Abstract 2622

A Phase 1/2 Study to Assess the Safety and Efficacy of Pazopanib and Pembrolizumab in Patients With Advanced Renal Cell Carcinoma

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BACKGROUND

- Pazopanib is an oral multi-kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet-derived growth factor receptor (PDGFR)-α and -β, and c-Kit indicated for the treatment of patients with advanced renal cell carcinoma (aRCC)[1]
- Pembrolizumab is a human programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults in Europe[2] and for the treatment of patients with metastatic melanoma and disease progression following treatment with ipilimumab[3]
- Preclinical data suggest that the combination of an antiangiogenic agent (pazopanib) and immunotherapy (pembrolizumab) may improve antitumor efficacy

OBJECTIVE

- To evaluate the safety and tolerability of pazopanib in combination with pembrolizumab and to assess the efficacy of pazopanib in combination with pembrolizumab for the treatment of patients with aRCC versus single-agent pazopanib and single-agent pembrolizumab

METHODS

- Part 1 is a phase 1 dose-escalation study of pazopanib plus pembrolizumab followed by an expansion cohort to determine the maximum tolerated dose and the recommended phase 2 dose (**Table 1**)
- Part 2 will further characterize the safety and efficacy of pembrolizumab and pazopanib using the dose and schedule identified in Part 1
- Patients with aRCC received pazopanib plus pembrolizumab until disease progression or unacceptable toxicity
- The starting dose of pazopanib was 800 mg/day orally; the starting dose of pembrolizumab was 2 mg/kg IV given once every 2 weeks (Q2W), with planned escalation to 10 mg/kg

Table 1. Dose-Escalation Scheme

Dose Level	Pazopanib, mg/day[a]	Pembrolizumab, mg/kg Q2W[a]
–1	600	2
0, start	800	2
1	800	10

Abbreviations: Q2W, every 2 weeks; Q3W, every 3 weeks.
[a] Intermediate dose levels may be assessed depending on toxicity seen at the starting dose level; pazopanib may be administered at 400 mg/day and pembrolizumab may be administered from 1 to 10 mg/kg and/or given on a Q3W schedule.

RESULTS

- At the time of data cut-off (August 7, 2015) 20 patients were enrolled and had received combination therapy (**Table 2**)

Table 2. Baseline Demographics and Disease Characteristics

	Pazopanib 800 mg + Pembrolizumab[a] (n = 10)	Pazopanib 600 mg + Pembrolizumab[b] (n = 10)
Age, median years (range)	61 (45-72)	57 (46-74)
Age group, n 65-74 years <65 years	 4 6	 1 9
Male sex, n	5	7
Histology at initial diagnosis, n Clear cell Predominantly clear cell	 9 1	 8 2
Median time since initial diagnosis, months (range)	(n = 9) 3.3 (1-19)	(n = 9) 24.0 (3-79)
Stage at screening, n IIIa IIIb IVa IVb	(n = 8) 0 1 5 2	(n = 9) 2 0 7 0
Histologic grade at initial diagnosis, n Well differentiated Poorly differentiated Undifferentiated Grade cannot be assessed	 4 3 3 0	 1 1 1 7
Measurable disease at screening, n Yes	 10	 10
Non-target lesions at screening, n Yes No	 9 1	 8 2
Metastatic disease at screening, n Yes	 10	 10
ECOG PS at baseline, n 0 1	 7 3	 9 1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.
[a] Six patients received pembrolizumab 2 mg/kg Q2W and 4 patients received pembrolizumab 2 mg/kg Q3W.
[b] All patients received pembrolizumab 2 mg/kg Q3W.

RESULTS (continued)

- 1 patient in the pazopanib 800-mg group experienced dose-limiting toxicity (DLT) with grade 3 elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase (ALP)
  - A safety review based on the first 6 patients enrolled in the dose-escalation cohort determined not to escalate the dose of pembrolizumab and also to explore a starting dose of pazopanib 600 mg
- All 20 patients experienced an AE, and most AEs were grade ≤ 2 (**Table 3**)
- The most common any-grade AEs (> 30%) in the pazopanib 800-mg group were ALT/AST elevation, nausea, diarrhea, headache, vomiting, arthralgia, and mucosal inflammation
- The most common any-grade AEs (> 30%) in the pazopanib 600-mg group were ALT/AST elevation, diarrhea, fatigue, headache, hypertension, rash, and cough
- The most common grade 3/4 AEs (> 30%) in both groups were ALT/AST elevation

Table 3. Summary of On-Therapy AEs (≥ 20%)

	Pazopanib 800 mg + Pembrolizumab[a] (n = 10)			Pazopanib 600 mg + Pembrolizumab[b] (n = 10)		
Preferred Term, n	Any Grade[c]	Grade 3	Grade 4	Any Grade[c]	Grade 3	Grade 4
Any event	10	5	2	10	8	1
ALT increased	7	5	1	6	5	1
AST increased	7	6	0	5	4	0
Nausea	7	0	0	3	0	0
Diarrhea	6	0	0	6	0	0
Headache	6	0	0	4	0	0
Vomiting	6	0	0	1	0	0
Arthralgia	5	0	0	2	0	0
Mucosal inflammation	4	0	0	1	0	0
Rash[d]	3	0	0	6	1	0
Fatigue	3	0	0	6	0	0
Hypertension	3	1	0	4	1	0
Hypothyroidism	3	0	0	2	0	0
Flushing/Hot flush	3	0	0	2	0	0
Pain in extremity	3	0	0	1	0	0
Musculoskeletal pain[e]	3	0	0	1	0	0
Edema[f]	3	0	0	1	0	0
Dysgeusia	2	0	0	3	0	0
Upper respiratory tract infection[g]	2	0	0	2	0	0
Dyspnea exertional	2	0	0	1	0	0
Oropharyngeal pain	2	0	0	0	0	0
Cough[h]	1	0	0	4	0	0
Hair color changes	1	0	0	3	0	0
Abdominal discomfort	1	0	0	2	0	0
Decreased appetite	0	0	0	3	0	0
Pyrexia	0	0	0	3	0	0
Chills	0	0	0	2	0	0
Contusion	0	0	0	2	0	0
Dry mouth	0	0	0	2	0	0
Insomnia	0	0	0	2	0	0
Venous thromboembolic event[i]	0	0	0	2	0	0
Not coded	0	0	0	2	0	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Six patients received pembrolizumab 2 mg/kg Q2W and 4 patients received pembrolizumab 2 mg/kg Q3W.
[b] All patients received pembrolizumab 2 mg/kg Q3W.
[c] Any grade includes grade 1-4 or missing grade.
[d] Rash includes rash, butterfly rash, rash pruritic, or rash maculo-papular.
[e] Musculoskeletal pain includes bone pain, musculoskeletal chest pain, musculoskeletal pain, or myalgia.
[f] Edema includes edema peripheral, edema, or periorbital edema.
[g] Upper respiratory tract infection includes upper respiratory tract infection or viral upper respiratory tract infection.
[h] Cough includes cough or upper-airway cough syndrome.
[i] Venous thromboembolic event includes portal vein thrombosis, pulmonary thrombosis, or venous thrombosis.

RESULTS (continued)

Table 4. Summary of Hepatobiliary Laboratory Abnormalities

Laboratory Criteria,[a] n	Pazopanib 800 mg + Pembrolizumab[b] (n = 10)	Pazopanib 600 mg + Pembrolizumab[c] (n = 10)
ALT > 3×ULN and total bilirubin ≥ 2×ULN[d]	1	1
ALT > 3×ULN and total bilirubin ≥ 2×ULN and ALP < 3×ULN/missing[d]	0	1
ALT (ULN)/ALP (ULN) ≥ 5 and ALT > 3×ULN	3	5
ALT or AST > 20×ULN > 8×ULN > 5×ULN > 3×ULN	 0 4 7 7	 1 5 6 6
ALT > 20×ULN > 8×ULN > 5×ULN > 3×ULN > 3×ULN and ≤ 3×ULN/missing at baseline	 0 3 7 7 7	 1 4 5 6 6
AST > 20×ULN > 8×ULN > 5×ULN > 3×ULN > 3×ULN and ≤ 3×ULN/missing at baseline	 0 4 6 7 7	 0 4 5 6 6
Total bilirubin ≥ 2×ULN ≥ 2×ULN and < 2×ULN/missing at baseline	 1 1	 1 1
ALP ≥ 3×ULN ≥ 3×ULN and < 3×ULN/missing at baseline	 3 3	 1 1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase, ULN, upper limit of normal.
[a] Patients may be counted in more than 1 category.
[b] Six patients received pembrolizumab 2 mg/kg Q2W and 4 patients received pembrolizumab 2 mg/kg Q3W.
[c] All patients received pembrolizumab 2 mg/kg Q3W.
[d] Bilirubin elevation can occur up to 28 days on or after ALT elevation.

- ALT or AST elevations > 5×ULN were observed in 7 and 6 patients in the pazopanib 800-mg group and 600-mg group, respectively; elevations in total bilirubin ≥ 2×ULN or ALP ≥ 3×ULN occurred less frequently (**Table 4**)
- After recovery from the first liver toxicity, 12 patients (out of 13 total) were re-challenged with pembrolizumab (2 mg/kg Q3W), and 8 of those patients subsequently resumed pazopanib
  - Liver function tests of all re-challenged patients remained grade ≤ 1 during pembrolizumab monotherapy
  - However, 6 patients experienced recurrence of ALT/AST elevation following re-challenge with pazopanib
    - All patients recovered with dose interruption/discontinuation plus corticosteroids
- The most common serious AEs (> 10%) were ALT/AST elevation (grade ≥ 3), which occurred in 13 patients (**Table 5**)
  - All patients subsequently recovered to grade ≤ 1 with dose interruption/discontinuation ± corticosteroids
- Preliminary pazopanib pharmacokinetics data were consistent with prior data

Table 5. Summary of Serious AEs

Preferred Term, n	Pazopanib 800 mg + Pembrolizumab[a] (n = 10)	Pazopanib 600 mg + Pembrolizumab[b] (n = 10)
Any event	6	5
ALT increased	3	4
AST increased	1	3
Atrioventricular block	1	0
Blood bilirubin increased	1	0
Cardiac failure congestive	1	0
Lipase increased	1	0
Nausea	1	0
Pathological fracture	1	0
Tubulointerstitial nephritis	1	0
Vomiting	1	0
Blood creatinine increased	0	1
Hypoglycemia	0	1
Venous thrombosis	0	1

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Six patients received pembrolizumab 2 mg/kg Q2W and 4 patients received pembrolizumab 2 mg/kg Q3W.
[b] All patients received pembrolizumab 2 mg/kg Q3W.

RESULTS (continued)

- 6 patients (60%) in the pazopanib 800-mg group and 4 patients (40%) in the pazopanib 600-mg group had discontinued pazopanib treatment
  - 4 discontinuations in each group were due to adverse events (AEs)
- 4 patients (40%) in each of the pazopanib 800-mg and 600-mg groups had discontinued pembrolizumab treatment
  - 3 patients in the pazopanib 800-mg group discontinued pembrolizumab due to disease progression
  - 3 patients in the pazopanib 600-mg group discontinued pembrolizumab due to AEs
- 6 patients in the pazopanib 800-mg group had pazopanib dose reductions due to AEs
  - Dose interruptions occurred in 8 patients mostly due to AEs (52%) or noncompliance (38%); most interruptions (63%) lasted ≤ 7 days
- 5 patients in the pazopanib 600-mg group had pazopanib dose reductions due to AEs
  - Dose interruptions occurred in 7 patients due to AEs; most interruptions (56%) lasted ≤ 7 days
- 6 patients had pembrolizumab dose delays in the pazopanib 800-mg group
  - Dose delays were due to AEs in 67% of cases and lasted ≤ 7 days in 50% of cases
- 4 patients had dose delays in the pazopanib 600-mg group
  - Dose delays were due to AEs in 50% of cases and lasted ≤ 7 days in 50% of cases

Efficacy

- The confirmed overall response rate was 60% in the pazopanib 800-mg group and 20% in the pazopanib 600-mg group (**Table 6**)
  - 1 patient in the pazopanib 800-mg group experienced a complete response

Table 6. Summary of Antitumor Activity

	Pazopanib 800 mg + Pembrolizumab[a] (n = 10)	Pazopanib 600 mg + Pembrolizumab[b] (n = 10)
Best response, n Complete response (CR) Partial response (PR) Stable disease Progressive disease	 1 5[c] 4 0	 0 2 7[d] 1
Overall response rate CR + PR, n 95% confidence interval	 6 (29.6%-90.4%)	 2 (0.0%-44.8%)

[a] Six patients received pembrolizumab 2 mg/kg Q2W and 4 patients received pembrolizumab 2 mg/kg Q3W.
[b] All patients received pembrolizumab 2 mg/kg Q3W.
[c] One additional CR was confirmed, but the site entered this information after data were transferred for output production.
[d] There were 2 unconfirmed PRs; those patients discontinued from the study.

CONCLUSIONS

- **Preliminary results of the combination of pazopanib plus pembrolizumab for the treatment of patients with aRCC showed significant hepatotoxicity, most likely secondary to pazopanib treatment**
- **Preliminary evidence of antitumor activity was observed**
- **New dosing schemes, such as sequential dosing, will be explored in the future**

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