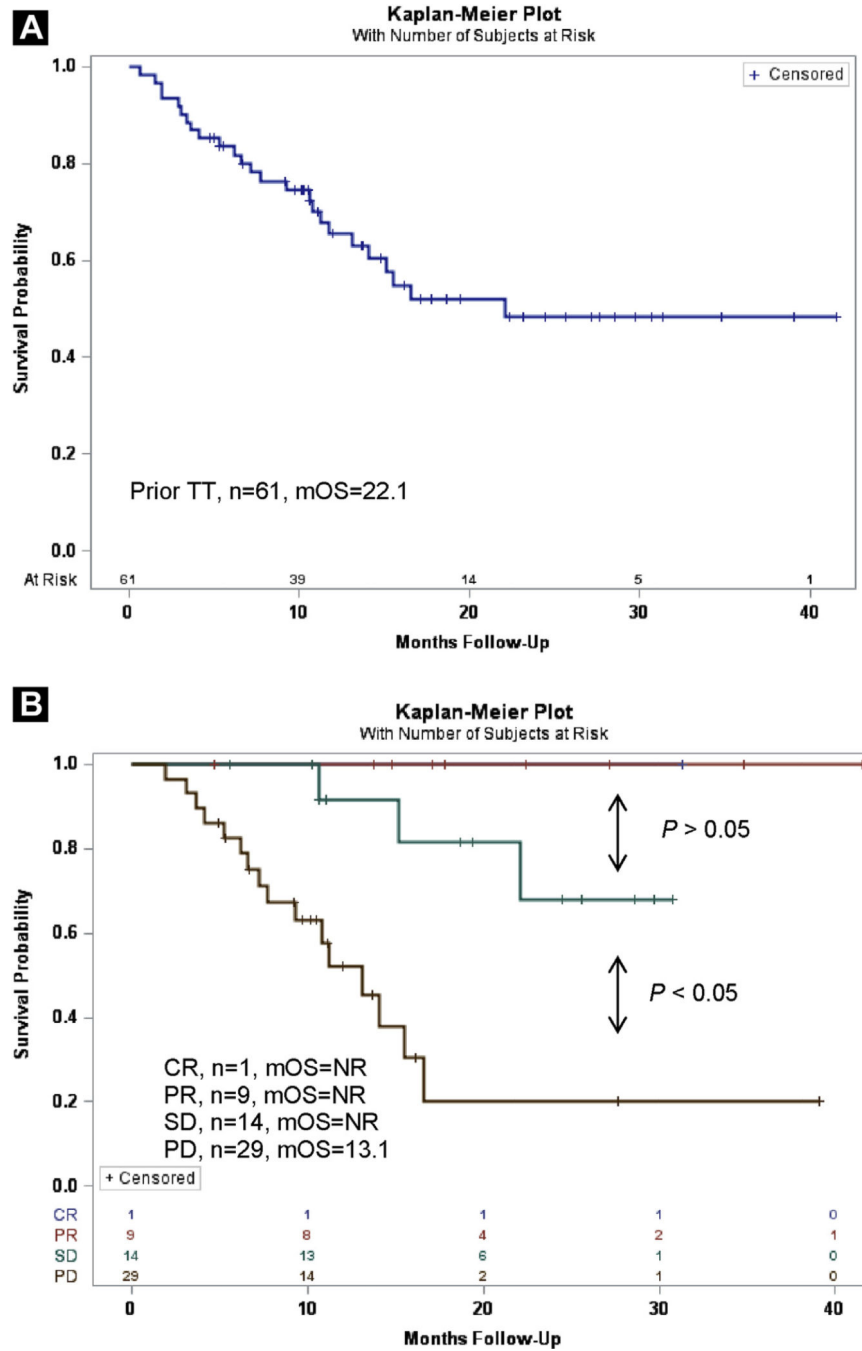NR = not reached.

Figure 3.
Kaplan-Meier Overall Survival of Patients Receiving Prior Targeted Therapy (TT). A,
Overall Survival of All Patients in the Prior TT Group. B, Overall Survival of Patients in the
Prior TT Group by Response to High-dose Interleukin-2 (HD IL-2). Vertical Bars Represent
Censored Subjects

Abbreviations: CR = complete response; mOS = median overall survival; NR = not reached;
PD = progressive disease; PR = partial response; SD = stable disease.
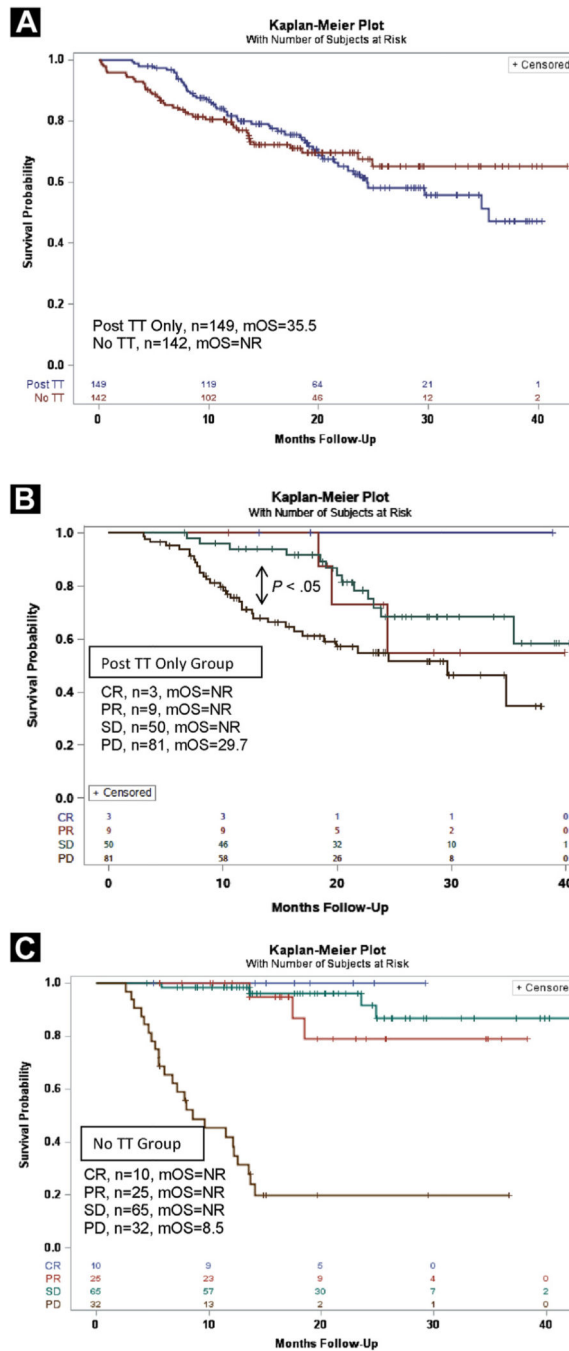
Figure 4.
Kaplan-Meier Overall Survival in Patients With HD IL-2 Alone or Post-targeted Therapy (TT). A, Overall Survival of Patients in the Post TT Only Group Compared With No TT Group ($P = .88$). B, Overall Survival of Patients in the Post TT Only Group by Response to High-dose Interleukin-2 (HD IL-2). Vertical Bars Represent Censored Subjects. C, Overall Survival of Patients in the No TT Group by Response to HD IL-2. Vertical Bars Represent Censored Subjects

Abbreviations: CR = complete response; mOS = median overall survival; NR = not reached; PD = progressive disease; PR = partial response; SD = stable disease.

Table 1

Patient Baseline Characteristics

Characteristics	N	%
Total	352	
Gender		
Female	96	27
Male	256	73
Age, y		
<65	281	80
65	71	20
Median	57	NA
Min, Max	25, 83	NA
ECOG PS		
0	237	70[a]
1	97	29[a]
2	5	1[a]
Missing	13	4
Race		
White	326	93
Black	8	2
Asian	4	1
Other	8	2
Decline	6	2
Clear cell		
No	23	7
Yes	329	93
Prior nephrectomy		
No	24	7
Yes	328	93
Total/partial[a]		
Partial	33	10
Total	295	90
Prior treatments		
Surgery	331	94
Chemotherapy	10	3
Radiation	55	16
Immunotherapy	6	2
Targeted therapy	61	17
Other	13	4
Metastases		
Skin, lungs, LNs only	165	48[a]

Characteristics	N	%
Skin, lungs, LNs, and other	180	52[a]
Missing	7	2

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HD IL-2 = high-dose interleukin-2; LN = lymph node.

[a]Does not include missing data in the denominator.

Table 2

Prior TT

Patients with Prior TT	Total (N = 61)	
	N	%
Last treatment before starting HD-IL2		
TT	51	84
Radiation	5	8
Immunotherapy	2	3
Other	3	5
No. of prior targeted therapies		
Only 1 prior TT	41	67
Only 2 prior TTs	4	7
Only 3–5 prior TTs	16	26
TTs used[a]		
Sunitinib	39	38
Pazopanib	19	18
Everolimus	12	12
Temsirolimus	11	11
Axitinib	10	10
Sorafenib	6	6
Bevacizumab	4	4
Other	3	3
Classification of TTs		
TKI only	37	61
mTOR only	6	10
VEGF only	1	2
mTOR and TKI	13	21
VEGF and TKI	1	2
TKI, VEGF, and mTOR	3	5

Abbreviations: HD IL-1 = high-dose interleukin-2; mTOR = mammalian target of rapamycin; TKI = tyrosine kinase inhibitors; TT = targeted therapy; VEGF = vascular endothelial growth factor.

[a]Based on patients with available data.