Validation of prognostic scoring systems for patients with metastatic renal cell carcinoma enrolled in phase I clinical trials

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ABSTRACT

Background For patients with metastatic renal cell carcinoma (mRCC) who progress on standard-of-care therapies, there is an unmet need for novel treatments. Phase I clinical trials are designed to test the safety, toxicity and optimal dosing of novel agents. Herein, we analysed the outcomes of patients with mRCC enrolled in phase I trials and assess the utility of prognostic scores.

Methods Patients with all histologies of mRCC were included if they received treatment on a phase I clinical trial at MD Anderson Cancer Center (MDACC). Survival outcomes were calculated using Cox proportional hazard model. Prognostic value of the International Metastatic RCC Database Consortium (IMDC), Royal Marsden Hospital (RMH) and MDACC scores was assessed using the likelihood ratio (LR) χ² test and the c-index.

Results Among 82 patients with mRCC who received treatment, 21 patients participated in more than one trial, resulting in 106 trial participants (TP). Median prior therapies was two. For all TPs, median overall survival (OS) was 31.2 months, progression-free survival (PFS) was 5.9 months and objective response rate was 22%. Median OS and PFS were significantly shorter with increasing IMDC, RMH and MDACC scores. The RMH and MDACC scores outperformed the IMDC score for predicting OS (RMH LR χ²=8.64; MDACC LR χ²=7.74; IMDC LR χ²=2.36) and PFS (RMH LR χ²=17.5; MDACC LR χ²=20.3; IMDC LR χ²=4.28).

Conclusions The RMH and MDACC prognostic scores can be used to predict OS for patients with mRCC in phase I trials and may guide patient selection. Patients with mRCC should be considered for phase I trials.

INTRODUCTION

Over the past decade, treatment options for patients with metastatic renal cell carcinoma (mRCC) have exponentially expanded to include vascular endothelial growth factor receptor (VEGFR)-targeted therapies, immune checkpoint inhibitors, mammalian target of rapamycin (mTOR) inhibitors and multi-target tyrosine kinase inhibitors. Accordingly, mRCC has become a disease with a large number of targeted therapies approved. While these therapies may prolong life, most patients with mRCC continue to progress and eventually die from their cancer. Many of the approved treatments for mRCC

To cite Hahn AW, Alhalabi O, Msaouel P, et al. Validation of prognostic scoring systems for patients with metastatic renal cell carcinoma enrolled in phase I clinical trials. ESMO Open 2020;5:e001073. doi:10.1136/esmoopen-2020-001073

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What is already known about this subject?

► Phase I clinical trials were designed to test the safety, toxicity and maximum tolerated or optimal biological dose of new treatments. Patients with metastatic renal cell carcinoma (mRCC) may be referred to phase I clinical trials after progression on standard-of-care therapy.

► Publication bias exists for reporting the results of clinical trials, so phase I clinical trial efficacy across all patients with mRCC is unknown.

► Furthermore, appropriate patient selection for enrolment in a phase I clinical trial is essential, and could be guided by validated prognostic scoring systems.

What does this study add?

► Our study reveals the efficacy of phase I clinical trials in all patients with mRCC who were enrolled in a phase I clinical trial at a tertiary cancer centre.

► In this context, phase I clinical trials appear to have clinical and therapeutic benefit for patients with all histologies of mRCC.

► Additionally, we show that prognostic risk scores improve patient selection for phase I clinical trials, and the Royal Marsden Hospital and MD Anderson Cancer Center scores performed better than the International Metastatic RCC Database Consortium score at time of enrolment on a phase I clinical trial.

How might this impact on clinical practice?

► This study may impact practice by providing clinicians and patients with mRCC evidence of the clinical and therapeutic benefit of phase I clinical trials. More importantly, this study might guide selection of patients with mRCC for enrolment in phase I clinical trials, thereby improving clinical outcomes.
have overlapping mechanisms of action and patterns of resistance, so there remains an unmet need for novel, life-prolonging treatments for patients with mRCC. Furthermore, registration trials for the above therapies were limited to patients with metastatic clear cell RCC (ccRCC). Patients with metastatic non-ccRCC (nccRCC) experience limited benefit from these therapies and have an urgent need for novel therapies.

Historically, phase I clinical trials were designed to test the safety, toxicity, maximum tolerated dose/recommended phase II dose, and/or optimal biological dose of new treatments. Patients with mRCC may be referred to phase I clinical trials after progression on standard-of-care therapy. The role for phase I clinical trials in drug development is evolving with the introduction of biomarker-guided trials, larger dose-expansion cohorts in early phase trials, and the US Food and Drug Administration’s approval of therapies based on results from expanded phase I trials. There is always debate about the clinical and therapeutic benefit for patients who are enrolled in phase I trials. The central tenet of drug development should be patient selection and offer ‘the right drug for the right patient at the right time’.

Herein, we analysed the outcomes of patients with mRCC enrolled in phase I trials and assessed the utility of established prognostic scores at the time of enrolment on a phase I clinical trial.

METHODS

Patients
Patients with all histologies of mRCC were included if they were enrolled and received treatment on a phase I clinical trial at the University of Texas MD Anderson Cancer Center (MDACC, Houston, Texas, USA). Baseline patient characteristics and clinical outcomes were collected retrospectively, and the Institutional Review Board (IRB) of...
Endpoints and prognostic scores

Clinical endpoints of interest included objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). ORR was defined as partial response plus complete response (CR), per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or immune-related RECIST. PFS was defined as time from trial enrolment until time of progression, last follow-up or death. OS was defined as time from trial enrolment until time of death or last follow-up. For each patient with clinical data available, an mRCC-specific prognostic score, the IMDC score and two phase I clinical trial prognostic scores, the RMH prognostic score and the MDACC prognostic score, were assessed at trial enrolment. The IMDC score includes haemoglobin-corrected limit of normal, platelets-upper limit of normal (ULN), absolute neutrophil count>ULN, corrected calcium>ULN, Karnofsky performance status<80% and <1 year from time of diagnosis to systemic therapy (online supplemental table 1).

The IMDC risk score N=106 (%)

| Characteristics                      | N=82 (106 trial participations, 40 unique trials) |
|--------------------------------------|--------------------------------------------------|
| Median age in years at trial enrolment (range; IQR in years) | 63 (23–77; 19) |
| Male (%)                             | 78 (73.6%) |
| Histology                            | n=82 (%) |
| Clear cell                           | 59 (72.0%) |
| Papillary                            | 7 (8.5%) |
| Renal medullary carcinoma            | 4 (4.8%) |
| RCC with sarcomatoid dediff          | 4 (4.8%) |
| Collecting duct carcinoma            | 2 (2.4%) |
| Unclassified                         | 2 (2.4%) |
| Chromophobe                          | 1 (1.2%) |
| Translocation                        | 1 (1.2%) |
| Other non-clear cell                 | 2 (2.4%) |
| Number of prior lines of therapy     | N=106 (%), median=2, range=0–9 |
| 0                                    | 8 (7.5) |
| 1                                    | 29 (27.4) |
| 2                                    | 22 (20.8) |
| ≥3                                   | 47 (44.3) |
| IMDC risk score                      | N=106 (%) |
| Favourable                           | 9 (8.5) |
| Intermediate                         | 67 (63.2) |
| Unfavourable                         | 18 (17.0) |
| Not available                        | 12 (11.3) |

Although LR χ² tests are the gold standard metric for model discrimination and are more sensitive than the c-index, the latter is presented for the sake of completeness.

Statistical analysis

Median follow-up time was calculated with the reverse Kaplan-Meier method. Survival outcomes were calculated using Cox proportional hazard models. Statistical significance was defined as a p value <0.05. The prognostic values of the IMDC, RMH and MDACC scores were assessed with the likelihood ratio (LR) χ² test and Harrell’s c-index. Although LR χ² tests are the gold standard metric for model discrimination and are more sensitive than the c-index, the latter is presented for the sake of completeness.

RESULTS

Baseline characteristics

Between April 2015 and September 2019, 100 patients with mRCC were consented for a phase I clinical trial at MDACC, and 18 patients did not receive treatment on a phase I trial due to not meeting inclusion criteria or withdrawing consent (figure 1). Of the 82 patients with mRCC who received treatment, 59 patients had metastatic ccRCC, while 23 had metastatic nccRCC (table 1). The most common nccRCC histologies were papillary (n=7, 8.5%), renal medullary (n=4, 4.8%) and RCC with sarcomatoid dedifferentiation present (n=4, 4.8%), two had ccRCC with sarcomatoid dedifferentiation, one had RCC with sarcomatoid and rhabdoid dedifferentiation, and one had mixed clear cell and papillary RCC with sarcomatoid dedifferentiation. Twenty-one patients (25.6%) participated in more than phase I clinical trial, which resulted in a total of 106 trial participants (TP) for the 82 patients evaluated in our study. At the time of trial enrolment, the median age was 63 (range 23–77 years, IQR 19 years) and median number of prior treatments was two (range 0–9, table 1). At time of initiation of a phase I clinical trial, 63.2% of participants had IMDC intermediate risk disease and 17% had IMDC poor risk disease (table 1).

Efficacy of phase I clinical trials for mRCC

Across the 106 TPs, the median PFS was 5.9 months, median OS was 31.2 months and ORR was 22% with 2% of patients achieving a CR (table 2). When assessed by histology, patients with metastatic ccRCC had numerically longer PFS (7.3 vs 2.5 months, HR 1.39, 95% CI 0.86 to 2.25, p=0.18) and OS (31.6 vs 23.9 months, HR 1.26, 95% CI 0.71 to 2.23, p=0.44) with wide CIs indicating substantial uncertainty (table 2, figure 2A,B).
Table 2  Efficacy of phase I clinical trials for all patients with metastatic renal cell carcinoma and by histology

|                  | All mRCC (n=106) | nccRCC (n=32) | ccRCC (n=74) | HR     | P value |
|------------------|------------------|---------------|--------------|--------|---------|
| PFS (95% CI)     | 5.9 m (4.8 to 9.3 m) | 2.5 m (2.1 to 9.3 m) | 7.3 m (5.5 to 12.4 m) | 1.39   | 0.19    |
| OS (95% CI)      | 31.2 m (24.9 to 38.7 m) | 23.9 m (11.4 to NR) | 31.6 m (27.6 to 41.5 m) | 1.26   | 0.44    |
| ORR (%)          | 22               | 17            | 24           | –      | –       |
| CR (%)           | 2                | 0             | 3            | –      | –       |
| PR (%)           | 20               | 17            | 21           | –      | –       |
| SD (%)           | 49               | 30            | 57           | –      | –       |
| PD (%)           | 29               | 53            | 19           | –      | –       |

ccRCC, clear cell renal cell carcinoma; CR, complete response; m, months; mRCC, metastatic renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; ORR, objective response rates; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

**Efficacy of phase I clinical trials by trial type**

Sixty-four TPs enrolled in a dose-escalation phase I trial, while 42 TPs enrolled in a dose-expansion phase I trial. Participants in dose-escalation trials had significantly longer PFS than their counterparts in dose-expansion trials (8.4 vs 3.6 months, HR 0.57, 95% CI 0.36 to 0.91, p=0.017, online supplemental figure 1A). Participants in dose-escalation trials also had significantly longer OS (38.7 vs 26.1 months, HR 0.44, 95% CI 0.25 to 0.75, p=0.003, online supplemental figure 1B). A detailed breakdown of the mechanisms of action of therapies that TPs received is available in online supplemental table 2.

**Clinical utility of prognostic scores at time of trial enrollment**

Table 3 lists the distribution of TPs across the IMDC, RMH and MDACC prognostic scores. Twelve TPs did not have the baseline laboratory values necessary to calculate their IMDC risk score at time of trial initiation, and the RMH and MDACC prognostic scores could not be calculated in 14 TPs. Median OS and PFS were significantly shorter with increasing IMDC, RMH and MDACC scores (table 3, figure 3A–F). The RMH (c-index=0.61, LR $\chi^2=8.64$, p=0.003) and MDACC scores (c-index=0.61, LR $\chi^2=7.74$, p=0.1) outperformed the IMDC score (c-index=0.57, LR $\chi^2=2.36$, p=0.10) in predicting OS. The IMDC, RMH and MDACC scores were also predictive of PFS, but the RMH (c-index=0.65, LR $\chi^2=17.5$, p<0.0001) and MDACC scores (c-index=0.65, LR $\chi^2=20.3$, p<0.001) again outperformed the IMDC score (c-index=0.59, LR $\chi^2=4.28$, p=0.04).

**DISCUSSION**

In a pooled phase I clinical trial experience for patients with mRCC from a large cancer centre, we demonstrate that phase I clinical trials may have therapeutic benefit for patients with
mRCC, as the median OS, PFS and ORR compare favourably to historical controls for second and third-line treatment (online supplemental table 3). Because the therapeutic benefit of phase I clinical trials remains controversial, we sought to assess the outcomes of all patients with mRCC who received treatment on a phase I clinical trial at a tertiary cancer centre. By performing a pooled analysis of all our phase I clinical trials, the bias of only publishing positive early phase trials was limited. Of note, our findings suggest that patients with all histologies of mRCC may derive clinical benefit from phase I clinical trials, although patients with metastatic ccRCC did have numerically longer survival, consistent with the established poor prognosis of metastatic nccRCC. Unexpectedly, dose-escalation phase I trials had significantly longer OS and PFS than dose expansion trials. Based on the rationale for dose expansion cohorts, we expected to observe longer survival with dose expansion cohorts, but this finding reaffirms that improvements in the design of phase I trials have positively changed the therapeutic benefit of these studies.

Patient selection for referral to a phase I clinical trial is challenging for clinicians. Beyond biomarkers, next generation sequencing for actionable alterations and ECOG PS, clinicians need pragmatic clinical prognosticators. For patients with mRCC, the IMDC risk score is a validated model to inform prognosis prior to first, second and third-line treatments. Alternatively, there are validated prognostic models for patients enrolling on a phase I clinical trial, such as the RMH and MDACC score. In this study, the IMDC, RMH and MDACC scores were all predictive of survival in patients with mRCC enrolling on a phase I clinical trial. However, the RMH and MDACC scores performed better than the IMDC score at time of enrolment on a phase I clinical trial, based on the much higher LR $\chi^2$ test. For comparison, the IMDC risk score was validated in the second-line setting with targeted therapy, where the c-index was 0.66, which is higher than its performance in the investigational setting after a median of two lines of therapy.

For patients with mRCC who progress on contemporary, first-line treatment, standard-of-care options include cabozantinib, lenvatinib plus everolimus, nivolumab, everolimus or VEGFR-targeted therapy; and many of these options are limited by similar patterns of resistance to first-line treatment. In our experience, phase I clinical trials had comparable efficacy to approved salvage therapies for patients with mRCC. Median OS was 21.4 and 25.8 months for salvage cabozantinib and nivolumab in the METEOR and CheckMate-025 trials, respectively. In patients with a median of two prior lines of therapy, phase I clinical trials produced a median OS of 31.2 months and ORR of 22%. Similarly, the efficacy of phase I clinical trials compared favourably

Table 3  Efficacy of phase I clinical trials by prognostic risk group*

|                  | Median OS | HR (95% CI) | P value | Median PFS | HR (95% CI) | P value |
|------------------|-----------|-------------|---------|------------|-------------|---------|
| IMDC fav. (n=9)  | NR        | Ref.        | N/A     | 21.4 m     | Ref.        | N/A     |
| IMDC int. (n=67) | 29.1 m    | 7.69        | 0.04    | 5.6 m      | 3.50        | 0.04    |
| (n=18)           | 23.9 m    | 6.53        | 0.08    | 3.7 m      | 3.78        | 0.04    |
| RMH 0 (n=36)     | 29.1 m    | Ref.        | N/A     | 14.9 m     | Ref.        | N/A     |
| RMH 1 (n=41)     | 29.2 m    | 1.70        | 0.12    | 4.8 m      | 2.29        | 0.003   |
| RMH 2 (n=12)     | 23.9 m    | 3.55        | 0.003   | 2.3 m      | 3.24        | 0.004   |
| RMH 3 (n=3)      | 20.9      | 3.58        | 0.10    | 1.7 m      | 15.07       | 4.32e-05|
| MDACC 0 (n=5)    | NR        | Ref.        | N/A     | NR         | Ref.        | N/A     |
| MDACC 1 (n=34)   | 38.7 m    | 1.45        | 0.62    | 14.8 m     | 3.58        | 0.21    |
| MDACC 2 (n=39)   | 29.2 m    | 2.33        | 0.26    | 4.8 m      | 7.27        | 0.05    |
| (n=11)           | 23.9 m    | 4.16        | 0.08    | 2.3 m      | 9.00        | 0.04    |
| MDACC 4 (n=3)    | 20.9 m    | 4.67        | 0.13    | 1.7 m      | 45.6        | 0.001   |

fav., favourable; IMDC, International Metastatic RCC Database Consortium; int., intermediate; m, months; MDACC, MD Anderson Cancer Center; N/A, not available; NR, not reached; OS, overall survival; PFS, progression free survival; Ref., reference value; RMH, Royal Marsden Hospital.


mRCC, as the median OS, PFS and ORR compare favourably to historical controls for second and third-line treatment (online supplemental table 3). Because the therapeutic benefit of phase I clinical trials remains controversial, we sought to assess the outcomes of all patients with mRCC who received treatment on a phase I clinical trial at a tertiary cancer centre. By performing a pooled analysis of all our phase I clinical trials, the bias of only publishing positive early phase trials was limited. Of note, our findings suggest that patients with all histologies of mRCC may derive clinical benefit from phase I clinical trials, although patients with metastatic ccRCC did have numerically longer survival, consistent with the established poor prognosis of metastatic nccRCC. Unexpectedly, dose-escalation phase I trials had significantly longer OS and PFS than dose expansion trials. Based on the rationale for dose expansion cohorts, we expected to observe longer survival with dose expansion cohorts, but this finding reaffirms that improvements in the design of phase I trials have positively changed the therapeutic benefit of these studies. Patient selection for referral to a phase I clinical trial is challenging for clinicians. Beyond biomarkers, next generation sequencing for actionable alterations and ECOG PS, clinicians need pragmatic clinical prognosticators. For patients with mRCC, the IMDC risk score is a validated model to inform prognosis prior to first, second and third-line treatments. Alternatively, there are validated prognostic models for patients enrolling on a phase I clinical trial, such as the RMH and MDACC score. In this study, the IMDC, RMH and MDACC scores were all predictive of survival in patients with mRCC enrolling on a phase I clinical trial. However, the RMH and MDACC scores performed better than the IMDC score at time of enrolment on a phase I clinical trial, based on the much higher LR $\chi^2$ test. For comparison, the IMDC risk score was validated in the second-line setting with targeted therapy, where the c-index was 0.66, which is higher than its performance in the investigational setting after a median of two lines of therapy. For patients with mRCC who progress on contemporary, first-line treatment, standard-of-care options include cabozantinib, lenvatinib plus everolimus, nivolumab, everolimus or VEGFR-targeted therapy; and many of these options are limited by similar patterns of resistance to first-line treatment. In our experience, phase I clinical trials had comparable efficacy to approved salvage therapies for patients with mRCC. Median OS was 21.4 and 25.8 months for salvage cabozantinib and nivolumab in the METEOR and CheckMate-025 trials, respectively. In patients with a median of two prior lines of therapy, phase I clinical trials produced a median OS of 31.2 months and ORR of 22%. Similarly, the efficacy of phase I clinical trials compared favourably
to population-based studies of third-line therapy. In the IMDC experience, median OS was 12.4 months with third-line VEGF-targeted therapies or mTOR inhibitors.20 These favourable comparisons reaffirm the therapeutic potential of early phase clinical trials for patients with mRCC. Yet, the significance of comparisons is limited due to a difference in time periods evaluated (2015–2019 in our study vs publications from 2015 and 2017).

Our study has several limitations due to its design. This study has limited generalisability because the data are from a single, tertiary academic centre where select faculty enrol patients on early phase trials. Also, detailed information regarding the treatments received is not available due to the pooled design of our analysis. Finally, there were a wide range of investigational therapies included in this analysis with heterogeneity in their mechanisms of action.

In conclusion, phase I clinical trials may confer clinical and therapeutic benefit for patients with all histologies of mRCC, and select patients with mRCC should be considered for phase I clinical trials. Prognostic risk scores, such as IMDC, RMH and MDACC, may help improve patient selection for phase I clinical trials, and the RMH and MDACC scores performed better than the IMDC score at time of enrolment on a phase I clinical trial.

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Acknowledgements We thank the patients and their families for their participation, and the investigators and site staff for their contributions.

Contributors AWH, OA, PM, JR and VS designed the study. AWH, OA, EC and HL collected data for the analyses. JR performed all statistical analyses and PM provided guidance on statistical design. FM-B, AN, EJ, SP-P, DH, SP, TY, NT and VS enrolled patients who were included in this study. All authors contributed to drafting and critical revisions of the manuscript.

Funding The University of Texas MD Anderson Cancer Center is supported by the National Institutes of Health (NIH) Cancer Center Support (grant CA016672). The University of Texas MD Anderson Cancer Center clinical trials programme is supported in part by Cancer Prevention Research Institute of Texas (grant RP110584) and National Center for Advancing Translational Sciences (grant UL1 TR000371; Center for Clinical and Translational Sciences). VS is supported by the NIH National Cancer Institute (grant 1R01CA242845-01A1). PM is supported by a Young Investigator Award by the Kidney Cancer Association, a Career Development Award by the American Society of Clinical Oncology, by a Concept Award by the US Department of Defense and by the MD Anderson Khalifa Scholar award.

Competing interests AWH, OA, EC, HL and JR have no conflicts to disclose. PM reports consultancy/honoraria to Pfizer, Bristol-Myers Squibb, Mirati, Exelixis and Axiom Healthcare Strategies; research funding to his institution from Mirati, Takeda, Bristol-Myers Squibb and Gateway for Cancer Research. FM-B reports consulting to Aduro BioTech, DebiPharm, eFFECTOR Therapeutics, F. Hoffman-La Roche, Genentech, IBM Watson, Jackson Laboratory, Kollon Life Science, ORIGI Med, PACT Pharma, Parexel International, Pfizer, Samsung Bioepis, Seattle Genetics, Tyra Biosciences, Xencor and Zymeworks. She reports honoraria from Chugai Biopharmaceuticals, Mayo Clinic and Rutgers Cancer Institute of New Jersey. She reports research funding to her institution from Aileron Therapeutics AstraZeneca, Bayer Healthcare Pharmaceutical, Calithera Biosciences, Curis, CytoX Therapeutics, Daiichi Sankyo, Debiopharm International, eFFECTOR Therapeutics, Genentech, Guardant Health, Millennium Pharmaceuticals, Novartis, Puma Biotechnology and Taiho Pharmaceutical. AR reports consulting to CytoM X Therapeutics, Novartis, Kymbra and Genome. He reports travel and accommodation expenses from ARMO BioSciences. He reports research funding to his institution from NCI, EMD Serono, MedImmune, Healios Onc. Nutrition, Attercor, Amplimmune, ARMO BioSciences, Eli Lilly, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Myers Squibb, Pfizer, CytoM X Therapeutics, Neon Therapeutics, Calithera Biosciences, TopAlliance Biosciences, Kymbra, Psilocybin and Immune Deficiency Foundation (Spouse). EJ reports research funding to his institution from Exelixis, Merck and Pfizer. He reports consulting for Eisai, Exelixis, Novartis, Merck, Pfizer, Roche. Sarina Piha-Paul reports research funding to her institution from AbbVie, ABM therapeutics, Aecopedia, Alkermes, Aminex Therapeutics, Amphivena Therapeutics, BioMarin Pharmaceutical, Boehringer Ingelheim, Bristol Myers...
Squi, Chugai Pharmaceutical, Daichi Sankyo, Eli Lilly, Five Prime Therapeutics, Genmab A/S, GlaxoSmithKline, Helix BioPharma, Incyte, Jacoble Pharmaceuticals, Medimmune, Medivation, Merck Sharp and Dohme, Novartis Pharmaceuticals, Pieris Pharmaceuticals, Pfizer, Principia Biopharma, Puma Biotechnology, Rapt Therapeutics, Seattle Genetics, Taiho Oncology, Tesaro and TransThera Bio. NMT reports consultancy and honoraria from Pfizer, Novartis, Bristol-Myers Squibb, Exelixis, Nektar, Eisai, Ono Pharmaceutical, Eli Lilly, Oncoreona, Ipsen, Surface Oncology and Neulokun Therapeutics. He reports research funding to his institution from Bristol-Myers Squibb, Exelixis, Pfizer, Nektar Therapeutics, Casanova, Bioscience, Eli Lilly, Mirati Therapeutics, Arrowhead Pharmaceuticals, Takeda, Epizyme and Eisai. He reports travel expenses from Pfizer, Novartis, Nektar, Bristol-Myers Squibb, Eisai, Onco Pharmaceuticals, Oncoreona, Surface Oncology, Lilly Oncology, Ipsen, and Neulokun Therapeutics. David S. Hong reports research funding to his institution from AbbVie, Adaptimmune, Aldi-Norte, Amgen, Astra-Zeneca, Bayer, BMW, Daichi-Sankyo, Eisai, Fata Therapeutics, Genentech, Genmab, GSK, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, Medimmune, Mirati, mirDNA, Molecular Templates, Moligen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda, and Turning Point Therapeutics. He reports travel expenses from Bayer, LOXO, mirDNA, Genmab, AOCR, ASCO, and SITC. He reports consulting for Alpha Insights, Amgen, Axiom, Adaptimmune, Baxter, Bayer, Genentech, GLG, Group H, Guidepoint, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Prime Oncology, Seattle Genetics, Takeda, Triage Therapeutics, and WebMD. He reports ownership interests in Molecular Match (Advisor), OncoResponse (Founder), Presagia Inc (Advisor). Subbham Pant reports research funding to his institution from Mirati Therapeutics, Eli Lilly, Red Hill Biopharma Ltd., Xencor, Five Prime Therapeutics, Novartis, Rgenix, Sanofi-Aventis, Arque, Bristol-Myers Squibb, Onco Response, Sanofi US Services Inc., and GlaxoSmithKline. Timothy Yap reports research funding to his institution from: AstraZeneca, Bayer, Clovis, Constellation, Cytel, Eli Lilly, EMD Serono, Forbiss/ Formation Biologics, F-Star, GlaxoSmithKline, Genentech, ImmuneSensor, Ipsen, Jounce, Karyopharm, Kyowa, Novartis, Pfizer, Ribbon Therapeutics, Regeneron, Sanofi, Seattle Genetics, Tesaro, and Vertex Pharmaceuticals. He reports consultancy from Almac, Aduro, AstraZeneca, Atrin, Axiom, Bayer, Calithera, Clovis, Cybrexa, EMD Serono, F-Star, Guidepoint, Ignyta, I-Mab, Jansen, Kyn Therapeutics, Merck, Pfizer, Roche, Seattle Genetics, and Zai Labs. Vivek Subbiah reports research funding to his institution from LOXO Oncology, Roche/Genentech, Novartis, Bayer, GlaxoSmithKline, Nanocharier, Vegenics, Celgene, Northwest Biotherapeutics, Berghera, Incyte, Fujifilm, Pharmamar, D3, Pfizer, Amgen, Multivir, Abbvie, Alpha-sigma, Agensys, Boston Biomedical, Idera Pharma, Inhibitx, Exelixis, Blueprint Medicines, Medimmune, Altum, Dragonfly Therapeutics, Takeda, National Comprehensive Cancer Network, Turning Point Therapeutics, and Boston Pharmaceuticals. He reports consultancy for Helsinn, Incyte, and QED Pharma. He reports travel expenses from Helsinn, Incyte, ASCO and ESMO.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The clinical data for this analysis is from numerous clinical trials and cannot be further shared, per the trial protocol agreements.

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| IMDC score | RMH score | MDACC score |
|------------|-----------|-------------|
| Factor     | Poor prognostic factor | Factor | Poor prognostic factor | Factor | Poor prognostic factor |
| HGB        | < LLN     | Albumin    | < 3.5 g/dL          | Albumin | < 3.5 g/dL |
| Plts       | > ULN     | LDH        | > ULN              | LDH     | > ULN     |
| ANC        | > ULN     | Metastatic sites | ≥ 3 sites | Metastatic sites | ≥ 3 sites |
| KPS        | < 80%     | -          | -                 | ECOG PS | ≥ 1       |
| Corrected calcium | > ULN | -          | -                 | Primary tumor site | Gastrointestinal |
| Dx to systemic tx | < 1 year | -          | -                 | -       | -         |

**IMDC risk group definitions**

- Favorable: 0 factors
- Intermediate: 1-2 factors
- Poor: ≥ 3 factors

**Supplemental Table 1:** Definitions of the IMDC, RMH, and MDACC prognostic scores

**Supplemental Table 1 Legend:** HGB = hemoglobin, LLN = lower limit of normal, g = grams, dL = deciliter, Plts = platelets, ULN = upper limit of normal, LDH = lactate dehydrogenase, ANC = absolute neutrophil count, ECOG = Eastern Cooperative Oncology Group, PS = performance status, KPS = Karnofsky performance status, Dx = diagnosis, tx = treatment
**Mechanism of action**

| Mechanism of action                                                                 |
|-----------------------------------------------------------------------------------|
| Anti-CSF1R + PD-1 checkpoint inhibitor                                           |
| Arginase inhibitor                                                                 |
| BET inhibitor                                                                     |
| CCR-4 inhibitor                                                                   |
| Coenzyme Q10 + gemcitabine                                                        |
| CTLA-4 inhibitor + TLR9 agonist                                                   |
| Exportin inhibitor + PD-1 checkpoint inhibitor                                   |
| EZH2 inhibitor + CTLA-4 checkpoint inhibitor                                      |
| Glutaminase inhibitor                                                             |
| Glutaminase inhibitor + mTOR inhibitor                                            |
| Glutaminase inhibitor + multi-target angiogenesis TKI                             |
| Glutaminase inhibitor + PARP inhibitor                                            |
| Glutaminase inhibitor + PD-1 checkpoint inhibitor                                |
| ICOS monoclonal antibody                                                          |
| IDO-1 inhibitor + JAK inhibitor                                                   |
| MDM2 inhibitor                                                                    |
| mTOR inhibitor + carboplatin + paclitaxel                                         |
| Multi-target angiogenesis TKI                                                     |
| Multi-target TKI + mTOR inhibitor                                                 |
| Nanoparticle drug conjugate + VEGF targeted therapy                               |
| PARP inhibitor                                                                    |
| PARP inhibitor + ATM inhibitor + cisplatin                                         |
| PD-1 checkpoint inhibitor                                                         |
| PD-1 checkpoint inhibitor + CTLA-4 checkpoint inhibitor                            |
| PD-1 checkpoint inhibitor + cyclophosphamide                                     |
| PD-1 checkpoint inhibitor + enterococcus                                          |
| PD-1 checkpoint inhibitor + LAG-3 checkpoint inhibitor                            |
| PD-L1 checkpoint inhibitor + 4-1BB agonist + OX40 inhibitor                        |
| Pegylated IL-10 + PD-1 checkpoint inhibitor                                       |
| PI3K inhibitor                                                                    |
| Proteasome inhibitor + VEGF targeted therapy                                     |
| Proteasome inhibitor + HDAC inhibitor                                             |
| STING pathway agonist                                                            |

**Supplemental Table 2**: Mechanisms of action of agents in phase 1 trials enrolling patients in the present study

**Supplemental Table 2 Legend**: TKI = tyrosine kinase inhibitor
| Study           | Population | Treatment(s) | OS     | PFS     | ORR   |
|----------------|------------|--------------|--------|---------|-------|
| Ko, et al<sup>18</sup> | IMDC, second-line | VEGF or mTOR inhibitor | 12.5 m | 3.9 m | N/A   |
| Wells, et al<sup>20</sup> | IMDC, third-line | VEGF or mTOR inhibitor | 12.4 m | 3.9 m | 10.4% |
| METEOR<sup>25</sup> | mccRCC after ≥ 1 prior VEGF TT | Cabozantinib vs. everolimus | 21.4 vs. 16.5 m | 7.4 vs. 3.9 m | 17% vs. 3% |
| CheckMate 025<sup>26</sup> | mccRCC after 1-3 prior lines | Nivolumab vs. everolimus | 25.0 vs. 19.6 m | 4.6 vs. 4.4 m | 25% vs. 5% |
| Hahn, et al | MDACC, median third-line* | Phase 1 clinical trial | 31.2 m | 5.9 m | 22%   |

**Supplemental Table 3:** Clinical outcomes for second-line or later treatment of metastatic renal cell carcinoma from select population-based studies and clinical trials.

**Supplemental Table 3 Legend:** OS = overall survival, PFS = progression-free survival, ORR = objective response rate, IMDC = International Metastatic RCC Database Consortium, VEGF = vascular endothelial growth factor, mTOR = mammalian target of Rapamycin, * = median third-line, but range from 0-9 prior lines of treatment.
