Evaluation of the Safety and Efficacy of Immunotherapy Rechallenge in Patients With Renal Cell Carcinoma

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Disclosure of Conflicts of Interest

- Dean Elhag, MD has no relevant financial relationships to disclose.

Learning Objective

- Use new knowledge to evaluate the safety and efficacy of immune checkpoint inhibitor(ICI) rechallenge in patients with metastatic renal cell carcinoma
- Explain limitations and advantages of rechallenging with ICI

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Background – Immune checkpoint inhibitors in Renal Cell Carcinoma

- Several Immune Checkpoint Inhibitors have been approved over the past several years for metastatic renal cell carcinoma
- Nivolumab + Ipilimumab
  - Median OS approaching 4 years in patients with intermediate or poor-risk disease (1)
- Pembrolizumab VEGF-TKI (i.e. axitinib)
  - Response rates of 40 – 60% (2)

Is rechallenge an option in RCC?

- ICI rechallenge has shown efficacy in patients with melanoma and non-small cell lung cancer
- ICI rechallenge in patients with melanoma who were ipilimumab refractory had an ORR of ~20% (Keynote 002, 3)
- In Keynote 010 trial ORR of 43% was seen in 14 patients who were retreated with pembrolizumab (4)
- We hypothesized that response to ICI-2 would be lower than to ICI-1 and that toxic effects may be increased
  - ICI-1 = First Line ICI
  - ICI-2 = Second line ICI

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Design

- Multicenter (9 institutions), retrospective cohort of patients with metastatic RCC
- Patients who received 2 separate lines of immune checkpoint inhibitor (ICI) (January 2012 – December 2019)
- ICI's included CTLA-4, PD-1, PDL-1 inhibitors alone or in combination with other therapies in at least 2 separate lines of therapy

Design

- 69 patients, median age at diagnosis of 61 years (36 – 86 years)
- Most commonly patients received single agent ICI (39%), or ICI in combination with targeted therapy (42%) upfront (ICI-1)
- For second line therapy (ICI-2) most common therapies were single agent (38%) or dual ICI (32%)

Design

- Outcomes were best overall radiographic response (per Response Evaluation Criteria in Solid Tumors version 1.1) and immune related adverse events (irAEs, graded using Common Terminology Criteria for Adverse Events version 5.0)
- Patients without a follow up scan were considered non-evaluable for response

Table 1. Baseline Characteristics of the Cohort

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Characteristic	No. (%)
Total No.	69
Age at diagnosis, median (range), y	61 (36-86)
Clear cell histology	60 (87)
IMDC risk at time of ICI-1 therapy	
Good	13 (19)
Intermediate	45 (65)
Poor	8 (12)
Not available	3 (4)

Line of ICI-1 therapy, median (range)	1 (1-6)
ICI alone	27 (39)
ICI + ICI	9 (13)
ICI + TT	29 (42)
ICI + chemotherapy	2 (3)
ICI + investigational agent	2 (3)
Reasons for discontinuation of ICI-1	
Disease progression	50 (72)
Toxic effects	16 (23)
Other	3 (4)

Line of ICI-2 therapy, median (range)	3 (2-8)
ICI alone	26 (38)
ICI + ICI	22 (32)
ICI + TT	13 (19)
ICI + chemotherapy	1 (1)
ICI + investigational agent	7 (10)

Abbreviations: ICI, immune checkpoint inhibitor; ICI-1, first line of ICI therapy; ICI-2, ICI rechallenge in patients who have already received an earlier line of ICI therapy; IMDC, International Metastatic RCC Database Consortium; TT, targeted therapy.

Results

- A total of 68 patients were evaluable for response at ICI-1
- For ICI-1 overall response rate (ORR) was 37% (n = 25), while 43% (n = 29) and 21% (n = 14) of patients had stable disease (SD) and progressive disease (PD)
- At ICI-2, the ORR was 23% (n = 15), while 41% (n = 26) and 36% (n = 23) of patients had SD and PD
  - 5 patients were not evaluable
- No complete responses with ICI-1 or ICI-2
- Median time to progression with ICI-1 compared to ICI-2 was 8.2 m vs 5.7 m (P = 0.045)

Results

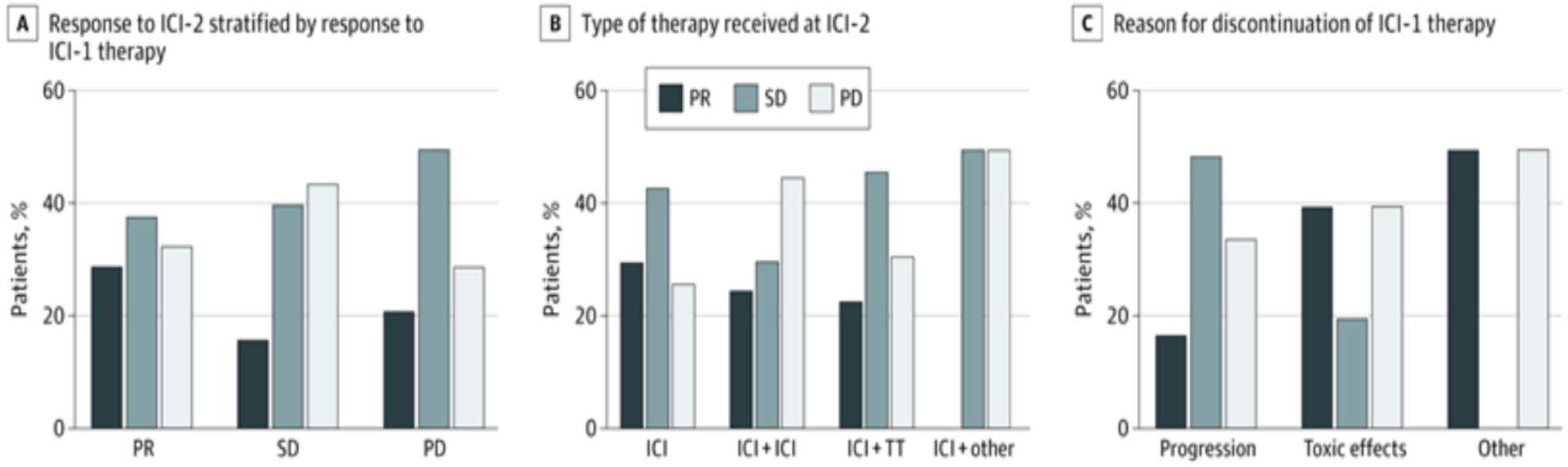
- Likelihood of a response to ICI-2 was greatest among patients who had previously responded to ICI-1 (29%)
- Responses at ICI-2 were seen in those who previously had **progressive disease** as best response (21%) and in those who received **single agent** ICI at ICI-2 (30%)
- Grade 3 immune related adverse events were seen in 26% of patients at ICI-1 and 16% at ICI-2
  - No treatment related deaths

Characteristics of Responders to ICI-2

- 15 responders in total
- 7 (47%) received single-agent ICI
- 5 (33%) received ICI + ICI
- 3 (20%) received ICI + targeted therapy
- A total of 7 (47%) responded to ICI-1, while 4 (27%) had SD to ICI-1 and 3 (20%) had PD to ICI-1. A total of 6 (40%) discontinued ICI-1 due to toxic effectsW

Characteristics of Responders to ICI-2

Figure. Responses to Immune Checkpoint Inhibitor Rechallenge (ICI-2) in Selected Patient Populations.



There were a total of 68 evaluable patients at first course of immune checkpoint inhibitor therapy (ICI-1) and 64 evaluable patients at ICI-2. PD indicates progressive disease; PR, partial response; SD, stable disease; TT, targeted therapy.

Safety

- Grade 3 or higher irAEs were seen in 18 patients (26%) and 11 patients (16%) with ICI-1 and ICI-2, respectively
- 3 patients (27%) who had a grade 3 or higher irAE at ICI-2 had previously experienced a grade 3 or higher irAE with ICI-1.
- The risk of experiencing an irAE with ICI-2 was higher in patients who had an irAE with ICI-1 (n = 20 [41%]) compared with those who did not (n = 4 [20%])

Limitations

- Retrospective nature of response determination and toxic effects by investigators
- Small sample size

Conclusions

- We found that ICI rechallenge in patients with mRCC was not associated with an increase in immunotherapy-related toxic effects and had an ORR of 23%.
- This response rate is like that seen with single-agent nivolumab in the second-line setting
- Prospective studies are needed to validate findings and role for sequential ICI regimens

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