Doxorubicin plus lurbinectedin in patients with advanced endometrial cancer: results from an expanded phase I study

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HIGHLIGHTS
- This phase I trial suggests a synergistic effect for lurbinectedin and doxorubicin.
- In the expansion phase, response rate was 42.1% and duration of response was 7.5 months for the combination of doxorubicin plus lurbinectedin.
- Median progression-free survival was 7.7 months and median overall survival was 14.2 months.

ABSTRACT
Objective Second-line treatment of endometrial cancer is an unmet medical need. We conducted a phase I study evaluating lurbinectedin and doxorubicin intravenously every 3 weeks in patients with solid tumors. The aim of this study was to characterise the efficacy and safety of lurbinectedin and doxorubicin for patients with endometrial cancer.

Methods Thirty-four patients were treated: 15 patients in the escalation phase (doxorubicin 50 mg/m² and lurbinectedin 3.0–5.0 mg) and 19 patients in the expansion cohort (doxorubicin 40 mg/m² and lurbinectedin 2.0 mg/m²). All histological subtypes were eligible and patients had received one or two prior lines of chemotherapy for advanced disease. Antitumor activity was evaluated every two cycles according to the Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.

Results Median age (range) was 65 (51–78) years. Eastern Cooperative Oncology Group performance status was up to 1 in 97% of patients. In the escalation phase, 4 (26.7%) of 15 patients had confirmed response: two complete and two partial responses (95% CI 7.8% to 55.1%). Median duration of response was 19.5 months. Median progression-free survival was 7.3 (2.5 to 10.1) months. In the expansion cohort, confirmed partial response was reported in 8 (42.1%) of 19 patients (95% CI 20.3% to 66.5%). Median duration of response was 7.5 (6.4 to not reached) months, median progression-free survival was 7.7 (2.0 to 16.7) months and median overall survival was 14.2 (4.5 to not reached) months. Fatigue (26.3% of patients), and transient and reversible myelosuppression (neutropenia, 78.9%; febrile neutropenia, 21.1%; thrombocytopenia, 15.8%) were the main grade 3 and higher toxicities in the expanded cohort.

Conclusions In patients with recurrent advanced endometrial cancer treated with doxorubicin and lurbinectedin, response rates (42%) and duration of response (7.5 months) were favorable. Further evaluation of doxorubicin and lurbinectedin is warranted in this patient population.

INTRODUCTION
Relapsed endometrial cancer has a poor prognosis with a median survival of 12–15 months. This patient population has a significant unmet clinical need and optimal treatment is yet to be established. There are promising signs of clinical efficacy with anti-programmed death-1 targeting drugs for mismatch repair deficient relapsed endometrial cancer and combination treatment with pembrolizumab plus lenvatinib in microsatellite stable recurrent endometrial cancer. Recently, dostarlimab was approved for second-line treatment of adult patients with advanced or recurrent mismatch repair deficient disease. Biomarkers such as overexpression of poly-merase epsilon, proto-oncogene Neu, and microsatellite instability or mismatch repair deficiency are increasingly being used in the setting of recurrent disease. However, single agent chemotherapy remains the most frequent treatment for relapsed endometrial cancer.

Lurbinectedin is a minor groove targeting DNA binder that interacts with specific factors involved in DNA repair and transcription pathways, thereby inhibiting trans-activated transcription in tumor cells, and also transcription and secretion of selected cytokines by tumor-associated macrophages. In June 2020, the United States Food and Drug Administration (FDA) granted accelerated approval to lurbinectedin for adult patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy. Lurbinectedin plus doxorubicin showed synergistic antitumor effect in small cell lung cancer xenografted tumors. Improved activity with this combination and activity observed for lurbinectedin.
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Original research

in a study of humans6 prompted a phase I trial to evaluate this combination in advanced solid tumors.7 During the dose escalation, activity was promising in two tumor types—small cell lung cancer and endometrial cancer—and expansion cohorts were evaluated. We show the results observed in advanced endometrial cancer during dose escalation and cohort expansion, exploring a modified regimen to reduce myelosuppression.

METHODS

Patients were enrolled in sites from Spain and the United Kingdom. The study followed the International Conference on Harmonization Good Clinical Practice guidelines, and was approved by the respective Research Ethics Committees for each country. Written informed consent was obtained from all patients. The trial is registered in the European Clinical Trials Register database (EudraCT 2010-024291-25) and at ClinicalTrials.gov (NCT01970540).

Eligibility Criteria

Eligible patients were aged 18 years and older with endometrial cancer treated with one or two prior lines of cytotoxic chemotherapy for advanced disease and were anthracycline naïve; had documented disease progression during or immediately after their last therapy in those treated in the expansion cohort; had recovered from previous toxicities (at least 3 weeks since last anticancer therapy; had life expectancy of 3 months or more; had Eastern Cooperative Oncology Group performance status of 2 or lower; had normal left ventricular ejection fraction; and had adequate bone marrow, hepatic and renal function, including albumin ≥3.0 g/dL. Prior endocrine therapy was allowed (not considered a line of treatment).

Patients were excluded if they had symptomatic progressive or corticosteroid-requiring brain metastases or leptomeningeal involvement; had prior bone marrow/stem cell transplantation, cardiac disease, uncontrolled alcohol consumption or cirrhosis, active uncontrolled infection, or any disease potentially interfering with the study outcome.

Study Design and Treatment

Study design is summarized in Figure 1. Dose escalation has been described elsewhere.7 Briefly, 74 patients with advanced solid tumors (15 patients with endometrial cancer) were included using a 3+3 cohort design. Four dose levels were evaluated: fixed doxorubicin 50 mg/m² as an intravenous bolus with escalating flat doses of lurbinectin (3.0, 3.5, 4.0 and 5.0 mg) intravenously over 1 hour on day 1 every 3 weeks. The recommended dose was doxorubicin 50 mg/m² plus lurbinectin 4.0 mg.

After identification of the recommended dose and encouraging antitumor activity, expansion cohorts were started in small cell lung cancer and advanced endometrial cancer. Results for the expanded small cell lung cancer cohort are described elsewhere.7 This report focuses on the endometrial cohort. In this expanded cohort, patients were treated with a new recommended dose, doxorubicin 40 mg/m² intravenous bolus plus lurbinectin 2.0 mg/m² 1 hour intravenous infusion, using the same schedule (day 1 every 3 weeks) as the dose escalation phase. Doxorubicin dose was lowered to 40 mg/m² and lurbinectin dose was transformed to a body surface area based dose to reduce severe myelosuppression. This change was introduced in a protocol amendment because dose-limiting toxicities were found in several patients with small cell lung cancer and endometrial cancer at the initial recommended dose (doxorubicin 50 mg/m² plus lurbinectin 4.0 mg). All dose-limiting toxicities reported in patients with endometrial cancer were neutropenia related and 86.4% of patients with small cell lung cancer had grade 4 neutropenia. These findings suggested that the initial recommended dose might not be feasible in these patient populations. Both doxorubicin and lurbinectin doses were capped at a body surface area of 2.0 m². Furthermore, to prevent cardiomyopathy,8 patients who received 10 cycles of the combination (before a

Figure 1 Study design. DLT, dose-limiting toxicity; FD, flat dose; MTD, maximum tolerated dose; q3wk, every 3 weeks; RD, recommended dose.
cumulative dose of 450 mg/m² was reached), or discontinued doxorubicin due to a cardiac adverse event, continued treatment with lurbinectedin alone (4.0 mg/m² on day 1 every 3 weeks).

All patients received standard antiemetic prophylaxis before each infusion. Treatment was given until disease progression, unacceptable toxicity, intercurrent illness precluding study continuation, patient refusal and/or non-compliance with study requirements, treatment delay greater than 15 days (except if clear clinical benefit), and requirement of more than two dose reductions.

Study Assessments
Antitumor activity was evaluated every two cycles according to the Response Evaluation Criteria in Solid Tumors version 1.1 (responses confirmed at least 4 weeks later). Overall response rate was the percentage of patients with confirmed complete or partial response. Time-to-event parameters were duration of response and progression-free survival. Progression-free survival was defined as the time from the date of first infusion of study treatment to the date of progression or death (due to any cause). Overall survival was reported only in the dose expansion phase as an exploratory assessment. Overall survival was defined as the time from the date of first infusion of study treatment to the date of death (due to any cause).

Adverse events were coded with the Medical Dictionary for Regulatory Activities version 14.1 and graded using the National Cancer Institute–Common Terminology Criteria for Adverse Events version 4. Laboratory abnormalities (hematological and biochemical) were measured weekly in the first cycle, and on day 1 and day 10 in further cycles, and graded using the National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.

Statistical Analysis
Continuous variables were presented with summary statistics and categorical variables in frequency tables. Time-to-event variables were calculated using the Kaplan-Meier approach. Binomial exact distribution was used to calculate 95% CI intervals for categorical variables.

RESULTS
Dose Feasibility for the New Recommended Dose
Forty-seven patients were treated with doxorubicin 40 mg/m² plus lurbinectedin 2.0 mg/m² every 3 weeks in the expansion cohort; 28 patients with small cell lung cancer and 19 patients with endometrial cancer. Dose-limiting toxicities occurred in four of 46 evaluable patients (9%); this percentage was lower than the threshold (one third) established by the study protocol to define the recommended dose, thereby confirming dose feasibility. All dose-limiting toxicities occurred in small cell lung cancer patients, and comprised grade 3/4 febrile neutropenia (n=2), grade four thrombocytopenia, and grade three decreased appetite (n=1 each).

Characteristics of Patients With Endometrial Cancer
Thirty-four patients with advanced endometrial cancer were treated in this phase I study: 15 patients during the escalation phase and 19 patients in the expansion cohort (Table 1). Median age was 64 (range 51–78) years in the escalation phase and 66 (55–73) years in the expansion cohort, and most patients (23/34; 67.6%) had Eastern Cooperative Oncology performance status score of 1.

| Table 1 | Baseline characteristics of patients with endometrial cancer |
|---------|---------------------------------------------------------------|
| Dose escalation phase (n=15)* | Expanded cohort (n=19)† |
| Median age (range) (years) | 64 (51–78) | 66 (55–73) |
| ECOG performance status | | |
| 0 | 4 | 26.7 |
| 1 | 11 | 73.3 |
| 2 | – | – |
| Median BSA (range) (m²) | 1.7 (1.4–2.1) | 1.8 (1.6–2.3) |
| Bulky disease (lesion >50mm) | 5 | 38.5 |
| Visceral disease | 7 | 46.7 |
| Histology | | |
| Endometrioid | 11 | 73.3 |
| Carcinosarcoma | 3 | 20.0 |
| Clear cell | 1 | 6.7 |
| Serous/papillary | – | – |
| Median No of sites (range) | 2 (1–5) | 2 (1–3) |
| Most common metastatic sites | | |
| Lymph nodes | 9 | 60.0 |
| Lung | 6 | 40.0 |
| Peritoneum | 2 | 13.3 |
| Pelvis | 2 | 13.3 |
| Liver | 2 | 13.3 |
| Prior therapy | | |
| Chemotherapy | 15 | 100.0 |
| Surgery | 10 | 66.7 |
| Radiotherapy | 6 | 40.0 |
| Hormonal therapy | 4 | 26.7 |
| Biological therapy | 1 | 6.7 |
| Prior chemotherapy lines | | |
| Median (range) | 1 (1–2) | 1 (1–2) |
| 1 | 11 | 73.3 |
| 2 | 4 | 26.7 |
| Lines for advanced disease, median (range) | 1 (0–2) | 1 (0–2) |
| Most common prior anticancer agents | | |
| Platinum compounds | 9 | 60.0 |
| Taxanes | 8 | 53.3 |
| Platinum-free interval | 4.5 (0.3–17.1) | 4.3 (0.3–16.5) |

*Patients treated at fixed doxorubicin dose (50 mg/m²) and escalating lurbinectedin doses (ranging from 3.0 to 5.0 mg flat dose) on day 1 every 3 weeks.
†Patients treated at the recommended dose of doxorubicin 40 mg/m² plus lurbinectedin 2.0 mg/m² on day 1 every 3 weeks.
BSA, body surface area; ECOG, Eastern Cooperative Oncology Group;
0.3–17.1) months in the escalation phase and 4.3 (0.3–16.5) months in the expansion cohort.

### Treatment Exposure

In the escalation phase, the median number of cycles per patient was 8 (range 1–52). Median relative dose intensity for doxorubicin and lurbinectedin was 95.0% and 83.7%, respectively. Treatment-related cycle delays, dose reductions and discontinuations were observed in 79%, 71% and 13% of patients, mainly because of hematological toxicity. In the expansion cohort, the median number of cycles per patient was 9 (range 1–28). Median relative dose intensity for doxorubicin and lurbinectedin was 95.0% and 90.3%, respectively. Treatment-related cycle delays, dose reductions and discontinuations were observed in 65%, 47% and 11% of patients, also mainly because of hematological toxicity.

### Efficacy

In the escalation phase, four (26.7%) of 15 patients had confirmed responses: two complete responses and two partial responses (95% CI 7.8% to 55.1%). The two patients with complete response were treated with lurbinectedin 4.0 and 5.0 mg/m²; the two patients with partial response were treated with lurbinectedin 3.0 and 4.0 mg/m². Median duration of response was 19.5 (8.2 to not reached) months and median progression-free survival was 7.3 (2.5 to 10.1) months (Table 2).

In the expansion cohort, 8 (42.1%) of 19 patients had confirmed partial responses (95% CI 20.3% to 66.5%). Median duration of response was 7.5 (6.4 to not reached) months, median progression-free survival was 7.7 (2.0 to 16.7) months and median overall survival was 14.2 (4.5 to not reached) months (Table 2).

In the escalation phase and 46.7% (21.3% to 73.4%) in the expansion cohort. The overall response rate in patients with non-endometrioid types (n=8) was 0% in the escalation phase and 25% (0.6% to 80.6%) in the expansion cohort. Duration of response in each responder patient is shown in Figure 3.

### Safety

The most frequent treatment-related (or with unknown relationship) adverse events reported in the escalation phase were fatigue (80.0%), nausea (80.0%), decreased appetite (60.0%), mucositis (46.7%) and vomiting (46.7%). Grade 3 and higher adverse events consisted of febrile neutropenia (40%), fatigue (20%), and diarrhea, nausea and vomiting (7% each). However, patients received different doses, some being lower or higher than the recommended dose. Hence, the safety results are more focused on the patients treated in the expansion cohort (Table 3). The most frequent adverse

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**Table 2** Efficacy results with lurbinectedin plus doxorubicin in patients with endometrial cancer

|                          | Dose escalation phase (n=15)* | Expanded cohort (n=19)† |
|--------------------------|-------------------------------|-------------------------|
| Objective response per RECIST v1.1. |                               |                         |
| CR, n (%)                | 2 (13.3)                      | –                       |
| PR, n (%)                | 2 (13.3)                      | 8 (42.1)                |
| SD ≥4 months, n (%)      | 5 (33.3)                      | 4 (21.1)                |
| SD <4 months, n (%)      | 3 (20.0)                      | 3 (15.8)                |
| PD, n (%)                | 3 (20.0)                      | 4 (21.1)                |
| ORR, % (95% CI)          | 26.7 (7.8 to 55.1)            | 42.1 (20.3 to 66.5)     |
| Disease control rate (95% CI) ‡ | 80.0 (51.9 to 95.7)           | 78.9 (54.4 to 93.9)     |
| Clinical benefit rate (95% CI) § | 60.0 (32.3 to 83.7)           | 63.2 (38.4 to 83.7)     |
| Median DoR (months) (95% CI) | 19.5 (8.2 to NR)              | 7.5 (6.4 to NR)         |
| Median PFS (months) (95% CI) | 7.3 (2.5 to 10.1)             | 7.7 (2.0 to 16.7)       |
| Median OS (months) (95% CI) | NA                            | 14.2 (4.5 to NR)        |

*Patients treated at fixed doxorubicin dose (50 mg/m²) and escalating lurbinectedin doses (ranging from 3.0 to 5.0 mg flat dose) on day 1 every 3 weeks.
†Patients treated at the recommended dose of doxorubicin 40 mg/m² plus lurbinectedin 2.0 mg/m² on day 1 every 3 weeks.
‡Objective response plus stable disease.
§Objective response plus stable disease ≥4 months.
CR, complete response; DoR, duration of response; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease.
events were fatigue (78.9%), nausea (68.4%), alopecia (52.6%), constipation (42.1%), and diarrhea, mucositis and vomiting (26.3% each). No cardiac toxicities related to left ventricular ejection fraction occurred. Grade 3 and higher adverse events consisted of fatigue (26.3%), febrile neutropenia (21.1%), and diarrhea, lower respiratory tract infection, neutropenic infection and renal failure acute (5.3% each).

In the escalation phase, grade 3 and higher hematological laboratory abnormalities consisted of anemia (80.0%), neutropenia (93.3%; grade 4, 86.7%), and thrombocytopenia (46.6%; grade 4, 33.3%). In the expansion cohort, grade 3 and higher hematological laboratory abnormalities consisted of anemia (31.6%), neutropenia (78.9%; grade 4, 63.2%), and thrombocytopenia (15.8%; grade 4, 10.5%) (Table 3). Grade 4 neutropenia was transient with a median duration of 2 days (range 1–6 days). Most biochemical laboratory abnormalities were grade 1 or 2 with no effects on the study treatment.

One patient died due to a doxorubicin-related adverse event, acute monocytic leukemia, which was detected 129 days after the last study treatment infusion (during follow-up for survival). This patient had previously received pelvic radiotherapy and brachytherapy as well as carboplatin and paclitaxel.

**DISCUSSION**

**Summary of Main Results**
The overall response rate was 42.1%, median duration of response was 7.5 months, median progression-free survival was 7.7 months and median overall survival was 14.2 months in patients with recurrent advanced endometrial cancer treated with doxorubicin (40 mg/m²) and lurbinectedin (2.0 mg/m²) on day 1 every 3 weeks.

**Results in the Context of Published Literature**
Based on the results from KEYNOTE-146/Study 111, the US FDA granted accelerated approval to pembrolizumab/lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high or mismatch repair deficient with disease progression following prior systemic therapy and in candidates for curative surgery or radiation.12 In this phase I/II study, the final primary efficacy analysis results in a group of 94 patients with microsatellite stable-H/mismatch repair proficient disease showed an overall response rate of 37.2%, disease control rate of 84.0% and clinical benefit rate of 58.5%.13 Time-to-event data were not available, and two confirmatory phase III trials (ClinicalTrials.gov identifier NCT03884101 and NCT03517449) are currently underway. Despite promising clinical efficacy, this study reported treatment-related adverse events leading to dose interruptions in 74% of patients and dose reductions in 53% of patients, with a high discontinuation rate (9%). Doxorubicin 40 mg/m² plus lurbinectedin 2.0 mg/m² every 3 weeks in combination showed similar antitumor activity than pembrolizumab/lenvatinib: overall response rate of 42.1% versus 37.2%; disease control rate of 78.9% versus 84.0%, and clinical benefit rate of 63.2% versus 58.5%; and activity was seen across both endometrioid and non-endometrioid histologies.

Furthermore, the results observed for the doxorubicin plus lurbinectedin combination compare favorably with those previously...
observed in advanced or relapsed endometrial cancer with several agents tested in the second-line setting. Overall, antitumor activity in these previous studies was modest, with response rate ranging between 0% and 27%, paclitaxel being the most active (Table 4).

The median progression-free survival (7.7 months) and median overall survival (14.2 months) observed with doxorubicin plus lurbinectin can be considered promising. The median progression-free survival was similar to the 7.4 months reported with pembrolizumab/lenvatinib. Shorter median progression-free survival (3.4–4.2 months) and overall survival (10.5–12.3 months) have been found with palliative chemotherapy and antiangiogenic therapies in recurrent endometrial cancer. Activity with lurbinectin has been found in other studies conducted in advanced endometrial cancer. In a phase II basket study, 40 patients with endometrial cancer treated with lurbinectin 3.2 mg/m² every 3 weeks showed an overall response rate of 12.5% (one complete and four partial responses), median

| Treatment-related adverse events ‡ | 1/2 | 3 | 4 | Total† |
|---|---|---|---|---|
| N | % | N | % | N | % | N | % |
| Fatigue | 10 | 52.6 | 5 | 26.3 | – | – | 15 | 78.9 |
| Nausea | 13 | 68.4 | – | – | – | – | 13 | 68.4 |
| Alopecia | 10 | 52.6 | – | – | – | – | 10 | 52.6 |
| Constipation | 8 | 42.1 | – | – | – | – | 8 | 42.1 |
| Diarrhea | 4 | 21.1 | 1 | 5.3 | – | – | 5 | 26.3 |
| Mucositis | 5 | 26.3 | – | – | – | – | 5 | 26.3 |
| Vomiting | 5 | 26.3 | – | – | – | – | 5 | 26.3 |
| Decreased appetite | 4 | 21.1 | – | – | – | – | 4 | 21.1 |
| Dysgeusia | 4 | 21.1 | – | – | – | – | 4 | 21.1 |
| Febrile neutropenia | – | – | 2 | 10.5 | 2 | 10.5 | 4 | 21.1 |
| Myalgia | 3 | 15.8 | – | – | – | – | 3 | 15.8 |
| Dyspepsia | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Epistaxis | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Pain in extremity | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Palmar-planter erythrodynesthesi syndrome | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Palpitations | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Peripheral edema | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Peripheral sensory neuropathy | 2 | 10.5 | – | – | – | – | 2 | 10.5 |
| Acute renal failure | – | – | 1 | 5.3 | – | – | 1 | 5.3 |
| Lower respiratory tract infection | – | – | 1 | 5.3 | – | – | 1 | 5.3 |
| Neutropenic infection | – | – | 1 | 5.3 | – | – | 1 | 5.3 |

Laboratory abnormalities

| Anemia | 13 | 68.4 | 6 | 31.6 | – | – | 19 | 100.0 |
| Neutropenia | 4 | 21.1 | 3 | 15.8 | 12 | 63.2 | 19 | 100.0 |
| Creatinine increased | 15 | 78.9 | – | – | 1 | 5.3 | 16 | 84.2 |
| Thrombocytopenia | 11 | 57.9 | 1 | 5.3 | 2 | 10.5 | 14 | 73.7 |
| AP increased | 10 | 52.6 | 1 | 5.3 | – | – | 11 | 57.9 |
| ALT increased | 8 | 42.1 | 2 | 10.5 | – | – | 10 | 52.6 |
| AST increased | 8 | 42.1 | – | – | – | – | 8 | 42.1 |
| Bilirubin increased | 2 | 10.5 | – | – | – | – | 2 | 10.5 |

*Adverse events and laboratory abnormalities ordered by incidence from higher to lower.
†No grade 5 adverse events were reported.
‡Including adverse events with unknown relationship.
AP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, v4.
A phase III trial compared ixabepilone with doxorubicin and demonstrated a synergistic effect of both lurbinectedin and doxorubicin when given in combination, concordant with observations in preclinical studies. The safety analysis supporting the accelerated approval included adverse events in 52% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Subsequent efforts are focused on exploiting the molecular biology of this disease for targeted-specific and immunotherapeutic approaches. However, patients with endometrial cancer are often older than 65 years and have comorbidities, and tolerability of treatment is an important consideration, especially with targeted therapy combinations. Pembrolizumab/lenvatinib is associated with substantial toxicity, with treatment-related and grade 3 or 4 adverse events observed in 97% and 67% of patients in the KEYNOTE-111 and monotherapy trials that evaluated the contribution of each drug to the safety profile of the combination. Fatal adverse reactions with pembrolizumab occurred in 57.4% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Immune-mediated adverse events or infusion-related reactions with pembrolizumab occurred in 57.4% of patients. The safety analysis supporting the accelerated approval included adverse events in 52% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Subsequent efforts are focused on exploiting the molecular biology of this disease for targeted-specific and immunotherapeutic approaches. However, patients with endometrial cancer are often older than 65 years and have comorbidities, and tolerability of treatment is an important consideration, especially with targeted therapy combinations. Pembrolizumab/lenvatinib is associated with substantial toxicity, with treatment-related and grade 3 or 4 adverse events observed in 97% and 67% of patients in the KEYNOTE-111 and monotherapy trials that evaluated the contribution of each drug to the safety profile of the combination. Fatal adverse reactions with pembrolizumab occurred in 57.4% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Immune-mediated adverse events or infusion-related reactions with pembrolizumab occurred in 57.4% of patients. The safety analysis supporting the accelerated approval included adverse events in 52% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Subsequent efforts are focused on exploiting the molecular biology of this disease for targeted-specific and immunotherapeutic approaches. However, patients with endometrial cancer are often older than 65 years and have comorbidities, and tolerability of treatment is an important consideration, especially with targeted therapy combinations. Pembrolizumab/lenvatinib is associated with substantial toxicity, with treatment-related and grade 3 or 4 adverse events observed in 97% and 67% of patients in the KEYNOTE-111 and monotherapy trials that evaluated the contribution of each drug to the safety profile of the combination. Fatal adverse reactions with pembrolizumab occurred in 57.4% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Immune-mediated adverse events or infusion-related reactions with pembrolizumab occurred in 57.4% of patients. The safety analysis supporting the accelerated approval included adverse events in 52% of patients. Hypothyroidism was the most frequent adverse event occurring in a greater proportion of patients (48%). Immune-mediated adverse events or infusion-related reactions with pembrolizumab occurred in 57.4% of patients.
well tolerated, and associated with manageable and predictable myelotoxicity. Patients received a median of nine cycles and relative dose intensity for lurbinectin and doxorubicin was 90.3% and 95.0%, respectively. Of note, the absence of cardiac events related to changes in left ventricular ejection fraction either during dose escalation or in the expansion cohort suggest that lurbinectin does not increase ventricular dysfunction over doxorubicin.18 Due to the incidence of febrile neutropenia, the use of growth colony-stimulating factors is mandatory for further studies.

**Strengths and Weaknesses**

A strength of this study was the inclusion of an expanded cohort to evaluate a new recommended dose. A limitation of this analysis is that data came from a phase I study with overall response rate assessed by the investigators and a small cohort of patients, which limits the conclusions that can be drawn. Furthermore, no molecular tests were done to check biomarkers in the population evaluated; so, for instance, no comparison with agents in advanced/recurrent mismatch repair deficient disease can be done.

**Implications for Practice and Future Research**

Because second-line treatment of advanced endometrial cancer is an unmet medical need, based on the preliminary efficacy results observed, further clinical development of the doxorubicin plus lurbinectin combination is warranted in relapsed endometrial cancer. This combination may provide a further option for patients with disease unlikely to be cross resistant with newer therapeutic paradigms such as single agent immunotherapy and pembrolizumab/lenitabinab.

**CONCLUSIONS**

Promising antitumor activity and a tolerable safety profile have been found for the combination of doxorubicin 40 mg/m² plus lurbinectin 2.0 mg/m² on day 1 every 3 weeks in patients with advanced endometrial cancer. The combination was generally well tolerated, with manageable and predictable myelotoxicity as the main toxicity.

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Original research

protocol considering that this trial started patient enrolment in 2014. Clinical trial summary results were uploaded to the European Clinical Trials Database (EudraCT: https://eudract.ema.europa.eu) and ClinicalTrials.gov (identifier: NCT01970540).

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