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Characterizing progression to subsequent lines of therapy in metastatic renal cell carcinoma (mRCC) after nivolumab + ipilimumab (Nivo+Ipi): Results from the International mRCC Database Consortium

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Background

- The standard of care first-line (1L) treatment for mRCC has changed in recent years towards immuno-oncology (IO) based combination therapies.
- Treatment patterns and number of lines of therapy beyond 1L are not well characterized in mRCC in the era of IO-based combinations.

Objective

- We aimed to quantify the attrition rates by line of therapy and to examine predictors of receiving second-line (2L) treatment.

Methods

Study population

- Patients from the IMDC who received 1L Nivolumab + Ipilimumab (Nivo + Ipi) were included in this real-world, retrospective database study.

Outcomes

- Primary outcome: Retention rate to 2L therapy, defined as the proportion of patients who started any 2L treatment out of the patients who stopped 1L.
- Secondary outcomes: Retention rates to third (3L) and fourth-line (4L) therapy, overall response rate (ORR) to 1L in the cohorts of patients who received and did not receive 2L, defined as per RECIST 1.1 criteria.

Statistical analysis

- Patients' characteristics and outcomes were described using the median values with their standard deviation (SD) for continuous variables and proportions for categorical variables.
- Differences between the patients who underwent 2L therapy and those who did not were compared using Pearson chi-squared test, with a significance value of $p<0.05$.
- A logistic regression model was used to assess potential predictors of getting 2L therapy.

Results

Population

- 995 patients were treated with 1L Nivo+Ipi, with a data cut-off date of October 2022, of whom 704 patients stopped first-line therapy and were deemed eligible for 2L.

Attrition rates

- The flow diagram in Figure 1 shows the attrition rates from 2L to 4L therapy.

Predictors of receiving 2L

- In univariable analysis, patients who started 2L were more likely to be younger, have clear-cell histology, bone metastases, only one site of metastases, and to have stopped 1L for progressive disease (PD) and less likely to be poor risk by IMDC criteria (Table 1).
- After adjusting for IMDC criteria, no predictors of receiving 2L therapy remained significant in multivariate analysis after Bonferroni correction.
- (Patients who stopped for PD were more likely to initiate 2L than those who stopped for other reasons (81.7% vs 43.0%, $p < 0.0001$)Table 2).

ORR

- The overall response rate to 1L therapy was lower in patients who received 2L than in those who did not: 18.5% (76/366) and 33.7% (99/245), respectively ($p < 0.001$, Table 4)

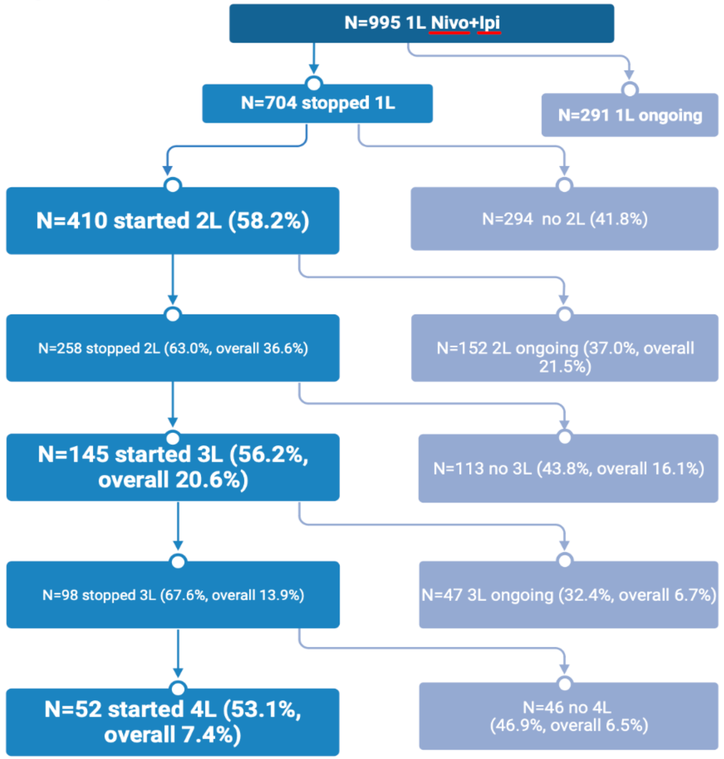
Limitations

- Potential biases include:
  - Selection bias, as all patients who had stopped 1L were deemed "eligible" for 2L.
  - Missing data from the IMDC database, which may bias study results if missingness is not random.
  - Potential unmeasured confounding could account for some of the associations observed.

Conclusions

- In this real-world analysis, over half of eligible patients received the subsequent line of therapy, with no identifiable predictors of 2L therapy initiation.
- Attrition rates between lines of therapy have important implications for patient counseling, cost analyses and clinical trial design.

Figure 1 : Flow diagram of patients between lines of therapy



Abbreviations: 1L: First-line, 2L : Second-line, 3L: third-line, 4L : Fourth-line

Table 1 : Characteristics of patients eligible for, and of patients who received or did not receive 2L

	Overall N=704		2L = NO (N=294)		2L= YES (N=410)		P value*
Median Age							
	63		66		62		*<0.0001*
Sex							
Male	504	71.6%	192	65.3%	303	73.9%	
Female	200	28.4%	93	31.6%	107	26.1%	0.06
Ethnicity							
Caucasian	417	59.2%	168	57.1%	249	60.7%	
Asian	68	9.7%	28	9.5%	40	9.8%	0.75
Black	8	1.1%	2	0.7%	6	1.5%	
Other	32	4.5%	11	3.7%	21	5.1%	
IMDC							
Favorable	58	8.2%	23	7.8%	35	8.5%	
Intermediate	350	49.7%	127	43.2%	223	54.4%	*0.03*
Poor	212	30.1%	101	34.4%	111	27.1%	
Histology							
ccRCC	493	70.0%	185	62.9%	308	75.1%	*0.02*
Sarcomatoid features	102	14.5%	46	15.6%	56	13.7%	0.13
Disease presentation							
De novo IV	388	55.1%	163	55.4%	225	54.9%	0.75
Recurrent IV	304	43.2%	124	42.2%	180	43.9%	
Nephrectomy							
Yes	417	59.2%	164	55.8%	253	61.7%	0.11
Site of metastases							
Brain	58	8.2%	31	10.5%	27	6.6%	0.06
Liver	129	18.3%	53	18.0%	76	18.5%	0.86
Bone	250	35.5%	87	29.6%	163	39.8%	*0.008*
>1 site of met	516	73.3%	218	74.1%	298	72.7%	*0.01*
Reason for stopping 1 L							
Progression	278	39.5%	51	17.3%	227	55.4%	
Death	30	4.3%	30	10.2%	0	0%	
Toxicity	176	25.0%	76	25.9%	100	24.4%	*<0.00001*
CR	11	1.6%	9	3.1%	2	0.5%	
Other or missing	209	29.7%	128	43.5%	81	19.8%	

Abbreviations: 2L: second-line, IMDC: International metastatic renal cell carcinoma database consortium, ccRCC: clear cell renal cell carcinoma, IV: stage IV disease, met: metastasis, 1L: First-line, CR: Complete response.
Note: Italics indicate p value <0.05. P values are comparisons of 2L=NO vs 2L= YES

Table 2 : Proportions of patients who did and did not receive 2L classified by reason for stopping 1L

Reason for stopping 1 L	2L=NO		2L=YES		P value
Progression (N=278)	51	18.3%	227	81.7%	< 0.0001
All other reasons (n=426)	243	57.0%	183	43.0%	
Toxicity (N=176)	76	43.2%	100	57.1%	
CR (N=11)	9	81.8%	2	18.2%	< 0.0001
Death (N=30)	30	100.0%	0	0.0%	
Unclassified (N=209)	128	61.2%	81	38.8%	

Abbrevia

Table 3 : Best responses and overall response rates to 1L therapy

Best response to 1L	Overall (N=704)		2L = NO (N=294)		2L =YES (N=410)		P value
Progression	225	32.0%	58	19.7%	167	40.7%	
Stable disease	211	30.0%	88	29.9%	123	30.0%	
PR	147	20.9%	76	25.9%	71	17.3%	< 0.00001
CR	28	4.0%	23	7.8%	5	1.2%	
Unknown	93	13.2%	49	16.7%	44	10.7%	
ORR	175	24.9%	99	33.7%	76	18.5%	< 0.001

Abbreviations: 1L:First-line, 2L: Second-line, PR: Partial response, CR: Complete response, ORR: Overall response rate.

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