# Outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with first-line Immuno-oncology (IO) agents who do not meet eligibility criteria for clinical trials

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## Background

- IO combination therapies [including IOIO and IO/vascular endothelial growth factor inhibitor (IOVE) combinations] in mRCC have been approved based on registration clinical trials that have strict eligibility criteria.
- In the IO era, the clinical outcomes of trial-ineligible patients who were treated with first-line IOIO or IOVE combinations are unknown.

## Methods

- Using the International mRCC Database Consortium (IMDC) database, patients with mRCC patients treated with first-line IOIO or IOVE were identified and retrospectively deemed ineligible for clinical trials (according to commonly used inclusion/exclusion criteria in IO trials, Table 2).
- Primary outcomes of interest were:
  - Overall response rate (ORR)
  - Time to treatment failure (TTF)
  - Time to next treatment (TTNT)
  - Overall survival (OS)
- Multivariable Cox regression models were performed to adjust for imbalances in IMDC risk factors.

## Results

- Overall, 26% (155/592) of patients were deemed ineligible for clinical trials. Baseline characteristics are reported in Table 1.
- Overall survival by trial eligibility is depicted in Figure 1. Other clinical outcomes are shown in Table 3.
- The most common toxicities leading to treatment discontinuation were hepatitis, colitis, and nephritis.
- The treatment discontinuation rate due to toxicities in the ineligible versus eligible patients was 33% vs. 37% (p=0.42), respectively.

**Table 1: Baseline characteristics and IMDC risk factors**

| Baseline characteristics | Trial-ineligible (N = 155) | Trial-eligible (N = 437) | P-value |
|---|---|---|---|
| Median age (yrs) | 62 | 63 | 0.24 |
| Male | 63% (98/155) | 73% (318/437) | 0.03 |
| Non-clear-cell histology | 40% (50/125) | 2% (7/310) | <0.01 |
| Sarcomatoid histology | 25% (29/115) | 20% (63/314) | 0.25 |
| Prior nephrectomy | 66% (102/155) | 75% (326/437) | 0.04 |
| Brain metastases | 19% (29/153) | 0% (0/408) | <0.01 |
| IOIO | 63% (97/155) | 57% (247/437) | 0.19 |
| IOVE | 37% (58/155) | 43% (190/437) | |
| Patients who had second line therapy | 33% (50/155) | 34% (148/437) | 0.72 |
| **IMDC risk groups** | | | |
| Favorable | 11% (15/138) | 19% (74/385) | <0.01 |
| Intermediate | 47% (65/138) | 65% (251/385) | |
| Poor | 42% (58/138) | 16% (60/385) | |
| **IMDC risk factors** | | | |
| KPS < 80% | 20% (31/152) | 5% (22/398) | <0.01 |
| Diagnosis to therapy < 1 yr | 73% (113/154) | 66% (285/434) | 0.08 |
| Calcium > ULN | 28% (37/132) | 11% (40/378) | <0.01 |
| Hemoglobin < LLN | 64% (96/150) | 41% (169/414) | <0.01 |
| Neutrophils > ULN | 19% (27/142) | 10% (38/401) | 0.03 |
| Platelet > ULN | 22% (32/148) | 10% (39/412) | <0.01 |

IOIO = Immuno-oncology agent combinations; IOVE = IO + vascular endothelial growth factor receptor inhibitor; KPS = Karnofsky performance status; LLN = lower limit of normal; ULN = upper limit of normal

**Figure 1: Overall survival of trial-ineligible vs. eligible patients**

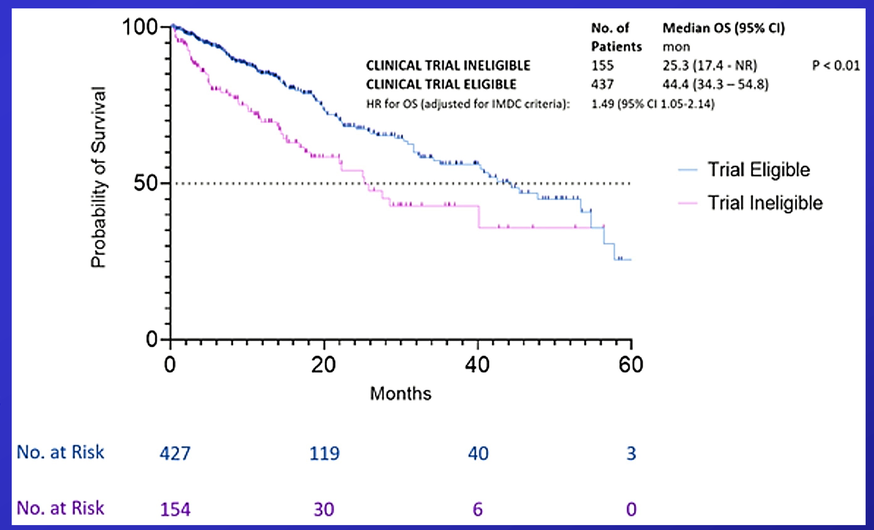


**Table 2: Number of patients excluded due to each exclusion criteria**

| Exclusion parameter† | Number of patients excluded due to this parameter/patients with available data %*(n/n) |
|---|---|
| No clear-cell component in histology | 34% (53/155) |
| Hemoglobin < 9.0 g/dL | 28% (44/155) |
| eGFR < 40 mL/minute | 19% (30/155) |
| Brain metastases | 19% (29/155) |
| KPS < 70% | 14% (21/155) |
| Platelet < 100 x $10^3$ /μL | 3% (4/155) |
| Neutrophil count < 1500/μL | 0% (0/155) |

eGFR = estimated glomerular filtration rate, KPS = Karnofsky performance status
†181 exclusion criteria met in 155 patients
*Total > 100% because patients may have had multiple exclusion parameters

**Table 3: Clinical outcomes of trial-ineligible vs. eligible patients**

| Clinical outcome | Trial-ineligible (N = 155) | Trial-eligible (N = 437) | P-value |
|---|---|---|---|
| **Response** | | | |
| ORR | 34% (42/124) | 46% (164/358) | 0.02 |
| Best response | | | |
| CR | 4% (5/124) | 4% (14/358) | |
| PR | 30% (37/124) | 42% (150/358) | |
| SD | 40% (49/124) | 34% (120/358) | |
| PD | 26% (33/124) | 20% (73/358) | |
| **Median TTF (mon) (95% CI)** | 4.2 (2.7-6.7) | 9.7 (7.79-11.3) | <0.01 |
| **Median TTNT (mon) (95% CI)** | 13.2 (7.9-16.6) | 19.7 (17.5-24.3) | <0.01 |

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR= overall response rate CI = confidence interval; TTF = time to treatment failure; TTNT = time to next treatment

## Conclusions

- The number of patients that are ineligible for clinical trials is substantial and their outcomes are inferior compared to trial-eligible patients.
- These data may guide patient counselling and inform real-world practice.
- Specific trials addressing the unmet needs of protocol-ineligible patients are warranted.

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