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# DKK1 is a predictive biomarker for response to DKN-01: Results of a phase 2 basket study in women with recurrent endometrial carcinoma

Rebecca Arend [a,*], Jhalak Dholakia [a], Cesar Castro [b], Ursula Matulonis [c], Erika Hamilton [d], Camille Gunderson Jackson [e], Kristopher LyBarger [f], Howard M. Goodman [g], Linda R. Duska [h], Haider Mahdi [i], Adam C. ElNaggar [j], Michael H. Kagey [k], Amy Liu [k], Diane Piper [k], Lisa M. Barroilhet [l], William Bradley [m], Jasgit Sachdev [n], Cynthia A. Sirard [k], David M. O'Malley [o], Michael Birrer [a]

[a] University of Alabama at Birmingham, Birmingham, AL, USA
[b] Massachusetts General Hospital, Boston, MA, USA
[c] Dana-Farber Cancer Institute, Boston, MA, USA
[d] Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA
[e] The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[f] Sarah Cannon-Research Institute at HCA Midwest, Kansas City, MO, USA
[g] Florida Cancer Specialists, West Palm Beach, FL, USA
[h] University of Virginia School of Medicine, Charlottesville, VA, USA
[i] Cleveland Clinic, Cleveland, OH, USA
[j] West Cancer Center, Memphis, TN, USA
[k] Leap Therapeutics, Inc., Cambridge, MA, USA
[l] University of Wisconsin Hospitals and Clinics, Madison, WI, USA
[m] Froedtert and Medical College of Wisconsin, Milwaukee, WI, USA
[n] HonorHealth Research Institute, Scottsdale, AZ, USA
[o] Ohio State University, Columbus, OH, USA

## HIGHLIGHTS

- Elevated DKK1 (Dikkhopf-1), mutations in the Wnt/B-catenin pathway are often found in GYN malignancies and endometrial cancer.
- DKN-01 Ab neutralizes DKK1: in preclinical data, this down-regulates tumor growth & facilitates an immuno-responsive TME.
- DKN-01 monotherapy shows promising objective response, disease control in high tumoral DKK1 recurrent endometrial cancer.
- Wnt pathway activating mutations correlated to high tumoral DKK1 expression, suggesting a potential biomarker/targeted therapy.

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## ABSTRACT

*Purpose.* Dickkopf-1 (DKK1) is a Wnt signaling modulator promoting tumor growth, metastasis, angiogenesis, and immunosuppression by regulating innate immunity. DKK1 is over-expressed in gynecologic cancers and is associated with shortened survival. DKN-01 is a humanized monoclonal antibody with DKK1 neutralizing activity that may provide clinical benefit to patients whose tumors have overexpression of DKK1 or Wnt genetic alterations.

*Methods.* We conducted an open-label, Phase 2 basket study with 2-stage design in patients with endometrial carcinoma (EC) and platinum-resistant/refractory epithelial ovarian cancer. DKN-01 was administered either as monotherapy or in combination with weekly paclitaxel at investigator's discretion. All patients underwent NGS testing prior to enrollment; tumor tissue was also tested for DKK1 expression by RNAscope pre-treatment and after cycle 1 if available. At least 50% of patients were required to have a Wnt signaling alteration either directly or tangentially. This publication reports results from the EC population overall and by DKK1-expression.

*Results.* DKN-01 monotherapy and in combination with paclitaxel was more effective in patients with high DKK1-expressing tumors compared to low-expressing tumors. DKN-01 monotherapy demonstrated an objective response rate [ORR] of 25.0% vs. 0%; disease control rate [DCR] of 62.5% vs. 6.7%; median progression-free survival

* Corresponding author at: Rebecca C. Arend, MD, MSPH, Associate Professor, University of Alabama at Birmingham, Division of Gynecologic Oncology, 619 19th Street South176F Rm 10250, Birmingham, Alabama 3524, USA.
*E-mail address:* rarend@uabmc.edu (R. Arend).

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[PFS] was 4.3 vs. 1.8 months, and overall survival [OS] was 11.0 vs. 8.2 months in DKK1-high vs DKK1-low patients. Similarly, DKN-01 in combination with paclitaxel demonstrated greater clinical activity in patients with DKK1-high tumors compared to DKK1-low tumors: DCR was 55% vs. 44%; median PFS was 5.4 vs. 1.8 months; and OS was 19.1 vs. 10.1 months. Wnt activating mutations correlated with higher DKK1 expression. DKN-01 was well tolerated as a monotherapy and in combination with paclitaxel.

*Conclusions.* Collectively, data demonstrates promising clinical activity of a well-tolerated drug, DKN-01, in EC patients with high tumoral DKK1 expression which frequently corresponded to the presence of a Wnt activating mutation. Future development will focus on using DKN-01 in DKK1-high EC patients in combination with immunotherapy.



## 1. Introduction

DKN-01 (Leap Therapeutics, Cambridge, Mass., USA) is a humanized monoclonal antibody (Mab) (immunoglobulin G4 [IgG4]) optimized for neutralizing activity against dickkopf-1 (DKK1), a modulator of Wnt signaling pathways that influences several important processes such as embryonic development and bone homeostasis [29,35]. DKK1 is best characterized as an inhibitor of the Wnt/β-catenin-dependent (canonical) signaling pathway; however, it has also been implicated in activating Wnt/β-catenin-independent (noncanonical) signaling pathways and PI3K/AKT signaling [21]. DKK1 activates PI3K/AKT signaling by binding to the CKAP4 receptor, thereby promoting tumor growth [24]. DKK1 modulates the tumor microenvironment by decreasing CD45+ leukocyte infiltration, reducing NK and CD8+ T cells, enhancing MDSC activity, and inhibiting NK mediated clearance of cancer cells [3,4,13,30]. These factors are thought to contribute to an immunosuppressive tumor phenotype.

DKN-01 binds to DKK1 with high affinity and has demonstrated single agent activity in multiple pre-clinical tumor models [18,46]. Additionally, clinical activity has been demonstrated both as a single agent and in combination with other anti-cancer agents in patients with solid tumors [22,50,51]. In a recent Phase Ib Study of DKN-01 in gastro-esophageal junction or gastric cancer (GEJ/GC), DKN-01 monotherapy demonstrated single agent activity as assessed by retrospective blinded independent review with 10% ORR and 30% SD. DCR was 40% at 12 weeks and the probability of clinical benefit for at least 6 and 12 months was 43% and 0% respectively [22]. Combination DKN-01 and pembrolizumab treatment demonstrated an 18.5% objective response rate (ORR) in anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1)-naïve GEJ/GC patients. In this population, patients with elevated DKK1 expression demonstrated higher ORR and longer survival benefits compared to DKK1-low patients (50% vs 0%, 22.1 vs 5.9 weeks, respectively) [22].

Aberrations in Wnt/β-catenin dependent signaling are common in endometrial hyperplasia, endometrial carcinoma (EC), and endometrioid ovarian cancer [8,27]. Alterations in a subgroup of genes have been associated with constitutive activation of Wnt/β-catenin dependent signaling (i.e. *CTNNB1*, *APC*, *AXIN1/2*, *RNF43*, *ZNRF3*, and *RSPO2/3)* [1,15,19,25,33,39,42,49,52]. The most frequently mutated gene is *CTNNB1*, encoding β-catenin [33]. Activation of Wnt/β-catenin dependent signaling via *CTNNB1* stabilizing mutations leads to increased DKK1 expression in the tumor [6,7,11,16,37]. These results suggest that patients with activated Wnt/β-catenin dependent signaling may have elevated DKK1 expression and therefore benefit from a DKK1 neutralizing therapy.

## 2. Materials and methods

### 2.1. Study design

This Phase 2 basket study was designed to evaluate DKN-01 in patients with recurrent EC or recurrent platinum-resistant epithelial ovarian cancer (EOC) who had received at least one prior systemic therapy. Our hypothesis was that the presence of a Wnt-related biomarker would be associated with response to DKN-01 independent of tumor histology [31,34,40]. Therefore, cohorts were enriched for Wnt signaling alterations (Fig. 1) to have an adequate number of patients with high DKK1 expression to compare to those with low expression given the association between activating mutations and DKK1 expression. This publication will focus on the ability of the DKK1 biomarker to be predictive of the clinical benefit to DKN-01 therapy in EC patients. Prior studies suggested possible synergy between paclitaxel and DKN-01 (Klempner, 2021); therefore, the two treatment groups in this study were DKN-01 alone or DKN-01 with weekly paclitaxel, which has been shown to have efficacy in recurrent EC and EOC. The treatment arm was at the discretion of the investigator and was not randomized.

Each EC cohort employed a Simon 2-stage Minimax design with the null hypothesis that ORR ≤5% versus the alternative hypothesis that ORR ≥20% and an alpha of 0.080 and a power of 0.803. In the monotherapy cohort, 12 evaluable patients were enrolled in Stage 1; if≥1 patient responded (i.e., complete or partial response [CR or PR]), an additional 9 evaluable patients were to be enrolled in Stage 2. If no patient responded in Stage 1, then no further patients were to be enrolled. In the combination cohort, 20 evaluable patients were enrolled in Stage 1, if ≥3 patients responded, an additional 11 evaluable patients were to be enrolled in Stage 2. If <3 patients responded in Stage 1, then no further patients were to be enrolled (Supplemental Fig. 1).

All patients received DKN-01300 mg intravenously (IV) over a minimum of 30 min and maximum of 2 h on D1 and 15 every 28 days. Patients who received combination therapy got paclitaxel 80 mg/m$^2$ IV over 1 h on D1, 8, and 15 every 28 days. Treatment was administered in 28 day cycles and continued until development of radiographic progressive disease (PD) or unacceptable toxicity, although the patient could remain on trial after PD if the investigator felt that the patient was receiving clinical benefit.

The institutional review boards at all participating sites approved the study, and all patients provided informed consent before the performance of any study-related procedures. The study was conducted in accordance with International Council for Harmonization and Good Clinical Practice (ICH-GCP) and Declaration of Helsinki. The study was registered at clinicaltrials.gov (NCT03395080).

Eligible patients were ≥18 years with EC (either primary surgical specimen or biopsy for recurrence) with at least 1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), who had received ≥1 prior systemic regimen. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were enrolled based on testing of the screening tumor tissue sample or previously documented alteration by a CLIA-accredited laboratory. At least 50% of the patients were required to have a Wnt signaling alteration (Fig. 2A).

### 2.2. Tumor specimens

Fresh tumor samples were collected from all patients when feasible during screening and on cycle 2 day 1 (C2D1) ±7 days, for translational

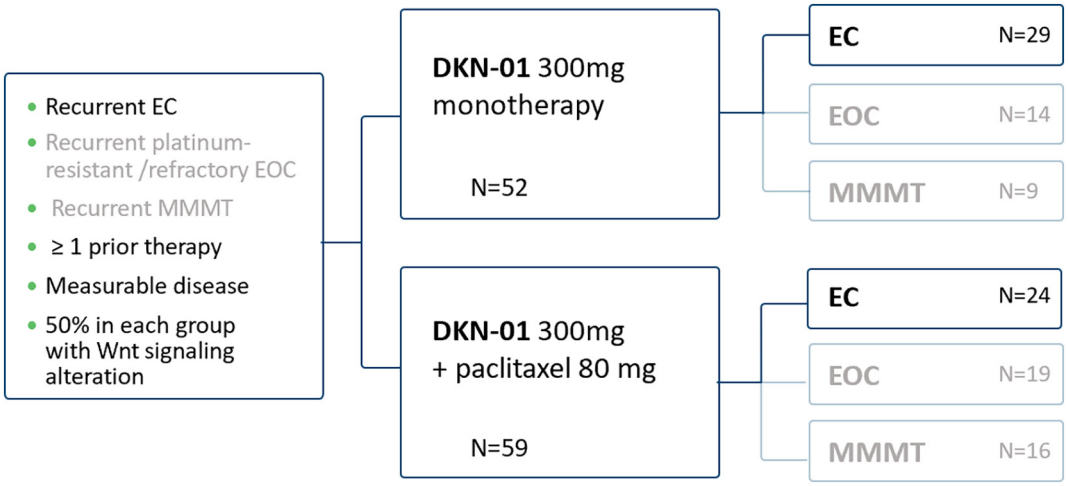



**Fig. 1.** Patient groups.
Legend: Schematic demonstrating inclusion criteria and treatment plan. (EC = endometrial carcinoma, EOC = epithelial ovarian carcinoma, MMMT = malignant mixed Mullerian tumor).

research. For the majority of patients, archival tumor was used for NGS testing. In addition to pre-screening NGS testing, genetic analysis, including microsatellite stability and tumor mutational burden (TMB), was conducted centrally at Foundation Medicine, Inc., (FMI, Cambridge, MA) using the FoundationOne (F1CDx) test.

Formalin-fixed, paraffin embedded patient tumor tissue was evaluated centrally at Advanced Cell Diagnostics (ACD, Newark, CA) for DKK1 expression. DKK1 messenger ribonucleic acid (mRNA) expression was measured by a single-plex RNAscope chromogenic in-situ hybridization (CISH) assay on the Leica Biosystems BOND RX platform [17,44]. DKK1 mRNA was detected in tumor cells using the QuPath open-source morphometric analysis program [2] or by manual read of the glass slide, and an H-score (range 0–300) was calculated by determining the percentage of low (1–3 dots/cell), medium (4–9 dots/cell) and high (10+ dots/cell) expressing tumor cells. H-score = (%low)*1 + (%medium)*2 + (%high)*3. DKK1 high is defined as H-score ≥ upper-tertile for the mono patients, while DKK1 low is H-score < upper-tertile. EC upper-tertile (DKK1-high) cut-off was identified as ≥18 for EC mono patients. The same cut-off was applied for the combination patients. The scoring pathologist was blinded to the NGS results.

### 2.3. Endpoints and assessments

Primary endpoint was overall response (ORR), the number of patients who exhibited CR (complete response) or PR (partial response). Secondary endpoints included: disease control rate [DCR], overall survival [OS], progression-free survival [PFS], and duration of response [DoR]. Responses and PD were assessed by the investigator using the RECIST 1.1. DCR was the number of patients exhibiting a CR, PR, or stable disease persisting for >6 weeks. PFS was defined as the time from the date of first dose of study treatment to the first date of objectively determined PD or death from any cause. Durable SD was defined as SD longer than 6 months. OS was defined as the time from date of first dose of study treatment until date of death due to any cause (date of death - first dose date+1). Duration of response (DoR) was defined as the time from initial response (≥PR) until radiographically documented PD or death. Time-to-event analyses were performed using Kaplan-Meier methods; median estimates were provided with corresponding 95% CIs. Disease status was assessed by computed tomography (CT) and/or magnetic resonance imaging (MRI) every 2 cycles (8 weeks), starting in Cycle 3, and response was assessed by the Investigator using RECISTv1.1. Treatment-emergent adverse events (TEAEs) were defined as AEs with the onset between the first treatment and 30 days after the last treatment with DKN-01. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Planned exploratory endpoints assessed the association between response and tumoral DKK1 expression.

### 2.4. Statistical analysis

No formal hypothesis testing was performed for this exploratory study. At least 50 % of patients had to have a Wnt signaling alteration (Fig. 1): a subset of these were expected to have a Wnt activating mutation. Summaries were tabulated for each cohort by DKK1 status (High, Low, Unknown) and presence of Wnt activating mutations. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) were presented for continuous variables; frequency distributions (counts and associated percentages) were presented for categorical variables. Median, 25th and 75th percentiles, and standard error were presented for time-to-event data. All confidence intervals (CIs) were 95% unless stated otherwise.

## 3. Results

From 05 March 2018 to 09 September 2020, 53 patients with recurrent EC were enrolled across 13 investigative sites, of whom 29 received DKN-01 as monotherapy (mono) and 24 received DKN-01 + paclitaxel (combo) (Fig. 1). Demographic and baseline characteristics are summarized in Table 1. Over-enrollment occurred to ensure sufficient subjects were evaluable, and because subjects who were in the consenting process as enrollment ended were allowed to enroll. As the study concluded, the total enrollment was 29 and 24 in EC mono and EC combo cohorts, respectively.

### 3.1. Monotherapy cohort

Among the 29 EC mono patients, mean age was 61.3 years, with $n = 10$ patients aged ≥65 years; 93.1% were white. Twenty-seven patients had a baseline ECOG score of 0 or 1, with two having a score of 2. Patients had received a mean of 2.6 prior lines of therapy.

Ten patients had Stage IV disease at original diagnosis. Twenty patients had at baseline high grade (G2/3) tumors. Most ($n = 23$) patients had endometrioid endometrial carcinoma; $n = 5$ had serous and n = 1 had clear cell histology. Median time from diagnosis and disease recurrence was 887 and 378 days (29.1 and 12.4 months) respectively. All but 1 patient had received prior treatment with a taxane-containing regimen. Of 21 patients with centrally available microsatellite stability

(A) Wnt Genetic Groups

**Wnt Signaling Alterations**

Genes that are associated with the Wnt signaling pathway, either directly or tangentially

Genes: *CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3,* WISP3, TNKS2, TERT, SOX9, SOX2, SLIT2, PAX5, NOTCH1, MLL2, LTK, LRP1B, GSK3B, GREM1, FOXP1, FBXW7, FAM123B, CREB, CDH20, CDC73, ARID1A and APCDD1

**Wnt Activating Mutations**

A well defined subgroup of the genes associated with Wnt Signaling Alterations

- Alterations that result in active Wnt/β-catenin dependent signaling
- Genes: *CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3*

| Gene | Genetic alteration |
|---|---|
| *CTNNB1* (β-catenin) | Protein stabilizing alteration (missense mutation of S33, S37, T41 or S45; exon 3 missense mutation or inframe deletion of all or part of exon 3) |
| *APC* | Loss of function alteration (truncation or deletion) |
| *AXIN1/2* | Loss of function alteration (truncation or deletion) |
| *RNF43* | Loss of function alteration (truncation or deletion) |
| *ZNRF3* | Loss of function alteration (truncation or deletion) |
| *RSPO2* | Fusion protein (EIF3E-RSPO2) |
| *RSPO3* | Fusion protein (PTPRK-RSPO3) |

(B) Distribution of DKK1 RNAscope H-scores by Wnt Activating Mutation Status in EC

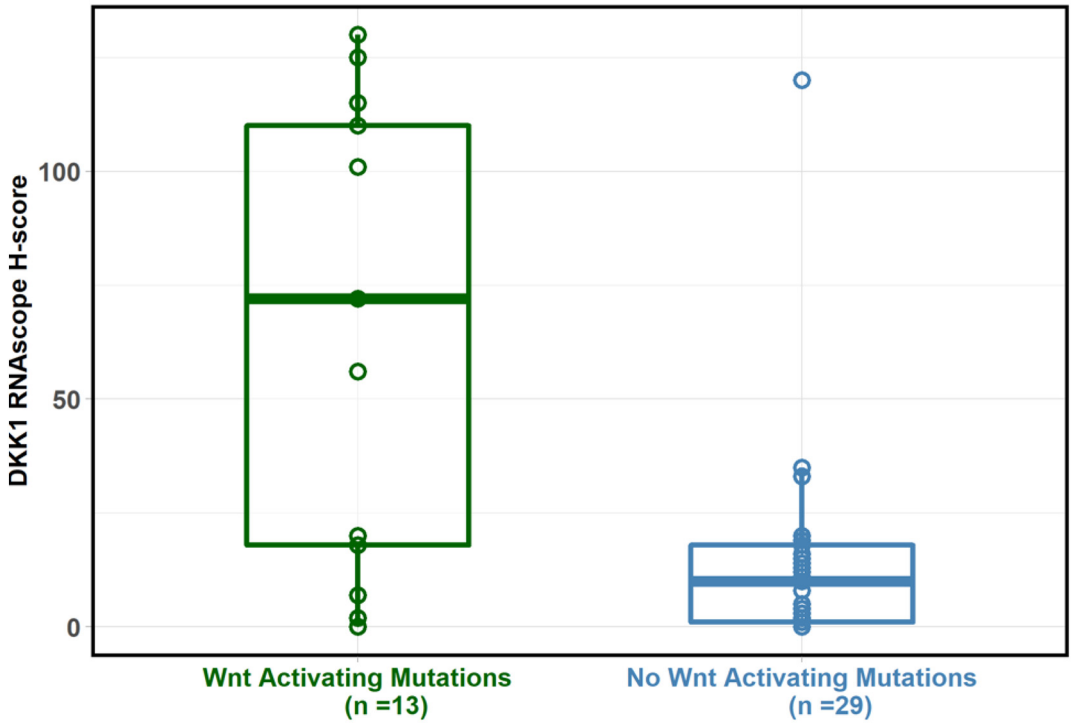



**Fig. 2.** Wnt signaling alterations and DKK1 RNAscope scores.
Legend: (A) EC patients enrolled on trial were enriched for those with Wnt signaling alterations, a subset of which were Wnt activating mutations. Genetic alterations of interest are individually listed. (B) Compared to absence of Wnt activating mutations, the presence of these mutations was associated with increased DKK1 RNAscope H-score.

data from FMI, 18 had microsatellite stable (MSS) tumors, 2 had microsatellite instability high (MSI-H) tumors, and 1 was microsatellite instability low (MSI-L)/ambiguous. Mean tumor mutational burden (TMB) was 7.0 mutations/mb, with most (15/21 patients) evaluated having a low TMB (0 to <6 mutations/mb).

Twenty-one patients (72.4%) had Wnt signaling alterations (Fig. 2A) demonstrated by either central analysis at FMI or historical data from a CLIA test. *ARID1A* was the predominant mutation (11/21, 52.4%) consistent with published results reporting *ARID1A* mutations in ~50% of ECs [36]. Furthermore, 9 patients had Wnt activating mutations (Table 1 and Fig. 2A), 6 with *CTNNB1* and 2 each with *APC* or *RNF43* mutations. One patient had both *CTNNB1* and *RNF43* mutations. A large percentage (45%) of patients had a PIK3CA alteration consistent with previously reported results [14].

Tumoral DKK1 status was determined retrospectively, including one patient's RNAscope H-score retrieved from a historical sample after database lock. Patients with tumor DKK1 RNAscope H-scores in the upper tertile (≥18, $n = 8$ in the monotherapy population) were defined as high DKK1 expressors (e.g., DKK1-high). Median H-score was 10.

The median duration of DKN-01 monotherapy was 43 days with a maximum of 729 days (24.0 months). The mean number of treatment cycles was 4.3 (range 1–27), with n = 8 patients receiving >4 cycles and $n = 5$ receiving >6 cycles of therapy.

### 3.2. Combination cohort

Among the 24 patients receiving combo therapy, mean age was 63.3 years, with half ($n = 12$) being aged ≥65 years; 87.5% were white. All patients had a baseline ECOG score of 0 or 1. Seven patients had Stage IV disease at original diagnosis. Fifteen patients at baseline had high grade (G2/3) tumors. Eleven combo patients had endometrioid EC, 8 patients had serous histology, 1 patient had mixed

**Table 1**
Demographics and baseline disease characteristics for EC patients.

| Parameter / Statistic | Monotherapy ($N = 29$) n (%) | Combination Therapy ($N = 24$) n (%) |
|---|---|---|
| Age (years), Mean (SD) | 61.3 (8.92) | 63.3 (8.80) |
| Age ≥ 65 years (n, %) | 10 (34.5) | 12 (50.0) |
| White race (n, %) | 27 (93.1) | 21 (87.5) |
| Baseline ECOG (n, %) | | |
| 0 | 14 (48.3) | 6 (25.0) |
| 1 | 13 (44.8) | 18 (75.0) |
| 2 | 2 (6.9) | 0 |
| Baseline serum DKK1 (ng/mL), mean (SD) | 11.82 (35.577) | 6.60 (3.191) |
| EC type, n (%) | | |
| Endometrioid | 23 (79.3) | 11 (45.8) |
| Serous | 5 (17.2) | 8 (33.3) |
| Clear cell | 1 (3.4) | 0 |
| Mixed epithelial tumor | 0 | 1 (4.2) |
| Other | 0 | 4 (16.7) |
| Stage at Diagnosis, n (%) | | |
| I | 12 (41.4) | 7 (29.2) |
| II | 4 (13.8) | 1 (4.2) |
| III | 3 (10.3) | 9 (37.5) |
| IV | 10 (34.5) | 7 (29.2) |
| Tumor Grade at Diagnosis, n (%) | | |
| G1 | 6 (20.7) | 6 (25.0) |
| G2 | 11 (37.9) | 1 (4.2) |
| G3 | 9 (31.0) | 14 (58.3) |
| Unknown | 2 (6.9) | 3 (12.5) |
| Median time from primary diagnosis (days) | 887 | 794 |
| Median time to recurrence/ progression (days) | 378 | 459 |
| Lines of prior therapy, mean (SD) | 2.6 (1.33) | 3.9 (2.17) |
| Prior therapy types, n (%): | | |
| Taxane | 28 (96.6) | 24 (100) |
| Platinum | 28 (96.6) | 24 (100) |
| VEGF Inhibitors | 7 (24.1) | 7 (29.2) |
| PARP Inhibitors | 1 (3.4) | 3 (12.5) |
| Immunotherapy (IO) | 5 (17.2) | 6 (25.0) |
| Hormonal Therapy | 12 (41.4) | 10 (41.7) |
| Wnt Activating mutation, n (%) | 9 (31.0) | 7 (29.2) |
| Microsatellite Status, n (%) | | |
| MSS | 18 (62.1) | 19 (79.2) |
| MSI-H | 2 (6.9) | 3 (12.5) |
| MSI-L | 1 (3.4) | 0 |

endometrioid and serous histology, and 4 had other histopathological characteristics. Median time since diagnosis and recurrence was 794 and 459 days (26.1 and 15.1 months), respectively. All patients had received a prior taxane-containing regimen and had received a mean of 3.9 prior lines of therapy. Of the 22 patients with centrally available microsatellite instability data from FMI, 19 (86.4%) were MSS and 3 (13.6%) were MSI-H. Mean TMB was 7.9 mutations/mb, with n = 12 patients having low (0 to <6 mutation/mb), and $n = 7$ and $n = 3$ having intermediate (6 to 19) or high (≥20) TMB respectively.

Sixteen combo patients had Wnt signaling alterations (Fig. 2A) by either central analysis at FMI or historical data from a CLIA test; *ARID1A* was the predominant mutation in this group as well (9/16, 56.3%). Seven had Wnt activating mutations, 5 with *CTNNB1* mutations, 2 with non-CTNNB1 mutations, including *APC* and *RNF43* mutations.

The median duration of DKN-01 and paclitaxel treatment was 87 days each, with a maximum of 386 days (12.7 months). The mean number of treatment cycles was 4.3 (range 1–14), with $n = 10$ patients receiving >4 cycles and n = 3 receiving >6 cycles of therapy.

### 3.3. DKK1 expression associated with Wnt activating mutations

There was an association of elevated DKK1 tumor expression in EC patients whose tumors harbored Wnt activating mutations compared to those without such mutations (Fig. 2B). Median H-score was 64 for monotherapy patients with Wnt activating mutations, while median H-score was 5 for those without Wnt activating mutations. Additionally, eleven out of 20 combo patients with RNAscope data were defined as DKK1-high (H-score ≥ 18). Median H-score was 101 for EC combo patients with Wnt activating mutations, while median H-score was 12 for those without Wnt activating mutations.

### 3.4. Clinical activity

Among all mono patients in the evaluable set (i.e., all patients who received any amount of DKN-01 and had at least 1 evaluable post-baseline RECIST 1.1 tumor response assessment or were discontinued due to death), the ORR was 7.7% (2/26) (95% CI 0.9, 25.1), with 1 patient experiencing a confirmed CR and 1 experiencing a confirmed PR. Additionally, 9 (34.6%) EC mono patients experienced stable disease with durability (>6 months) for 7 of these patients. The DCR was therefore 42.3% (95% CI: 23.4, 63.1). No patient treated with the combo experienced a CR or PR; however, 12 patients experienced stable disease, 3 of which were durable, making the DCR 57.1% (95% CI 34.0, 78.2). Thirteen evaluable patients were enrolled onto Stage 1of the EC mono cohort, one of which experienced a PR, therefore 13 additional patients were enrolled. For the EC combo group 21 evaluable patients were enrolled on to Stage 1 and none of the patients were responders, so no further patients were added.

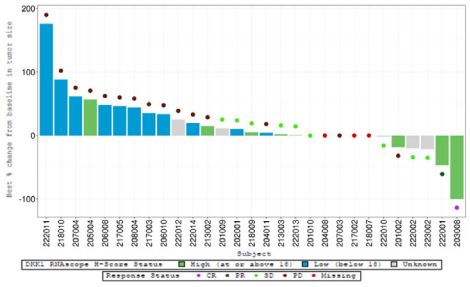
Exploratory treatment activity analyses of disease outcomes among monotherapy patients by DKK1 expression level (high versus low) revealed improved clinical outcomes in high DKK1 expressors relative to low expressors (Fig. 3A, B.) Both ORR and DCR were improved among high DKK1 expressors versus low expressors, (25.0% versus 0%) and DCR (62.5% versus 6.7%), respectively. Furthermore, high DKK1 expressors had longer PFS (4.3 versus 1.8 months; HR 0.26; 95% CI: 0.09, 0.75) and OS (11.0 versus 8.2 months; HR 0.81; 95% CI: 0.26, 2.48) than low expressors (Fig. 3C, E).

Exploratory treatment activity analyses of disease outcomes among combo patients by DKK1 expression level (high versus low) revealed a similar trend in improved clinical outcomes in high DKK1 expressors relative to low expressors. As noted previously, there were no responders in the combo EC group. However, the DCR and survival outcomes were improved among high DKK1 expressors versus low expressors, DCR (55% versus 44%); longer PFS (5.4 versus 1.8 months; HR 0.34; 95% CI: 0.12, 0.97) and OS (19.1 versus 10.1 months; HR 0.31; 95% CI: 0.09, 1.08) than low expressors (Fig. 3D, F).

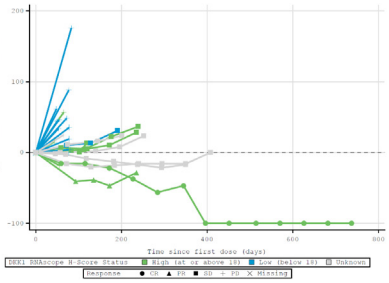
Among 29 patients receiving monotherapy who had Wnt mutational status assessed in the study, 9 had Wnt activating mutations: this correlated with higher DKK1 H-scores. Improved clinical outcomes also were seen among those with tumoral Wnt-activating mutations versus those without Wnt activating mutations (Fig. 4). The DCR in this subset was 66.7% (6/9) (95% CI 29.9, 92.5), with $n = 4$ (44.4%) experiencing durable response. In contrast, the DCR among mono patients with non-Wnt activating mutations was 29.4% (5/17) (95% CI 10.3, 56.0). PFS and OS were longer among EC mono patients with Wnt-activating mutations versus those without (median PFS 5.5 months [95% CI 1.0, 11.1] versus 1.8 months [95% CI 1.4, 2.3]; median OS not reached versus 12.2 months [95% CI 3.3, not estimable]) (Fig. 4C and E). A DCR of 57.1% (4/7) (95% CI 18.4, 90.1) was observed in the EC combo patients with Wnt-activating mutations. (Of note, both mono responders (1 CR, 1 PR) had *PIK3CA* mutations.

Among 22 patients receiving DKN-01 in combination with paclitaxel who had Wnt mutational status assessed in the study, 7 had Wnt activating mutations. The Kaplan-Meier estimated median PFS time favored subjects with EC with Wnt-activating mutations; median PFS 5.1 months [95% CI 1.84, not estimable]; versus 3.7 months [95% CI 1.84, 6.90]; however, this did not translate into an OS advantage (median OS 10.1 months [95% CI 5.26, not estimable]; versus 12.2 months [95% CI 6.54, not estimable]) (Fig. 4D, F).

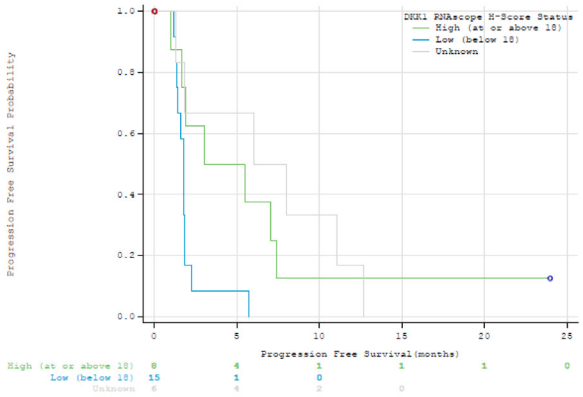
(A) Waterfall Plot of Best Overall Response in EC Mono Patients by DKK1 RNAscope H-score Status



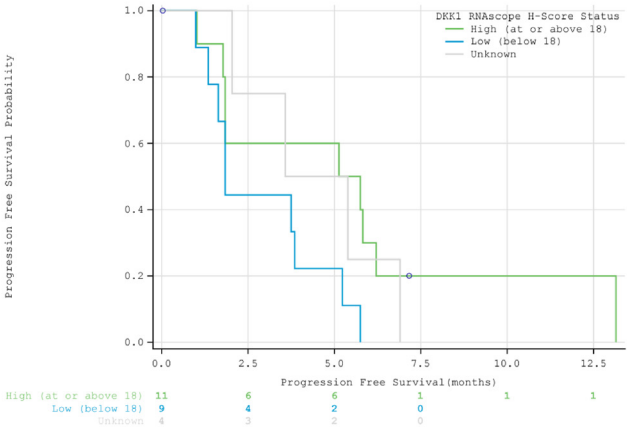
(B) Spider Plot of Percent Change in Target Lesion Measurements in EC Mono Patients by DKK1 RNAscope H-score Status



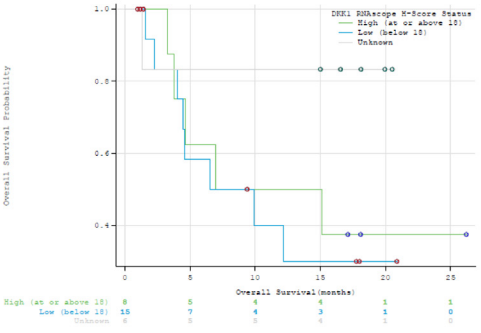
(C) Kaplan-Meier Estimates for Progression-free Survival in EC Mono Patients by RNAscope H-score Status




(D) Kaplan-Meier Estimates for Progression-free Survival in EC Combo Patients by RNAscope H-score Status




E) Kaplan-Meier Estimates for Overall Survival in EC Mono Patients by RNAscope H-score Status




(F) Kaplan-Meier Estimates for Overall Survival in EC Combo Patients by RNAscope H-score Status

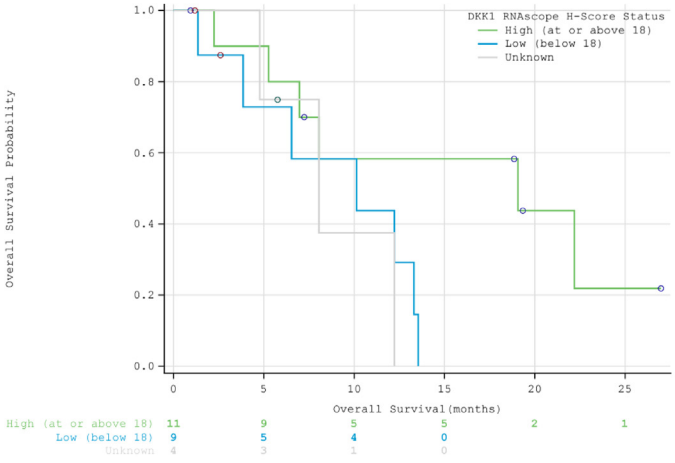


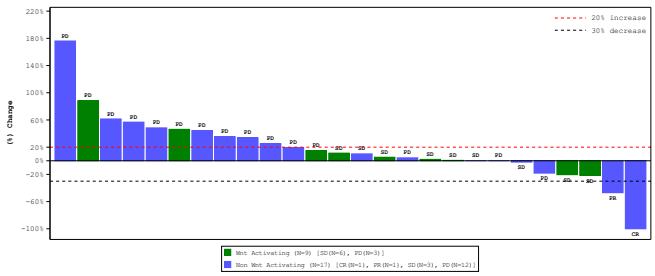

**Fig. 3.** Disease outcomes in EC patients treated with DKN-01 monotherapy by DKK1 tumoral expression.
Legend: Patients with high DKK1 RNAscope H-score experienced better overall responses compared to those with low scores when receiving DKN-01 monotherapy (A); these patients also exhibited a longer duration of response (B). Kaplan-Meier curves show improved progression free survival (C) in DKK1-high patients on monotherapy when compared to DKK1-low patients (4.3 m vs 1.8 m) and (D) DKK1-high patients on combination when compared to DKK1-low patients (5.4 m vs. 1.8 m). Median OS in the monotherapy DKK1-high group was 11.0 m vs. 8.2 m in the DKK1-low group (E) and median OS in combination the DKK1-high group was 19.1 m vs. 10.1 m in the DKK1-low group (F).

### *3.5. Safety*

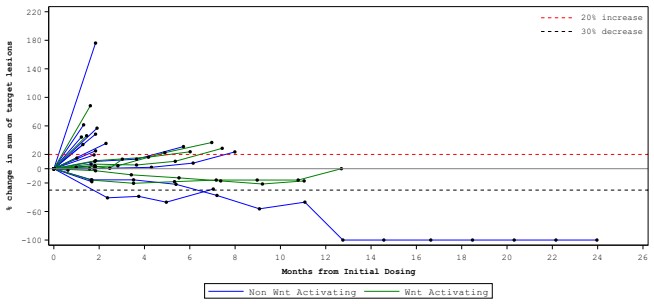
DKN-01 was well tolerated. The safety profile of the combination patients was similar to that established with paclitaxel [32,38,41,43], indicating that DKN-01 did not exacerbate toxicities generally associated with paclitaxel. Only 6 patients experienced grade ≥ 3 AEs related to DKN-01. Only 1 patient discontinued DKN-01 due to a TEAE (hyperbilirubinemia) which was assessed by the investigator to be treatment-related. Only eight patients on monotherapy experienced a serious adverse event (SAE), although nausea was the only SAE treated in >1 patient ($n = 2$; 7%) (Table 2) and only 2 had SAEs (6.9%) related to DKN-01.

Thirteen (54.2%) combo patients experienced an SAE, with small intestinal obstruction and deep vein thrombosis being the SAEs reported

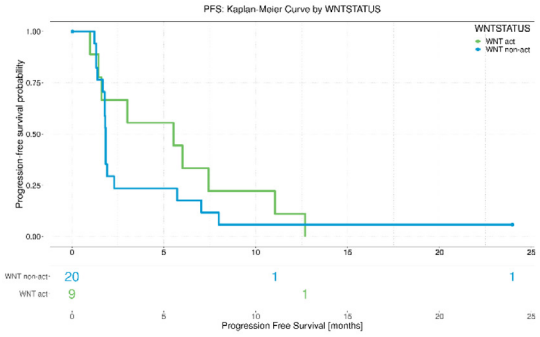
(A) Waterfall Plot of Best Overall Response in EC Mono Patients by Wnt Activating Mutational Status



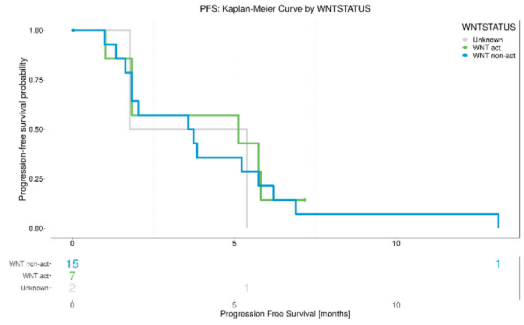

(B) Spider Plot of Percent Change in Target Lesion Measurements in EC Mono Patients by Wnt Activating Mutational Status



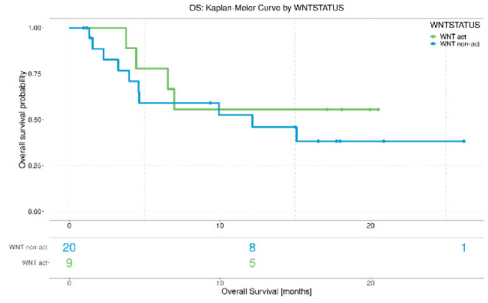

(C) Kaplan-Meier Estimates for Progression-free Survival in EC Mono Patients by Wnt Activating Mutational Status




(D) Kaplan-Meier Estimates for Progression-free Survival in EC Combo Patients by Wnt Activating Mutational Status




(E) Kaplan-Meier Estimates for Overall Survival in EC Mono Patients by Wnt Activating Mutational Status




(F) Kaplan-Meier Estimates for Overall Survival in EC Combo Patients by Wnt Activating Mutational Status

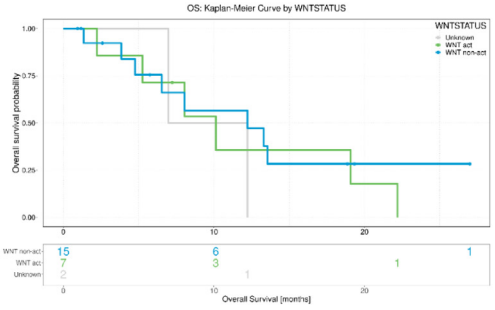



**Fig. 4.** Disease outcomes in EC patients treated with DKN-01 monotherapy and in combination by Wnt activating mutation status.
Legend: Patients with Wnt activating mutations experienced improved disease control compared to those without Wnt activating mutations (A); these patients also exhibited a longer duration of response (B). Kaplan-Meier curves show improved progression free survival (C) in patients with Wnt activating mutations on monotherapy when compared to those without Wnt activating mutations (5.5 m vs 1.8 m) and patients with Wnt activating mutations on combination when compared to those without Wnt activating mutations (5.1 m vs 3.7 m) (D). Median OS in monotherapy patients with Wnt activating mutations was not reached vs. 12.2 months in those without Wnt activating mutations (E). Median OS in patients treated in combination with Wnt activating mutations was 10.1, vs. 12.2 m in those without Wnt activating mutations (F).

for >1 patient (n = 2, 8% each). Only 1 patient discontinued treatment in the combination arm due to a TEAE (small intestinal obstruction), considered by Investigator as unrelated to study treatment (Table 2.) There were 3 patients who had SAEs (8.3%) and 10 patients who had Grade ≥ 3 TEAE (41.7%) related to treatment. No deaths due to TEAEs (ie, Grade 5) occurred in either cohort.

## 4. Discussion

The development of molecular-targeted therapies has been a growing area of interest for the treatment of both endometrial and ovarian carcinomas [9,26,50,51]. Molecularly targeted agents hold the potential for greater selectivity with lower toxicity than conventional chemotherapy. DKN-01 is a humanized monoclonal antibody with neutralizing activity against DKK1, a modulator of Wnt signaling pathways that is over-expressed in gynecologic cancers and associated with shortened survival (Kagey, 2017). We demonstrated promising clinical activity of DKN-01, particularly in patients with high tumoral DKK1 expression, with overall high tolerability and safety, in patients with heavily pretreated recurrent EC. This highlights the potential role of DKK1 tumoral expression as a marker for selecting DKN-01 therapy.

We enriched for Wnt signaling alterations and analyzed a smaller subset of Wnt activating mutations to identify a genetic signature that correlates with DKK1 expression (Fig. 2A). Patients treated with DKN-

**Table 2**
Safety summary: Overall incidence of treatment-emergent adverse events.

| Parameter | Monotherapy (N = 29) n (%) | Combination Therapy (N = 24) n (%) |
|---|---|---|
| Any TEAE | 29 (100.0) | 24 (100.0) |
| Nausea | 14 (48.3) | 10 (41.7) |
| Fatigue | 13 (44.8) | 11 (45.8) |
| Anemia | 7 (24.1) | 13 (54.2) |
| Vomiting | 7 (24.1) | 6 (25.0) |
| Arthralgia | 6 (20.7) | 4 (16.7) |
| Constipation | 5 (17.2) | 6 (25.0) |
| Abdominal pain | 5 (17.2) | 5 (20.8) |
| Decreased appetite | 5 (17.2) | 5 (20.8) |
| AST increased | 5 (17.2) | 0 |
| Peripheral edema | 4 (13.8) | 8 (33.3) |
| Diarrhea | 4 (13.8) | 7 (29.2) |
| Abdominal distension | 4 (13.8) | 6 (25.0) |
| Urinary tract infection | 4 (13.8) | 6 (25.0) |
| Dyspnea | 4 (13.8) | 5 (20.8) |
| Myalgia | 3 (10.3) | 5 (20.8) |
| Hyperglycemia | 3 (10.3) | 5 (20.8) |
| Cough | 2 (6.9) | 7 (29.2) |
| Hyponatremia | 1 (3.4) | 6 (25.0) |
| Neutropenia | 1 (3.4) | 5 (20.8) |
| Lymphopenia | 1 (3.4) | 5 (20.8) |
| Alopecia | 0 | 8 (33.3) |
| Any ≥Grade 3 TEAE | 17 (58.6) | 19 (79.2) |
| Anemia | 5 (17.2) | 5 (20.8) |
| Abdominal pain | 2 (6.9) | 2 (8.3) |
| Nausea | 2 (6.9) | 1 (4.2) |
| Small intestinal obstruction | 2 (6.9) | 2 (8.3) |
| Vomiting | 2 (6.9) | 1 (4.2) |
| Acute kidney injury | 2 (6.9) | 0 |
| Urinary tract obstruction | 2 (6.9) | 0 |
| Alanine aminotransferase increased | 2 (6.9) | 0 |
| Arthralgia | 2 (6.9) | 1 (4.2) |
| Lymphopenia | 1 (3.4) | 2 (8.3) |
| Deep vein thrombosis | 0 | 2 (8.3) |
| Hypertension | 0 | 2 (8.3) |
| Hyponatraemia | 0 | 4 (16.7) |
| Hyperglycaemia | 0 | 2 (8.3) |
| Neutropenia | 0 | 2 (8.3) |
| Ascites | 0 | 2 (8.3) |
| Any DKN-01-related TEAE | 24 (82.8) | 22 (91.7) |
| Anemia | 3 (10.3) | 11 (45.8) |
| Diarrhea | 3 (10.3) | 5 (20.8) |
| Nausea | 9 (31.0) | 4 (16.7) |
| Fatigue | 9 (31.0) | 9 (37.5) |
| Any Paclitaxel-related TEAE | – | 22 (91.7) |
| Any SAE | 8 (27.6) | 13 (54.2) |
| Any TEAE Leading to DKN-01 Dose Reduction | 1 (3.4) | 3 (12.5) |
| Any TEAE Leading to DKN-01 Interruption | 1 (3.4) | 1 (4.2) |
| Any TEAE Leading to DKN-01 Discontinuation | 1 (3.4) | 1 (4.2) |
| Any TEAE Resulting in Death | 0 | 0 |

01 monotherapy who harbored Wnt-activating mutations demonstrated better disease control compared to those without Wnt-activating mutations (66.7% versus 29.4%); they also experienced longer median PFS (5.5 versus 1.8 months [HR 0.69; 95% CI: 0.30, 1.58]). Furthermore, of the DKK1 unknown patients, all three with Wnt-activating mutations demonstrated SD with 2 durable SD (>6 months). This suggests that Wnt-activating mutations represent a genetic signature that may predict favorable response to DKN-01.

In this vein, we observed an overall concordance of high DKK1 expression with Wnt-activating mutations of 55.6% (10/18). However, the remainder of the high DKK1 patients (44.4%) did not harbor Wnt-activating mutations, suggesting the involvement of other signaling pathways in promoting DKK1 expression. Some potential explanations include crosstalk between the tyrosine kinase signaling pathways (PI3K/AKT, EGF, VEGF, MAP Kinase, etc.) and the Wnt pathway [5,23,28]. Research to identify a genetic signature or panel that is predictive of tumor DKK1 expression is an ongoing area of investigation and remains an unmet need in translational therapeutics.

Of note, no responders were observed in the combination treatment group. Several factors may have contributed to the limited treatment activity observed in the combination group, including a lower incidence of endometrioid histology (45.8% versus 79.3%), higher grade tumors at diagnosis (Grade 3 in 53.8% versus 31.0%), lower incidence of Wnt-activating mutations (25.9% versus 31.0%), and greater number of prior therapies (≥ 3 in 70.8% versus 44.8%). In addition, all patients in this cohort had received a prior taxane-containing regimen. Future research will explore how prior therapies influence the activity of DKN-01 as monotherapy or in combination in endometrial cancer.

DKN-01 was well tolerated in this study either when given as monotherapy or in combination with paclitaxel. Consistent with the known safety profile of DKN-01, gastrointestinal disorders (nausea, vomiting, constipation) as well as fatigue were the most common types of related TEAEs. Discontinuations due to treatment were rare, and no treatment-related fatalities were noted.

Taken together, these results indicated that there is a potential role for DKN-01 therapy in gynecologic malignancies, particularly in patients with elevated tumoral expression of DKK1. Although this study did not demonstrate additive benefit in combination with paclitaxel, recent research suggests a potential synergy of DKN-01 with immunotherapy.

Preclinically, DKN-01 reverses innate immune suppression in the tumor microenvironment and has additive efficacy in combination with anti-PD-1 inhibitors in animal cancer models [18]. In a Phase 1 study, the combination of DKN-01 and pembrolizumab in anti-PD-1/programmed death-ligand 1-naïve GEJ/GC demonstrated improved efficacy and survival outcomes in patients with high DKK1-expressing tumors compared to low DKK1-expressing tumors, with longer PFS (22.1 vs 5.9 weeks; HR: 0.24, 95% CI: 0.08–0.67), OS (31.6 vs. 17.4 weeks; HR: 0.41, 95% CI: 0.16–1.07), higher ORR (50% vs 0), and higher ODCR (80% vs 20%) [22]. This evidence suggests that DKN-01 has immunomodulatory properties and synergizes with checkpoint inhibitors, providing a rationale for the future clinical development of a DKN-01 anti-PD-1 combination in endometrial cancer patients with elevated tumoral expression of DKK1.

Our study is the first phase 2 trial to provide clinical evidence for the use of DKK1 as a biomarker in gynecologic malignancies, demonstrating the potential impact of DKN-01 treatment in patients with high expression. Future areas of research include development of a genetic signature to identify patients who might most benefit from this therapy, investigation into other combination therapies, and better understanding of the role of DKN-01 as a synergistic agent for immunotherapy in the treatment of endometrial cancer.

## Rebecca Arend – Conflict of Interest

Company
AstraZeneca – Advisory Board
Caris Life Sciences – Advisory Board
Clovis – Advisory Board
Merck – Steering Committee
Seagen – Advisory Board
Sutro – Advisory Board
GSK – Advisory Board
VBL Therapeutics – Steering Commitee

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## CRediT authorship contribution statement

**Rebecca Arend:** Conceptualization, Methodology, Resources, Investigation, Supervision, Writing – original draft. **Jhalak Dholakia:** Formal analysis, Writing – review & editing. **Cesar Castro:** Resources, Investigation. **Ursula Matulonis:** Resources, Investigation. **Erika Hamilton:** Resources, Investigation. **Camille Gunderson Jackson:** Resources, Investigation. **Kristopher LyBarger:** Resources, Investigation. **Howard M. Goodman:** Resources, Investigation. **Linda R. Duska:** Resources, Investigation. **Haider Mahdi:** Resources, Investigation. **Adam C. ElNaggar:** Resources, Investigation. **Michael H. Kagey:** Resources, Investigation. **Amy Liu:** Resources, Investigation. **Diane Piper:** Resources, Investigation. **Lisa M. Barroilhet:** Formal analysis, Data curation, Visualization, Writing – original draft. **William Bradley:** Formal analysis, Data curation, Visualization, Writing – original draft. **Jasgit Sachdev:** Formal analysis, Data curation, Visualization, Writing – original draft. **Cynthia A. Sirard:** Methodology, Supervision, Resources. **David M. O'Malley:** Resources, Investigation, Supervision. **Michael Birrer:** Conceptualization, Methodology, Supervision.

## Declaration of Competing Interest

Dr. Arend participates in Data Safety Monitoring/Advisory Boards (DSMB) for Astra Zeneca, Caris Life Sciences, Clovis, Merck, Seagen, Sutro, Glaxo Smith Kline, VBL Therapeutics. Dr. Matulonis reports relationships with the Med Learning Group and participates in DSMB for: Allarity, NextCure, Alkermes, Symphogen, Trillium, Agenus, Immunogen, Novartis, Boerhinger Ingelheim, Rivkin Foundation, Ovarian Cancer Research Alliance, Clearity Foundation, and Morphosys. Dr. Kagey and Dr. Sirard are employed by and own stock in Leap Therapeutics. Dr. Hamilton reports consulting or advisory for: Pfizer (Inst), Genentech/Roche (Inst), Lilly (Inst), Puma Biotechnology (Inst), Daiichi Sankyo (Inst), Mersana (Inst), Boehringer Ingelheim (Inst), AstraZeneca (Inst), Novartis (Inst), Silverback Therapeutics (Inst), Black Diamond (Inst). Dr. Sachdev participates in DSMB for Pfizer, Immunomedics, AstraZeneca, Tempus, and Ipsen; discloses stock/options in Biosplice Therapeutics; and is employed by Biosplice Therapeutics. Dr. Duska reports royalties from JB Learning, consulting fees from UpToDate, serves as an expert law review, and participates in DSMB for Regeneron and Inovio. She reports leadership in SGO, ASCO, the NCI, and the British Journal of OBGYN. Dr. ElNaggar reports employment and stock/options with Natera. Ms. Liu and Ms. Piper were employed by LEAP Therapeutics during manuscript preparation. Dr. O'Malley participates in DSMB for: AbbVie, AdaptImmune, Agenus, Arquer Diagnostics, Arcus Biosciences, AstraZeneca, Atossa Therapeutics, Boston Biomedical, Cardiff Oncology, Celcuity, Clovis Oncology, Corcept Therapeutics, Duality Biom, Eisai, Elevar, Exelixis, Genentech, Genelux, GlaxoSmithKline, GOG Foundation, Hoffman-LaRoche, ImmunoGen, Imvax, InterVenn, INXMED, IOVANCE Biotherapeutics, Janssen, Laekna, Leap Therapeutics, Luzsana Biotechnology, Merck, Merck Sharp & Dohme, Mersana, Myriad, Novartis, NovoCure, OncoC4, Onconova, Regeneron, RepImmune, R Pharm, Roche, SeaGen, Sorrento, Sutro, Tarveda, Toray, Trillium, Umoja, Verastem, VBL Therapeutics, Vincerx, Xencor, Zentalis. All other authors report no disclosures.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.03.013.

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