Response to Treatment With nab-Sirolimus Among Patients with Primary Uterine PEComa: A Subanalysis From AMPECT

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BACKGROUND

- Malignant perivascular epithelioid cell tumor (PEComa) is an aggressive, rare sarcoma, with a strong female predominance, for which cytotoxic chemotherapies provide limited patient benefit
- PEComas most frequently affect the uterus within the female genital tract1
- Inactivation of TSC1 or TSC2 tumor suppressor genes, upstream of mTORC1, is commonly associated with malignant PEComa; therefore, the mammalian target of rapamycin (mTOR) pathway presents an opportunity for targeted therapy
- The treatment of uterine or gynecologic PEComa with mTOR inhibitors (mTORis) has been reported in a small number of patients in the medical literature to have high response rates2
- A retrospective analysis by Sanfilippo et al. reported that patients with uterine PEComas had numerically lower response rates to mTORis compared to those with extraterine primary tumors, confirming that further studies are needed in the uterine PEComa subset3
- nab-Sirolimus is a novel intravenous mTORi that utilizes albumin-bound nanoparticle technology to achieve greater tumor growth inhibition, higher intratumoral drug levels and more complete pathway suppression than conventional mTORis4
- nab-Sirolimus is approved by the US Food and Drug Administration for the treatment of adults with locally advanced unresectable or metastatic malignant PEComa based on the primary analysis results of the AMPECT trial, which showed a confirmed overall response rate (ORR) of 38.7%, regardless of mutational status5
- Here, we describe outcomes of a subset of patients with primary uterine PEComas, representing 23% of the efficacy-evaluable patients in AMPECT

METHODS

- AMPECT was an open-label, multicenter, phase 2 registration study in adult patients (≥18 years) with a histologically confirmed diagnosis of malignant PEComa by a gynecological pathologist, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≤1
- All 7 patients had ≥1 TRAE (grade 3, 43%); no grade ≥4 or serious TRAEs occurred
- Of the 31 efficacy-evaluable patients in AMPECT, 7 patients with uterine PEComas were treated with nab-sirolimus and were evaluable for both safety and efficacy
- The ECOG PS at baseline was 0 for all 7 patients with uterine PEComas
- The median age of all 7 females was 64 years, and 71% (n=5) were White
- Three patients (43%) had grade ≥3 elevated amylase and insomnia
- Grade 3 nonhematological TRAEs were as follows: stomatitis (86%); edema and rash (each 71%); decreased appetite, fatigue, and nausea (each 57%)
- The most common nonhematological TRAEs were as follows: stomatitis (86%); edema and rash (each 71%); decreased appetite, fatigue, and nausea (each 57%)
- Treatment Phase: nab-sirolimus (100 mg/m2) on Days 1 and 8 of a 21-day cycle until progression or unacceptable toxicity (Figure 1)
- Follow-up: Key Eligibility
- Treatable, histologically confirmed malignant PEComa
- Locally advanced unresectable or metastatic disease
- Nab-sirolimus-related TRAEs
- The primary endpoint was ORR (defined as the number of patients with a partial response [PR] and complete response [CR]) by independent radiology review
- Secondary endpoints included time to response, duration of response (DOR), progression-free survival, and safety, including treatment-related adverse events (TRAEs), serious TRAEs, and TRAEs leading to drug withdrawal or dose reduction
- The disease control rate (DCR); an exploratory endpoint, was defined as CR + PR + stable disease (SD) of ≥12 weeks
- The ORR was 42.9% (95% CI, 9.9%–96.3%).

RESULTS

- Of the 31 efficacy-evaluable patients in AMPECT, 7 patients with uterine PEComas were treated with nab-sirolimus and were evaluable for both safety and efficacy
- The median age of all 7 females was 64 years, and 71% (n=5) were White
- Of the 7 patients, 2 had TSC2, and 7 had TSC1 inactivating alterations
- Six of the 7 patients presented with ≥1 metastatic sites at baseline, and 1 patient presented with ≥2 metastatic sites
- Prior treatment included surgery for all 7 patients (100%) and prior chemotherapy for 1 patient (14%)
- The ECOG PS at baseline was 0 for all 1 patients
- The ORR was 42.9% (95% CI, 9.9%–96.3%)
- Three patients (43%, 95% CI, 9.9%–81.8%) had a confirmed PR, of which all 3 responses (Figure 2) were seen in patients with tumors harboring somatic inactivating alterations in TSC1 or TSC2
- Two patients (28.6%, 95% CI, 7.7%–71.0%) had confirmed SD with at least 12-week duration, and 2 patients (28.6%, 95% CI, 3.7%–71.0%) had progressive disease
- DOR (n=5) was 71.4% (95% CI, 29.0%–96.3%)
- Time to response for the 3 responders was rapid (1.4, 1.4, and 1.5 months; Figure 3)
- DOR was 5.6, 36.0+, and 39.7 months for the 3 responders (Figure 3)
- Median DOR was 39.7 months (95% CI, 5.6 months to not evaluable [NE] for responders
- Median progression-free survival was 6.9 months (95% CI, 1.3 months to not reached)
- All 7 patients had ≥1 TRAE (grade 3, 43%); no grade ≥4 or serious TRAEs occurred
- Four patients (57%) and 2 patients (29%) experienced a TRAE that led to drug interruption or dose reduction, respectively; however, no patients had the drug withdrawn due to a TRAE

CONCLUSION

- The ORR of 42.9% was similar to that reported for the overall population treated in AMPECT (ORR = 38.7%) and contrasts with a retrospective report of lower antitumor activity (12.5% ORR) in uterine PEComas with the use of mTORis6
- Responses were rapid and durable
- Notably, all responders in this uterine malignant PEComa subset had TSC1 or TSC2 inactivating alterations, although there were too few patients included to draw conclusions regarding efficacy in tumors without these alterations
- The safety profile for this subset of patients was consistent with what has been observed with nab-sirolimus and other mTORis; TRAEs were manageable without leading to drug discontinuation
- nab-Sirolimus is being further evaluated in a tumor-agnostic trial of patients with TSC1 or TSC2 inactivating alterations (PRECISION; NCT07510308)

REFERENCES