Poster No. CTR14

Characterization and Management of Adverse Reactions in Patients With Advanced Renal Cell Carcinoma Receiving Lenvatinib + Pembrolizumab (CLEAR Study)

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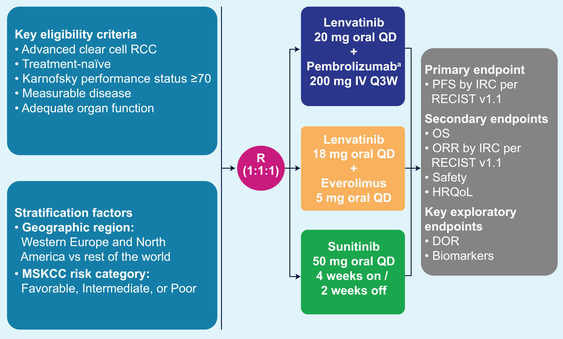
INTRODUCTION

- In the CLEAR study, lenvatinib + pembrolizumab showed significantly improved outcomes versus sunitinib in patients with advanced renal cell carcinoma (aRCC)[1,2]:
  - Progression-free survival (PFS) as assessed by independent review committee was significantly improved with lenvatinib + pembrolizumab (median 23.9 months) versus sunitinib (median 9.2 months; hazard ratio [HR] 0.39, 95% confidence interval [CI] 0.32–0.49; *P* < 0.001).
  - Overall survival (OS) was significantly longer with lenvatinib + pembrolizumab versus sunitinib (HR 0.66, 95% CI 0.49–0.88; *P* = 0.005).
  - Objective response rate (ORR) as assessed by independent review committee was greater with lenvatinib + pembrolizumab (71.0%) versus sunitinib (36.1%; relative risk 1.97, 95% CI 1.69–2.29; nominal *P* < 0.001).
  - Based on the results of the CLEAR study, lenvatinib + pembrolizumab has been approved by the US Food and Drug Administration (FDA) for the first-line treatment of adult patients with aRCC.[3,4]
- The safety profile of lenvatinib + pembrolizumab was considered manageable and generally consistent with the established profiles of each monotherapy.[3,4]
  - Clinicians play a critical role in prompt identification of adverse reactions (ARs) and the AR-directed management of patients with aRCC.
- Herein, we characterize common ARs in patients with aRCC in the lenvatinib + pembrolizumab arm of the CLEAR study, as well as management strategies for selected ARs.

METHODS

- In the CLEAR study, patients were randomly assigned (1:1:1) to receive either lenvatinib 20 mg orally once daily + pembrolizumab 200 mg intravenously once every 3 weeks; lenvatinib 18 mg orally once daily + everolimus 5 mg orally once daily; or sunitinib 50 mg orally once daily (4 weeks on/2 weeks off) (**Figure 1**).

Figure 1. Design of the CLEAR Study



[a]Patients could receive a maximum of 35 pembrolizumab treatments.

DOR, duration of response; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenously; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; Q3W, once every 3 weeks; R, randomization; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

- Dose modifications were used to manage ARs; these approaches included dose reductions for lenvatinib (eg, from 20 mg to 14 mg, 14 mg to 10 mg, and 10 mg to 8 mg) and dose interruptions for both lenvatinib and pembrolizumab.
- ARs (grouped preferred terms per FDA definitions) were categorized in accordance with the FDA prescribing information (PI) for lenvatinib (**Table 1**).[3,4]
  - Key ARs (**Table 1**) were chosen based on frequency of occurrence (≥ 30%).
  - ARs could have occurred while receiving lenvatinib and/or pembrolizumab or within the protocol-defined follow-up period after discontinuation of both study drugs.

Table 1. Preferred Terms Included in Each Adverse Reaction

Adverse Reaction	Preferred Terms
Fatigue	Fatigue, asthenia, malaise, and lethargy
Diarrhea	Diarrhea and gastroenteritis
Musculoskeletal pain	Arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, noncardiac chest pain, pain in extremity, and pain in jaw
Hypothyroidism	Hypothyroidism, increased blood thyroid-stimulating hormone, and secondary hypothyroidism
Hypertension	Essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, and labile blood pressure
Stomatitis	Aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis
Decreased appetite	Decreased appetite and early satiety
Rash	Genital rash, infusion site rash, penile rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular
Nausea	Nausea
Dysphonia	Dysphonia
Proteinuria	Hemoglobinuria, nephrotic syndrome, and proteinuria
Weight decreased	Weight decreased

RESULTS

Patients

- Of the 1069 patients randomly assigned to a treatment in the CLEAR study, 355 were assigned to lenvatinib + pembrolizumab.[1]
- Baseline characteristics of patients have been previously reported[1] and are summarized in **Table 2**.

Table 2. Patient Demographics and Baseline Characteristics[1,5]

Characteristic	Lenvatinib + Pembrolizumab (n = 355)
Median age (range), years	64 (34, 88)
Geographic region, % Western Europe and North America Rest of the world	 55.8 44.2
MSKCC prognostic risk group, % Favorable / Intermediate / Poor	 27.0 / 63.9 / 9.0
IMDC risk group, % Favorable / Intermediate / Poor	 31.0 / 59.2 / 9.3
Sarcomatoid features, %	7.9
PD-L1 combined positive score, % ≥ 1 / < 1 / not available	 30.1 / 31.5 / 38.3
Patients with target kidney lesions, %[5] Yes / no	 21.9 / 78.0
Number of metastatic organs or sites, % 1 / ≥ 2	 27.3 / 71.5
Prior nephrectomy, %	73.8

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed cell death ligand 1.

Adverse Reactions: Frequency and Characterization

- Of the 352 patients who received lenvatinib + pembrolizumab, 45% were ≥ 65 years of age; no overall differences in safety profiles were observed between patients who were ≥ 65 years old and those who were < 65 years old.[3]
- The most common ARs (≥ 30% any grade) in the lenvatinib + pembrolizumab group are shown in **Table 3**.
  - ARs occurring in > 50% of patients included fatigue (63.1%), diarrhea (61.9%), musculoskeletal pain (58.0%), hypothyroidism (56.8%), and hypertension (56.3%).

Table 3. Adverse Reactions With Incidence ≥ 30% in the Lenvatinib + Pembrolizumab Group

	Lenvatinib + Pembrolizumab (n = 352)[a]	
Adverse Reaction, %	**Any Grade**	**Grade ≥ 3**
Fatigue	63.1	9.4
Diarrhea	61.9	9.9
Musculoskeletal pain	58.0	3.7
Hypothyroidism	56.8	1.4
Hypertension	56.3	28.7
Stomatitis	43.2	2.0
Decreased appetite	40.6	4.0
Rash	37.2	4.5
Nausea	35.8	2.6
Dysphonia	29.8	0
Proteinuria	29.8	7.7
Weight decreased	29.8	8.0

[a]All safety analyses included patients who received at least 1 dose of any study drug.

- When adjusted for exposure, the most frequent of the key ARs (n/total exposure > 0.6) were diarrhea, musculoskeletal pain, fatigue, and hypertension (**Table 4**).

Table 4. Exposure-Adjusted Incidence of Key Adverse Reactions

Parameter	Lenvatinib + Pembrolizumab
Patients exposed	352
Total exposure[a], person-years	524.9
Adverse Reaction Category, n[b] (n/total exposure)	
Diarrhea	567 (1.08)
Musculoskeletal pain	480 (0.91)
Fatigue	370 (0.70)
Hypertension	340 (0.65)
Hypothyroidism	249 (0.47)
Stomatitis	241 (0.46)
Decreased appetite	220 (0.42)
Nausea	218 (0.42)
Rash	199 (0.38)
Proteinuria	197 (0.38)
Dysphonia	134 (0.26)
Weight decreased	125 (0.24)

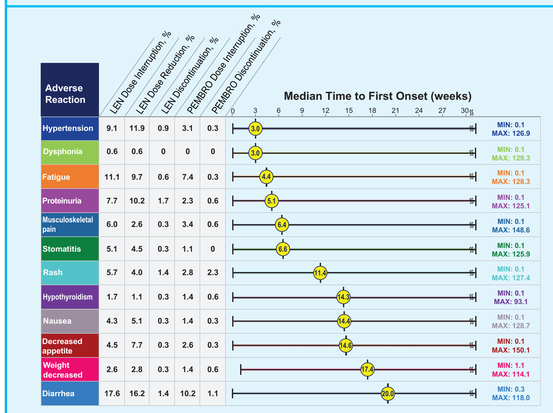
[a]Drug exposure was defined as the interval between the first dose date + 1 day and the earlier of the last dose date + 30 days or the database cutoff date.

[b]Total number of episodes; episode is based on MedDRA Lowest Level Term. A single episode is defined from onset through resolution or, if ongoing, to the end of reporting period.

MedDRA, Medical Dictionary for Regulatory Activities.

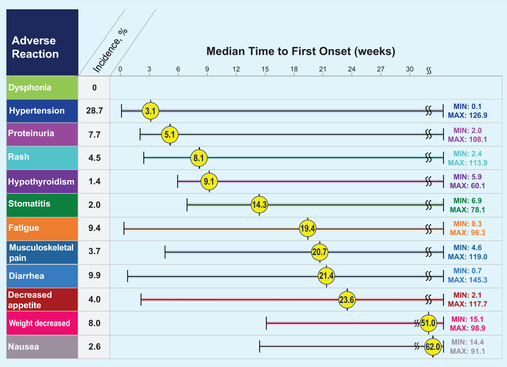
- Median time to first onset of key ARs in this analysis occurred within approximately 5 months of treatment initiation (**Figure 2**).
  - ARs with the shortest median time to onset included hypertension (3.0 weeks), dysphonia (3.0 weeks), and fatigue (4.4 weeks).
  - ARs with a relatively longer median time to onset included diarrhea (20.0 weeks), weight decreased (17.4 weeks), and decreased appetite (14.6 weeks).
- First onset of ARs of grade ≥ 3 severity during lenvatinib + pembrolizumab treatment is shown in **Figure 3**.

Figure 2. Median Time to First Onset of Key Adverse Reactions (All Grades) and Dose Management



LEN, lenvatinib; PEMBRO, pembrolizumab.

Figure 3. Median Time to First Onset of Key Adverse Reactions (Grade ≥ 3)



Adverse Reactions: Management

- Baseline monitoring of blood pressure, urine protein levels, and thyroid and liver function prior to lenvatinib treatment are recommended.[3]
- Dosing interventions, including dosing interruptions for lenvatinib and pembrolizumab and dose reductions for lenvatinib, are important management strategies for ARs (**Figure 4**).
- Judicious use of lenvatinib dose modifications were undertaken in the CLEAR study[1] to manage ARs as appropriate.
  - Due to an AR, dose interruptions of lenvatinib, pembrolizumab, or both occurred in 78% of patients receiving the combination therapy (lenvatinib, 73%; both drugs, 39%).[3]
  - Lenvatinib dose was reduced in 69% of patients.[3]
  - Due to an AR, permanent discontinuation of lenvatinib, pembrolizumab, or both occurred in 37% of patients (lenvatinib, 26%; pembrolizumab, 29%; both, 13%).[3]
  - Median time to first dose reduction of lenvatinib was 1.87 months (range: 0.10–37.98); median time to first dose interruption of lenvatinib was 4.14 months (range: 0.07–30.59).

Figure 4. Management Guidelines for Adverse Reactions According to the US Lenvatinib Prescribing Information

Lenvatinib PI Recommendations	
Severity	**Dosage Modifications for Lenvatinib**
• Persistent or intolerable **grade 2** or **grade 3**[a]	• Withhold until AR severity improves to grade ≤ 1 or baseline, then resume lenvatinib at reduced dose
• **Grade 4**[a]	• Permanently discontinue lenvatinib

Dose Levels							
Starting Dosage of Lenvatinib		**First Dosage Reduction to**		**Second Dosage Reduction to**		**Third Dosage Reduction to**	
20 mg orally, once daily	2 × 10-mg capsules	14 mg orally, once daily	1 × 10-mg capsule + 1 × 4-mg capsule	10 mg orally, once daily	1 × 10-mg capsule	8 mg orally, once daily	2 × 4-mg capsules

When administering lenvatinib in combination with pembrolizumab for the treatment of aRCC:
- Interrupt 1 or both drugs or dose-reduce lenvatinib as appropriate
- No dose reductions are recommended for pembrolizumab
- Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab PI[a]
- Refer to the lenvatinib full PI for additional details[3]

[a]Please note there are exceptions to the grade 3- and grade 4-severity advice; some grade 3 ARs require treatment discontinuation, whereas some grade 4 ARs do not.

AR, adverse reaction; aRCC, advanced renal cell carcinoma; PI, prescribing information; US, United States.

- Optimal medical management should be utilized when available and applicable (per PI) prior to lenvatinib dose reduction (eg, for nausea, vomiting, hypertension, diarrhea, and hypothyroidism); lenvatinib and/or pembrolizumab dose interruptions or lenvatinib dose reductions should be initiated according to the respective product PI.
- For most of the key ARs (ie, musculoskeletal pain, fatigue, nausea, diarrhea, decreased appetite, stomatitis, hypothyroidism, weight decreased, dysphonia, and rash), the management advice from the lenvatinib PI[3] is to withhold lenvatinib treatment for persistent or intolerable grade 2 or grade 3 severity. Upon resolution to grade ≤ 1 (or baseline) severity, lenvatinib treatment can be resumed at a lower dose.
  - Per the CLEAR study protocol,[1] an anti-diarrheal agent should be recommended to the patient at the start of study treatment; patients should be educated to initiate the anti-diarrheal agent at the first onset of soft bowel movements.
- For hypertension, specific patient monitoring and management parameters are provided in the lenvatinib PI.[3]
  - Briefly, blood pressure should be controlled prior to initiating lenvatinib. Blood pressure should then be monitored after 1 week of treatment and then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment.
  - For grade 3 hypertension that persists despite optimal antihypertensive therapy, lenvatinib treatment should be withheld and then resumed at a lower dose upon resolution of the hypertension to grade ≤ 2 severity.
  - Per the CLEAR study protocol,[1] management of hypertension includes the use of a new antihypertensive agent if the patient is not on any medication; if the patient is already receiving an antihypertensive, then the dose of the current agent could be increased, if appropriate, or 1 or more agents of a different class could be added.
- Management and monitoring strategies for proteinuria are included in the lenvatinib PI.[3]
- For most ARs, if the severity reaches grade 4, it is recommended to permanently discontinue lenvatinib; in general, pembrolizumab should be discontinued for grade 4 immune-mediated ARs.[3,4]
- In the CLEAR study, 14.8% of the patients treated with lenvatinib + pembrolizumab concomitantly received high-dose corticosteroids (≥ 40 mg prednisone daily equivalent) to manage immune-mediated adverse events.[6]
  - High-dose corticosteroids were taken by 18 (5.1%) and 6 (1.7%) patients for ≥ 14 days and ≥ 30 days consecutively, respectively.
- Clinicians are advised to refer to the lenvatinib and pembrolizumab PIs for patient monitoring and management details on other important, but less common, ARs that may occur during treatment with lenvatinib + pembrolizumab, but are not described in this poster.[3,4]

Adverse Reactions Attributable to Lenvatinib or Pembrolizumab Treatment

- Certain ARs (eg, diarrhea) may be attributable to either lenvatinib or pembrolizumab at first onset.
  - Therefore, it is important to try to determine which is the causative agent to properly manage the AR. The timing of first onset of such ARs may be critical in making this determination.
  - Since lenvatinib is administered daily and has a shorter half-life, dose interruption of lenvatinib may be considered as a first-line approach to determine whether clinical resolution can be obtained.
  - If there is no clinical improvement, an immune-mediated AR may be considered.
- Severe ARs may sometimes require interruption of both study drugs and initiation of concomitant medications.

CONCLUSIONS

- A proactive approach in addressing treatment-emergent ARs is critical when treating patients with lenvatinib + pembrolizumab.
- In general, ARs reported with lenvatinib + pembrolizumab therapy were as expected and often occurred within 5 months of treatment initiation.
  - Close monitoring of patients at the beginning of treatment is therefore critical, as ARs can often be managed with additional medical therapy if they are diagnosed early.
- Clinicians play a critical role in the prompt identification and management of ARs in patients with aRCC treated with lenvatinib + pembrolizumab.
  - Prompt management of ARs may potentially reduce treatment interruption(s) and/or lenvatinib dose reduction and allow patients to continue receiving therapy.

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