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ORIGINAL ARTICLE

Real-world patterns of treatment and response in metastatic renal cell carcinoma: a multicentre UK-wide review with UK Renal Oncology Collaborative (UK ROC)

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Background: The introductions of immunotherapy and first-line combinations have led to major changes in systemic anti-cancer treatment (SACT) options and outcomes in metastatic renal cell carcinoma (mRCC).

Objectives: To evaluate current real-world UK practice in the immunotherapy era looking at survival outcomes by International Metastatic RCC Database Consortium (IMDC) risk stratification and prescribing patterns/drop-off rates of SACT in mRCC.

Materials and methods: This is a retrospective multi-institutional cohort of SACT patients for mRCC at 17 centres across the UK from 1 January 2018 and 30 June 2021. Patient characteristics, IMDC risk group and lines of therapy were recorded. Overall survival (OS) and progression-free survival (PFS) for IMDC groups were analysed.

Results: Of the 1319 patients, 22.3%, 52.7% and 24.3% were IMDC group favourable, intermediate and poor, respectively. Across all risk groups and censoring for patients who have not progressed on their current therapy line, 59.2%, 23.5% and 6.3 % of first-line patients with SACT received second-, third- and fourth-line treatments; 40.1%, 33.2% and 44.2%, respectively, did not receive immunotherapy at any stage in their treatment. Median PFS was statistically different by IMDC risk group: 14.0, 8.2 and 4.8 months in the favourable, intermediate and poor groups ($P < 0.0001$). Median OS was statistically different by risk group and were 40.9, 24.1 and 10.2 months for favourable, intermediate and poor risk groups, respectively.

Conclusions: The majority of patients receive only one or two treatment lines in mRCC. The IMDC prognostic risk groups remain valid in the immunotherapy era. A significant group of patients in this cohort did not receive immunotherapy at any stage.

Key words: renal cell carcinoma, drop-off rates, treatment sequencing, IMDC, immunotherapy

INTRODUCTION

There have been significant developments in the treatment landscape for metastatic renal cell carcinoma (mRCC) in the past 5 years. Developments include the introduction of immunotherapy to the treatment paradigm and the increased use of immunotherapy containing doublets. These doublets consist of combination immunotherapy with ipilimumab and nivolumab (IO/IO) and combination immunotherapy with vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (IO/TKIs).

There have been many clinical trials demonstrating the benefit of these doublet therapies over single-agent anti-VEGF TKI therapy. The licensed doublet treatments investigated in different phase III clinical trials have used the same comparator arm of single-agent sunitinib.[1-5]

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In 2018, Fife et al[6] reported 236 patients who started mRCC first-line treatment between 2012 and 2016. In absolute numbers, 46%, 16%, and 4% of first-line mRCC patients received second, third, or fourth-line treatment, respectively. This was in the preimmunotherapy era of mRCC treatment. The high drop-off rate was thought to be a result of less efficacious frontline therapies and a lack of effective subsequent line therapies.

In clinical practice, decision making requires a comprehensive assessment of the optimal initial systemic anticancer treatment (SACT) and subsequent treatment options. In the National Health Service (NHS), this is based on clinical and reimbursement guidelines.[7] With the new treatment choices and increased combinations, we may expect patients to receive more lines of SACT during their cancer journey. It is reasoned that if most patients receive multiple lines as opposed to a single line of therapy, then the choice of first-line SACT will have less impact on survival outcomes.

The data from clinical trials have resulted in international guidelines recommending immunotherapy (given as either IO/TKI doublet or IO/IO doublet), in eligible patients, in preference to single-agent TKI therapy.[7,8] If patients are only receiving one or two treatments, then this should include an immunotherapy agent upfront to ensure that they do not miss the opportunity for a durable response that immunotherapy can confer.

The main factor in determining treatments for patients with mRCC is selection by the International Metastatic RCC Database Consortium (IMDC) risk group.[9,10] The IMDC prognostic groups were developed in the pre-immunotherapy era and relate to the TKI therapy. A recent dataset from the IMDC shows that these groups remain prognostic in the immunotherapy era.[11]

IMDC risk stratification is not biomarker driven but split into prognostic groups based on performance status, time from nephrectomy to developing metastatic disease, full blood count and calcium. There is a desire for more biomarker-driven work to help us choose which patients may get the optimal response from different first-line therapies.[12-14]

Biomarker-related data suggest that favourable risk disease is typically more angiogenic driven and intermediate and poor risk are more immunogenic.[12] Despite this, within the favourable risk category, there is a subset of patients that responds well to immunotherapy, and within the intermediate and poor risk category, some patients will still respond well to TKI therapy.

We sought to explore the ongoing debate regarding lines of therapy administered and IMDC prognosis groups by exploring the UK Renal Oncology Collaborative (UK ROC) real-world evidence dataset.

Aims

The review focussed on the following four questions from the real-world evidence review:

1. How many lines of therapy are UK NHS patients receiving in the immunotherapy era for mRCC?
2. What treatments are patients receiving in subsequent lines of therapy?
3. What are the changing trends in first-line prescribing in mRCC?
4. Do IMDC prognostic groups still predict survival differences in the immunotherapy era?

METHODS

This was a retrospective review of cases of mRCC identified from 17 centres across the UK. The UK ROC is a collaboration of UK NHS cancer centres that collect and analyse real-world evidence in patients with metastatic renal cancer.

Patients with a clinical, radiological or pathological diagnosis of metastatic renal cancer (mRCC) who started first-line SACT between 1 January 2018 and 30 June 2021 were included. Patients who were $<$18 years of age or who started first-line SACT for mRCC outside the aforementioned period were excluded.

As this is a real-world data collection, all histological subtypes and all patterns of initial metastatic sites, including brain metastases, were included.

Patient characteristics such as sex, IMDC risk group, nephrectomy status, pattern of metastatic disease at presentation and lines of therapy were recorded.

Digital records were reviewed retrospectively by a treating clinician and data were anonymised to ensure that the study was conducted in accordance with the principles of governance and General Data Protection Regulation. This study was reported using the ESMO Guidance for Reporting Oncology Real-World Evidence guidelines for real-world data reporting.[15]

Statistical analysis

We primarily used descriptive statistics to address questions relating to treatment flows and sequences. To estimate differences in prognosis by risk group, we used Kaplan–Meier curves with log-rank tests for overall differences by risk group within outcome. A significance level of 0.05 was used for all tests. Analyses were undertaken in Stata version 17 (StataCorp, College Station, TX).

The progression of the disease was defined by clinical teams using clinical and radiological assessment. Progression-free survival (PFS) was calculated from the date of starting first-line SACT to the date of progression. Overall survival (OS) was calculated from the first-line SACT to the date of death from any cause or, for surviving patients, to the date of last follow-up.

RESULTS

A total of 17 UK NHS centres across the UK were involved in this study; 1319 patients were identified who met the eligibility criteria. Patients were predominately male (71%) with a median age at diagnosis of 64 years (range 21-84

Table 1. Baseline patient and tumour characteristics

Characteristics	Values (N = 1319)
Sex, *n* (%)	
Male	937 (71)
Female	382 (29)
Age at diagnosis of mRCC, mean (range), years	64 (21-84)
IMDC prognostic group, *n* (%)	
Favourable	294 (22.3)
Intermediate	695 (52.7)
Poor	321 (24.3)
N/A	9 (0.7)
Prior nephrectomy, *n* (%)	715 (54.2)
Histology, *n* (%)	
Clear cell	1092 (82.8)
Nonclear cell	217 (16.5)
Not available	10 (0.8)
Sarcomatoid changes on histology, *n* (%)	102 (7.7)

IMDC, International Metastatic RCC Database Consortium; mRCC, metastatic renal cell carcinoma.

years). Patient demographics, tumour subtype and characteristics are summarised in Table 1. The median duration of follow-up was 16 months.

About 83% of patients had metastatic clear cell histology, with papillary (5.6%) and unclassified (4.3%) identified as the next two most common subtypes; 7.7% of patients had a sarcomatoid component to their histology.

Question 1

How many lines of therapy are UK NHS patients receiving in the immunotherapy era for mRCC?

Drop-off rates between each line of therapy were calculated with two different methodologies: (i) absolute and (ii) censored.

The absolute and censored patient drop-off rate numbers are listed in Table 2.

i) The absolute percentage corresponds to those patients who received each line of treatment as a portion of those who received first-line therapy. In Figure 1, the censored drop-off rates are shown graphically.

ii) In the censored approach, patients are censored if they have not progressed through first-line treatment, meaning that the second-line rate is calculated only from those patients who have progressed or stopped treatment, and thus could have received second-line treatment.

Table 2. Percentage of patients receiving a subsequent line of therapy—absolute and censored fraction of the patients receiving first-line therapy

All comers	Total number	Ongoing	Stopped due to toxicity/ progressive disease/death	Continuation rate percentage eligible (censored)	Absolute rate, %
First line	1319	251	436	100	100
Second line	632	158	260	59.2	47.8
Third line	214	57	103	23.5	16.2
Fourth line	54	15	39	6.3	4.1

Table 3. Percentage of patients by the IMDC risk group receiving a subsequent line of therapy—absolute and censored fraction of the patients receiving first-line therapy

	Total number	Ongoing	Stopped due to toxicity/ progressive disease/death	Continuation rate percentage eligible (censored)	Absolute rate, %
Favourable					
First line	294	81	213	100	100
Second line	144	51	93	67.6	49.0
Third line	56	22	34	34.6	19.0
Fourth line	13	6	7	9.3	4.4
Intermediate/poor					
First line	1016	168	848	100	100
Second line	482	103	379	56.8	47.4
Third line	156	34	122	20.9	15.4
Fourth line	40	9	31	5.6	3.9
Intermediate					
First line	695	132	563	100	100
Second line	351	78	273	62.3	50.5
Third line	120	26	94	24.7	17.3
Fourth line	30	7	23	6.5	4.3
Poor					
First line	321	36	285	100	100
Second line	131	24	107	46.0	40.8
Third line	36	8	28	13.8	11.2
Fourth line	10	2	8	3.8	3.1

IMDC, International Metastatic RCC Database Consortium.

Within the favourable risk group, we can also see a significant absolute drop-off rate between therapy treatment lines (Table 3).

Question 2

What treatments are patients receiving in subsequent lines of therapy?

The most common second line treatment in patients who receive first-line single-agent TKI was nivolumab. Among those patients who received first-line combination therapy, most also received cabozantinib in the second line. In patients for whom a TKI was prescribed in the second-line setting, cabozantinib was the most commonly prescribed TKI, regardless of first-line treatment choice, and accounts for 71.8% of these patients.

A total of 492 (37.3%) patients did not receive immunotherapy at any stage of treatment for mRCC over the timeframe of this cohort (130 favourable, 229 intermediate and 129 poor IMDC groups). Correspondingly, 44.2%, 32.9% and 40.1% of the total IMDC favourable, intermediate and poor patients did not receive immunotherapy at any stage in their treatment.

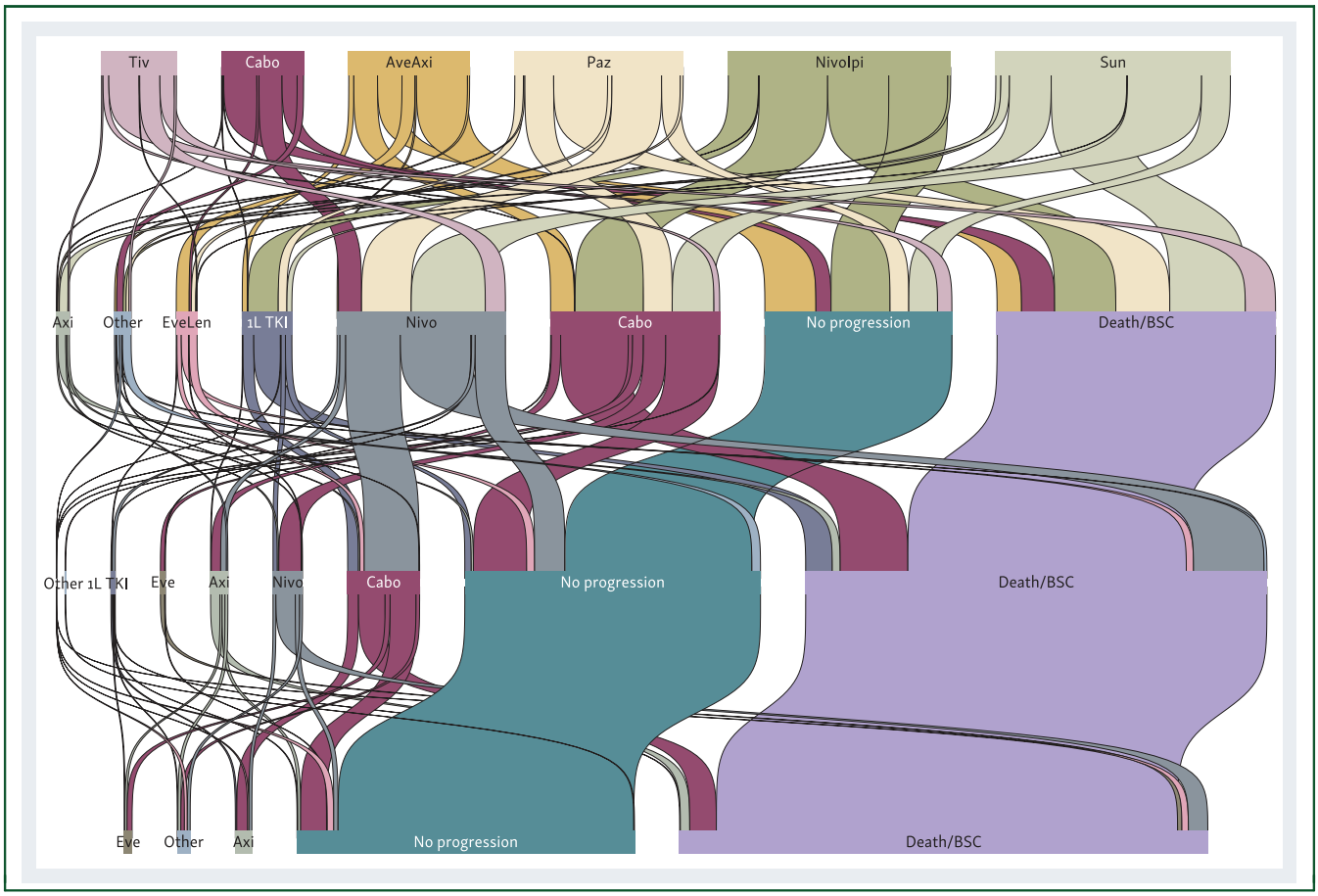

Figure 1. Sankey diagram showing the percentage of patients who received which treatment per line of therapy and how treatment in the previous line influenced the choice in the subsequent line.

AveAxi, avelumab plus axitinib; Axi, axitinib; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; EveLen, everolimus plus lenvatinib; 1L, first line; Nivo, nivolumab; Nivolpi, nivolumab plus ipilimumab; Paz, pazopanib; Sun, sunitinib; Tiv, tivozanib; TKI, tyrosine kinase inhibitor.

Among the 778 patients who received first-line single-agent TKI, 400 made it to the second line. Of these 400 patients, the second-line treatment option chosen was nivolumab in 229 (57.3%) and cabozantinib in 107 (26.8%). Of patients receiving first-line ipilimumab and nivolumab, 142 received second-line therapy, with 93 patients receiving cabozantinib.

Question 3

What are the changing trends in first-line prescribing over time in mRCC?

With the availability of different combination therapies evolving over the time frame of the data collection, we have seen first-line prescribing practice evolve and change.

When considering all comers (all risk groups collectively) in 2018, TKI was the main treatment choice, with 93.9% of patients prescribed this in the first-line setting (Figure 2). The use of TKI in the first-line setting has dropped to 28% in the 2021 cohort, with 69% starting combination therapy with immunotherapy (32% IO/IO and 37% IO/TKI). Despite several trials demonstrating primary endpoint advantages for IO-based combinations in the intermediate and poor IMDC risk groups, 28% of patients in these two groups are still receiving TKI as first-line therapy as of 2021.

Question 4

Do IMDC prognostic groups still predict survival differences in the immunotherapy era?

Comparisons by IMDC risk category suggested that both OS and PFS curves were significantly different by risk category (Figure 3). The median PFS for the overall group was 8.4 months. There was a significant difference in PFS by the IMDC group. In the favourable risk group, the median PFS was 14.0 months compared with 8.2 months in the intermediate risk group and 4.8 months in the poor risk group ($P < 0.0001$). The median OS for the overall group was 25.0 months. There was a significant difference in OS by the IMDC risk group. In the favourable risk group, the median OS was 40.9 months compared with 24.1 months in the intermediate risk group and 10.2 months in the poor risk group ($P < 0.0001$). We include results stratified by clear-cell histology in the Supplementary Materials, available at https://doi.org/10.1016/j.esmorw.2024.100027.

DISCUSSION

The landscape for mRCC continues to evolve. Treatment options over recent years have significantly increased. These

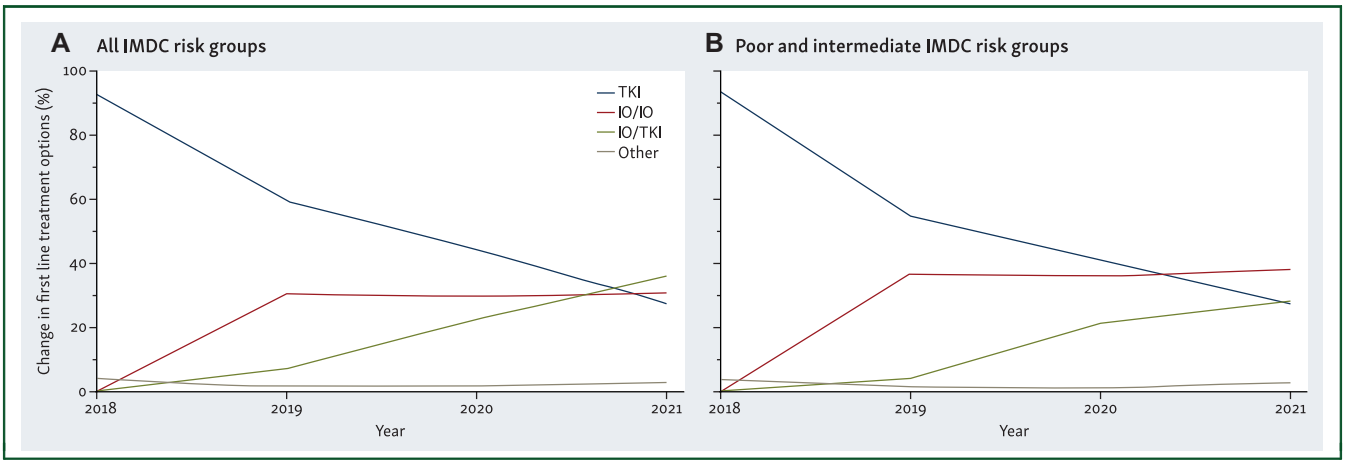

Figure 2. Changes in first-line treatment options over time in (1) all International Metastatic RCC Database Consortium (IMDC) risk groups and (2) poor and intermediate IMDC risk groups.
TKI, tyrosine kinase inhibitor.

developments offer patients the potential for improved outcomes. Decision making regarding the optimal first-line SACT is a complex process. In our real-world study, a significant drop-off rate remains with 40% of patients not receiving second-line therapy when censored for patients still on first-line therapy. The absolute percentage of patients reaching the second line is <50%. There has been no significant improvement in the number of treatment lines patients received compared with the preimmunotherapy period, for example drawing on earlier datasets such as the 2012-2016 data from Fife et al.[6] This is despite a recent increase in available effective treatments. These data are important in the decision-making process for optimal first-line SACT and highlight the importance of prescribing the most effective treatment first.

Based on the registration trials, international guidelines and the real-world evidence in our study, in patients with advanced renal cancer, the optimal SACT in the first-line setting would be a combination therapy that includes immunotherapy. Disease progression and death are the two main reasons patients do not receive further treatment in our study. This, together with the significant drop-off rates for subsequent lines of SACT, makes it even more important to optimise the first-line therapy to improve real-world outcomes.

Importantly this real-world evidence shows that more than one-third of patients (37.3%) did not receive immunotherapy at any stage of treatment for mRCC. This is despite later-line nivolumab being available and reimbursed for the entirety of the time frame of this study. Our study provides real-world evidence that patients who start on single-agent TKI may never receive immunotherapy with a potential loss of durable outcomes.

IMDC risk groups remain relevant for prognosis for PFS and in the immunotherapy era in this UK cohort. Its use as a predictive tool is still strongly debated and the hope is that over the coming years, we will move to molecular subtyping to optimise treatment selection and improve outcomes in mRCC.[14] Ernst et al.[16] have shown a correlation between the IMDC risk group and survival outcomes in patients with

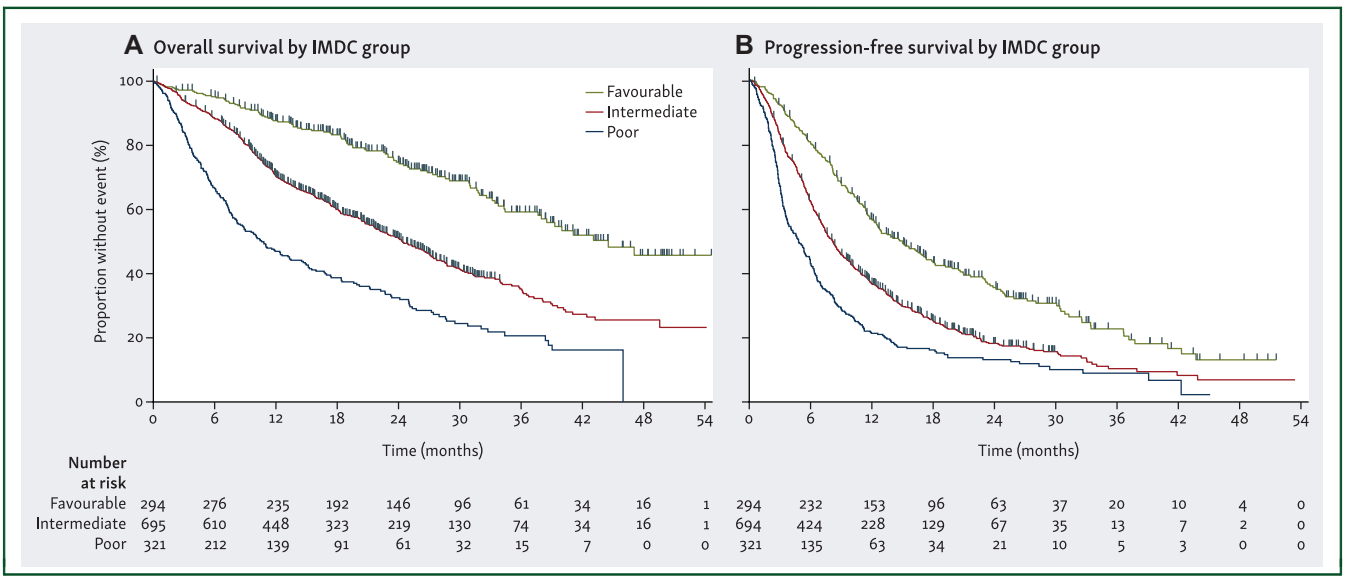

Figure 3. (A) Progression-free survival and (B) overall survival by International Metastatic RCC Database Consortium (IMDC) risk group.

mRCC treated with contemporary first-line IO combination therapies and provided real-world survival benchmarks compared with VEGF TKI.

This large UK dataset has several limitations that are inherent to the real-world aspect of data collection and analysis. This was a retrospective data collection. There were no data collected for response rate and limited data collected regarding treatment toxicity and patient comorbidity and its impact on treatment choice. We acknowledge that a prospective data collection including these parameters will add more information; however, as has been acknowledged by several real-world data analyses across the spectrum of oncology, these require robust infrastructure and support. Due to the evolving nature of this treatment space, we now also have additional first-line combinations that were not in routine use during the timeframe of this study.[1,2] Licensing of adjuvant pembrolizumab in the nonmetastatic setting[17] will further impact treatment choices.

In our data, there is significant prescribing of single-agent TKI in the poor and intermediate risk group despite the improved response rates, PFS and OS trend or survival advantage across several trials of combination treatment. The reasons for this are likely multifactorial. These may include clinician experience, familiarity with established TKI therapy, concerns regarding immunotherapy toxicity and the belief that multiple treatment lines offer the possibility of later-line nivolumab. The coronavirus disease 2019 (COVID-19) pandemic may also have had some impact on treatment choices. Early in the COVID-19 pandemic, guidance supported the de-escalation of treatment intensity to avoid potential toxicity-related hospital admissions.[18] In the favourable IMDC group the lack of OS benefit for IO/TKI compared with single-agent TKI in trials has created equipoise for first-line SACT choice. The data presented strongly support combination therapy for this risk group where possible.

The UK ROC hope that this data set will inform real-world practice and ensure patients receive the most efficacious options and in doing so, help improve patient outcomes across the UK.

Participating UK ROC centres

1. Velindre Cancer Centre, Cardiff
2. Royal Cornwall Hospital, Truro
3. Bristol Haematology and Oncology Centre, Bristol
4. Musgrove Park Hospital, Taunton
5. Edinburgh Cancer Centre, Edinburgh
6. Northern Ireland Cancer Centre, Belfast
7. Mount Vernon Cancer Centre, Middlesex
8. University Hospitals Southampton, Southampton
9. Newcastle Cancer Centre, Newcastle
10. Royal Preston Hospital, Preston
11. South West Wales Cancer Centre, Swansea
12. Plymouth Oncology Centre, Plymouth
13. Oxford University Hospitals, Oxford
14. Hull University Teaching Hospitals NHS Trust, Hull
15. University Hospitals Dorset, Bournemouth
16. Torbay and South Devon NHS Foundation Trust, Torbay
17. Royal Devon University Healthcare NHS Foundation Trust, Exeter

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