Management of adverse events in the AMPECT trial of *nab*-sirolimus for the treatment of advanced malignant perivascular epithelioid cell neoplasm (PEComa)

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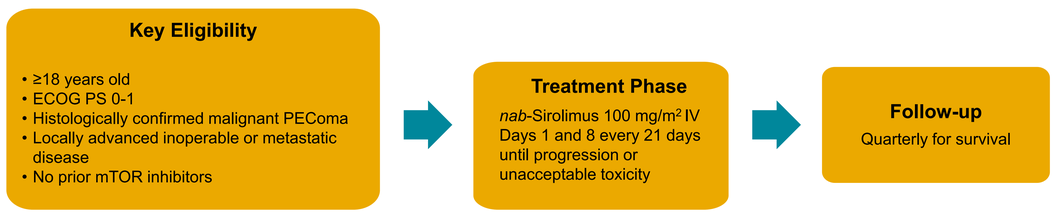
INTRODUCTION

- *nab*-Sirolimus is a mTOR inhibitor (mTORi) that utilizes albumin-bound nanoparticle technology and is approved in the United States for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumors (PEComas) based on the primary analysis results of the AMPECT trial, performed 6 months after the last patient enrolled[1,2]
- In preclinical animal models, treatment with *nab*-sirolimus resulted in significantly higher tumor uptake and tumor growth inhibition, and improved mTOR target suppression, with a distinct pharmacokinetic profile, relative to oral mTORi[3]
- Here, we describe adverse event (AE) management in AMPECT through 3 years after the primary analysis (database lock: April 29, 2022)

METHODS

- The AMPECT trial was an open-label, multicenter phase 2 single-arm study in adult patients (age ≥18 years) with a histologically confirmed diagnosis of malignant PEComa and Eastern Cooperative Oncology Group performance status score of ≤1 (**Figure 1**)

Figure 1. Study Design



ECOG, Eastern Cooperative Oncology Group; IV, intravenously; mTOR, mammalian target of rapamycin; PEComa, perivascular epithelioid cell tumor; PS, performance status.

- Patients received intravenous *nab*-sirolimus 100 mg/m^2 weekly for 2 weeks, on Days 1 and 8, in a 21-day cycle
- Treatment was continued until unacceptable toxicity, disease progression, withdrawal of consent, or removal due to physician discretion
- If a clinically significant AE occurred, dose reductions or delays of *nab*-sirolimus were considered
- Two sequential dose reductions to 75 and 56 mg/m^2 were permitted for management of AEs

RESULTS

- All treated patients (N=34) experienced ≥1 treatment-related AE (TRAE), including 8 patients with serious TRAEs and 2 treatment discontinuations due to TRAEs (anemia and noninfectious cystitis)
- The majority of TRAEs (>90%) were grade 1 or grade 2 events
- AEs of special interest (AESIs) were preidentified at the start of the study on the basis of class effects of mTORis and frequency in the first in-human dose-finding safety study (NCT00635284)
  - AESIs included stomatitis and pneumonitis, which occurred in 28/34 (82%) and 7/34 (21%) patients, respectively
  - Of the 56 stomatitis events among 28 patients, 91% (51/56) resolved; 45% (23/51) resolved without action taken, and 55% (28/51) resolved with dose modifications, and/or concomitant medications
    - Stomatitis was most commonly managed with steroid mouthwash, and 68% of all patients received stomatological preparations (most frequently magic mouthwash, sucralfate, nystatin, and dexamethasone)
  - Of the 22 pneumonitis events in 7 patients, 95% (21/22) resolved; 33% (7/21) resolved without intervention, and 67% (14/21) resolved with dose modifications, and/or concomitant medication/procedure
    - For grade 2 pneumonitis events, study drug was held for up to 3 weeks until resolution to grade ≤1 followed by a dose reduction, and for grade ≥3, the patient was permanently removed from protocol treatment; however, there were no discontinuations due to pneumonitis
- Of the 31 efficacy-evaluable patients, 14 patients had at least 1 dose reduction, and 3 of the 14 patients received 2 dose reductions during the study (**Figure 2**)
- Most (76%) dose reductions occurred within the first 3 months of treatment
  - For the 3 patients experiencing 2 dose reductions, the first reduction occurred at 0.7, 1.2, and 38.5 months, and the second dose reduction occurred at 1.9, 2.1, and 57.6 months, respectively
- Thirteen of the 14 patients had a dose reduction due to AEs, all of which were deemed treatment-related by the investigator
- Patients with at least 1 dose reduction (**Figure 2**) discontinued study drug due to disease progression (patients 3-7, 10, and 13-14), death (patient 8), commencement of new treatment (surgery; patient 9), withdrawal of consent (patients 11 and 12), study closure by sponsor (patient 1), and unknown (patient 2)
  - None of the patients who received a dose reduction discontinued *nab*-sirolimus due to an AE
- The most frequent TRAEs leading to dose reduction were pneumonitis (5/18) and stomatitis (3/18); others included alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, acute coronary syndrome, abdominal pain, hyperglycemia, thrombocytopenia, increased creatinine, weight decreased, dehydration, and fatigue, all in 1 patient each (**Table 1**)

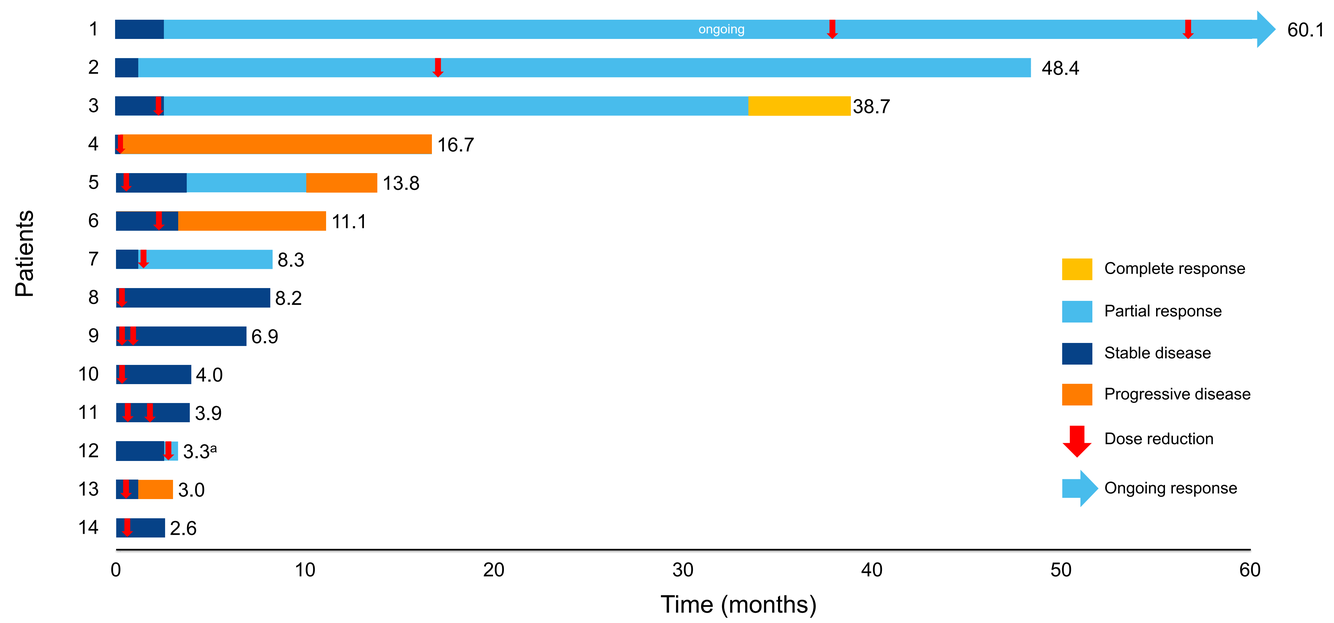
Table 1. Frequency of TRAEs Leading to Dose Reduction

TRAE (N = 18)	Frequency, n (%)
Pneumonitis	5 (27.8)
Stomatitis	3 (16.7)
Abdominal pain	1 (5.6)
Acute coronary syndrome	1 (5.6)
Dehydration	1 (5.6)
Fatigue	1 (5.6)
Hyperglycemia	1 (5.6)
Increased ALT	1 (5.6)
Increased AST	1 (5.6)
Increased creatinine	1 (5.6)
Thrombocytopenia	1 (5.6)
Weight decreased	1 (5.6)

Frequency (>5%) of TRAEs leading to dose reduction. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

- Seventeen of the 18 TRAEs leading to dose reduction ultimately resolved
- Five of 14 patients with a dose reduction had a confirmed response either prior to (3/5) or after (2/5) their first dose reduction
- All 5 responders maintained their response for 6.1 to 37.3 months following the first dose reduction (**Figure 2**)
- Two patients with dose reductions at 38.5 and 18.4 months were on *nab*-sirolimus 60.1 and 48.4 months, respectively, with a partial response
- One patient with a dose reduction at 2.1 months converted to a complete response at 33.9 months (**Figure 2**)

Figure 2. Patients With at Least 1 Dose Reduction



Best overall responses shown in figure 2 are based on independent radiologist review; however, treatment decisions were made by the treating investigator based on radiology review and clinical symptoms. [a]The patient had unconfirmed PR and discontinued therapy due to an AE without a confirmatory scan. AE, adverse event.

CONCLUSION

- AEs due to *nab*-sirolimus treatment in the AMPECT trial were manageable, and dose reductions for AE management did not appear to compromise efficacy in responders

REFERENCES

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