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Clinical development of WEE1 inhibitors in gynecological cancers: A systematic review

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ABSTRACT

Introduction: The anti-tumor activity of WEE1 inhibitors (WEE1i) in gynecological malignancies has recently been demonstrated in clinical trials and its rationale is based on biological/molecular features of gynecological cancers. With this systematic review, we aim to outline the clinical development and current evidence regarding the efficacy and safety of these targeted agents in in this patient group.

Methods: Systematic literature review of trials including patients with gynecological cancers treated with a WEE1i. The primary objective was to summarize the efficacy of WEE1i in gynecological malignancies regarding objective response rate (ORR), clinical benefit rate (CBR), overall survival (OS) and progression-free survival (PFS). Secondary objectives included toxicity profile, Maximum Tolerated Dose (MTD), pharmacokinetics, drug-drug interactions and exploratory objectives such as biomarkers for response.

Results: 26 records were included for data extraction. Almost all trials used the first-in-class WEE1i adavosertib; one conference abstract reported about Zn-c3. The majority of the trials included diverse solid tumors (n = 16). Six records reported efficacy results of WEE1i in gynecological malignancies (n = 6). Objective response rates of adavosertib monotherapy or in combination with chemotherapy ranged between 23% and 43% in these trials. Median PFS ranged from 3.0 to 9.9 months. The most common adverse events were bone marrow suppression, gastrointestinal toxicities and fatigue. Mainly alterations in cell cycle regulator genes *TP53* and *CCNE1* were potential predictors of response.

Conclusion: This report summarizes encouraging clinical development of WEE1i in gynecological cancers and considers its application in future studies. Biomarker-driven patient selection might be essential to increase the response rates.

Introduction

Gynecological cancers are a major burden of disease for a significant group of women [1,2]. Disease recurrence is common and platinum resistance is a notable issue for these patients. For example, a substantial group of ovarian cancer (OC) patients have disease recurrence within six

Abbreviations: CBR, Clinical Benefit Ratio; DCR, Disease Control Rate; mOS, median Overall Survival; mPFS, median Progression Free Survival; MTD, Maximum Tolerated Doses; OC, Ovarian Cancer; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression Free Survival; RP2D, Recommended Phase-II Doses; SAE, Serious Adverse Events; SLR, Systematic Literature Review; WEE1i, WEE1 inhibitor(s).

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months after completion of first line platinum-based chemotherapy [3]. Moreover, durable responses to second line treatments are scarce, although a subset of patients with *BRCA1/2*-mutated ovarian cancer benefit from PARP-inhibitor treatment [4] and a subgroup of patients with cervical cancer and high PD-L1 expression benefit from immunotherapy with checkpoint inhibition [5]. For the large majority of patients, limited therapeutic options exist for metastasized gynecological cancers. The resulting poor overall survival rates emphasizes the unmet need for better treatment options for these patients.

An independent prognostic marker of poor survival in post-chemotherapy serous ovarian carcinoma is the overexpression of the tyrosine kinase WEE1 [6,7]. Such WEE1 overexpression is also described in cervical cancer cells [7]. WEE1 is a tyrosine kinase that functions as a cell cycle regulator, which prevents entry into mitosis following DNA damage (Fig. 1)[8–10]. When DNA damage is signaled through the ATR-CHK1-WEE1 pathway, WEE1 keeps CDK1 in its inactive form, preventing progression through the G2/M cell cycle checkpoint, allowing for DNA repair [8–10]. This expression protects cells with signaled DNA damage from entering mitosis resulting in mitotic catastrophe [11–14]. Some cancer cells rely extra on the G2/M checkpoint for survival, as other main transition checkpoints such as G1/S, can become ineffective due to mutations in tumor suppressors genes *TP53* and/or *RB* [13]. Hallmark features of cervical, ovarian and uterine cancer indeed include high genomic instability and inactivating *TP53*-mutations, making these tumors vulnerable to therapeutic interventions on the G2/M checkpoint [15–19]. The resulting dependence of the G2/M checkpoint can be further amplified by additional DNA damage (e.g. irradiation or chemotherapy) [12]. Exploiting this checkpoint dependency in cancer is a novel therapeutic strategy. When cancer cells are stuck in the G2 phase because of DNA damage, hence preventing entering the M phase through the G2/M checkpoint, they could be forced to (prematurely) enter mitosis by inhibiting the cell cycle regulator WEE1, resulting in mitotic catastrophe and cancer cell death [11,12].

The last few years, several phase-I and phase-II trials reported about the anti-tumor activity of WEE1 inhibitor(s) (WEE1i) in gynecological malignancies [18–24]. The efficacy of this new class of WEE1i, and in particular adavosertib (previously known as MK1775 or AZD1775), has been demonstrated in other cancer types such as head and neck squamous cell carcinoma, locally advanced pancreatic cancer and metastatic colorectal cancer [8,25–28]. However, important progress in clinical development of adavosertib has recently been made in landmark OC trials [19–24], making WEE1i of special interest in this tumor type. Encouraging results have also been published in recurrent uterine serous carcinoma and preclinical effects have been demonstrated for cervical cancer [18,29]. Given the biological and molecular features of gynecological cancers these cancers are particularly vulnerable to WEE1 inhibition [18,19]. Therefore, WEE1 inhibition seems a promising treatment strategy in gynecological cancers.

We aim to systematically summarize and appraise the present literature regarding the efficacy and safety of all WEE1i in clinical development for gynecological malignancies.

Methods

General methodology

The aim of this report is to evaluate clinical efficacy and safety of WEE1i in gynecological cancers using data from clinical studies. A systematic literature review (SLR) was conducted to identify records of relevant trials with patients with gynecological cancers, treated with a WEE1i. The SLR protocol was registered in PROSPERO (CRD420 21295447). This SLR was described according to the preferred reporting items for systematic reviews and *meta*-analyses (PRISMA 2020 guidelines) and its searching extension (PRISMA-S) [30,31]. There were no differences between the registered protocol and the final SLR.

Search strategy

The search encompassed literature databases, trial registries databases, and grey literature sources, from database inception to December 2021. We searched Medline via Ovid, Embase.com, Web of Science Core Collection (SCI-EXPANDED, SSCIO, AHCI, ESCI) and lens.org. For trial registry databases Cochrane CENTRAL, WHO ICTRP, clinicaltrials.gov and clincaltrialsregister.eu were searched. Moreover, we searched abstracts from meetings/conferences including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) using Embase.com. Additionally, as grey literature search, both Google and Google Scholar were used. All searches were performed on

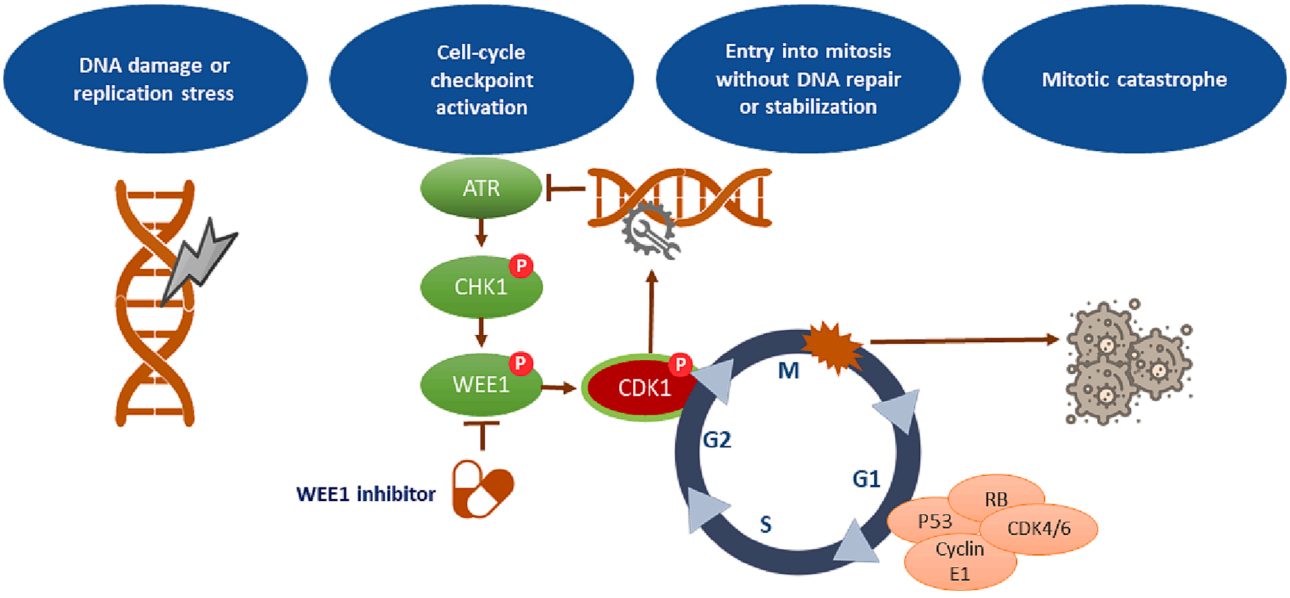

Fig. 1. A simplified and schematic overview of the mechanism of action of WEE1 and WEE1 inhibition. When DNA damage is signaled through the ATR-CHK1-WEE1 pathway, WEE1 keeps CDK1 (cyclin-dependent kinase 1) in its inactive form, preventing progression through the G2/M cell cycle checkpoint, allowing for DNA repair. This expression protects cells with signaled DNA damage from entering mitosis resulting in mitotic catastrophe. Gynecologic cancer cells reside and rely extra on the G2/M checkpoint for survival, as other checkpoints have become ineffective due to common mutations in tumor suppressors genes *TP53* and/or *RB*.

2021–11-04, with exception of the Google and Google Scholar searches which were performed on 2021–12-20 and 2021–12-21, respectively. No federated searches were done.

The schematic search strategy for the databases was: (WEE1 inhibitor OR adavosertib) AND (female reproductive cancers OR phase I/II trials). We used both thesaurus terms (where applicable) and searched in titles, abstracts and author keywords of articles. Complete search queries can be found in APPENDIX-1 and were checked and approved by two information specialists (acknowledgements). For the trial registers and ESMO/ASCO the schematic search strategy was: (WEE1 inhibitor OR adavosertib).

In the regular (databases and register) search no limits, filters or adapted previous search strategies were used. For the grey literature search in Google we limited screening of the results to the 50 hits and for Google Scholar to the first 200. Due to term and character restrictions of Google and Google Scholar we needed to limit the query to the substance names in combination with "trial" or "phase". No other sources or methods were used to identify records of interest (e.g. contacting authors/experts).

To track and find possibly missed relevant literature, Scopus [3] was used for forwards and backwards citation chasing on 2022–01-11. The results were de-duplicated using Bramer's method steps A-D [32]. Afterwards, a manual check was performed to remove remaining duplicates(SvM).

Study selection

Eligibility criteria for the SLR included all clinical trials assessing the efficacy and safety of the previously noted interventions of interest for the treatment of adult patients (≥18 years of age) with gynecological cancers (or solid tumors in general). Clinical efficacy and safety outcomes of interest are described in the following subsection. Studies in English, Dutch, French or the German language were included. After removal of duplicate records, two researchers (TS and AE) independently reviewed remaining publications using Rayyan[33]. Any discrepancies regarding inclusion of articles or data extraction were resolved first by a discussion to reach consensus and if differences would persist by involving a senior reviewer (FO) to reach agreement.

Data extraction and outcomes

Predefined study characteristics and outcomes were extracted from the included records using a data extraction document by two researchers (TS and AE). These relevant data points included study interventions and dosage regimens, sample size, demographic details, previous lines of therapy and the main outcomes of interest. For the primary outcome, efficacy, extracted data included response rates (Objective response rate (ORR), clinical benefit ratio (CBR), overall survival (OS), progression free survival (PFS)). Safety end points were evaluated and included: all reported (treatment) related adverse events, incidence and description of grade ≥ 3 toxicities, incidence and description of serious adverse events (SAE), the maximum tolerated doses (MTD) and recommended phase-II doses (RP2D) of the WEE1i, either monotherapy or in combination with chemotherapy regimens, the pharmacokinetic profiles of the WEE1i(PK), drug-drug interaction data and exploratory objectives such as biomarkers for response and resistance.

Data synthesis, study quality assessment

All results are described narratively, no *meta*-analysis was performed given the heterogeneous patient populations. As a result, no data conversions were performed and no bias due to missing results was analyzed. Possible impact of heterogeneity between studies will be discussed narratively. All outcomes are presented in tables, with the outcomes of effectiveness and the safety endpoints presented separately. The validity of included full-text studies was assessed for Risk of Bias (RoB), using the RoB 2 tool for randomized studies and ROBINS-I tool for the non-randomized studies [34,35]. Two researchers (TS and AE) appraised all included full-text articles using the applicable tool, and discussed the results together. If appraised differences persisted, a third reviewer and senior researcher (FO) was involved. No formal certainty assessment was performed.

Results

Search results

Our search strategy identified 2199 records (excluding Google and Google Scholar). After removing duplicates, we screened the titles and abstracts of 1432 records, excluded 1312 records and selected 120 for full-text reading. We excluded 93 of these 120 records: 64 records did not report on the predefined selected outcome measures of which 22 studies were ongoing trials without results (Table 1**).** 42 exclusions were doubles, including trial registry records with reported results in conference abstract or full-text article. From the original search we included 26 records, 11 full-text articles, 13 conference abstracts and 2 trial registries providing limited results of early terminated trials (clinicaltrials.gov, NCT01047007 and NCT01076400) [36,37].

Citation chasing of the included references lead to 629 references and the grey literature search yielded 250 records. After removing 344 duplicates, we screened the 535 titles and abstracts of these records, selecting 35 for full-text reading. Finally, we excluded all these 35 records, as all were doubles of the original/regular search. The flow diagram of the process of study identification and selection is presented in Fig. 2.

Study characteristics

Of the 26 included records, year of publication ranged 2010–2021, for the full texts this ranges 2015–2021, with 8/11 articles being published in the last two years (2020 & 2021). All studies were early clinical development studies (i.e. phase-I, Ib, or II) and no phase-III or IV studies were identified. Five individual randomized trials were included (for one trial, 2 records reported different outcome measures) [19,38]. Two individual randomized trials were placebo controlled [19,20]. The number of enrolled patients treated with a WEE1i ranged from 18 to 202 (excluding two early terminated trials, counting only WEE1i treated patients in placebo controlled trials). Eight studies specifically included patients with exclusively gynecologic malignancies, of whom five full-texts [18–22], two conference abstracts [38,39] and one trial registry [36]. Eighteen records were studies including patients with solid malignancies in general (however patients with gynecological cancers were/could be included in these trials), of whom six full-texts [8,23,24,28,40,41], eleven conference abstracts and one trial registry [37]. Altogether, the included studies were highly heterogeneous regarding included disease and tumor genetic alterations (*CCNE1/TP53/BRCA1/2*), previous lines of therapy and the interventions studied (either WEE1i monotherapy or combined with other (chemo)therapy, in different schedules). Therefore, a (formal) *meta*-analysis was not possible yet and results are presented narratively.

WEE1 inhibiting Investigational Medicinal Products

Among the different WEE1 inhibiting Investigational Medicinal Products (Table 1, Appendix-2), the large majority of included studies encompass trials with adavosertib (all 11 full-text articles, all but one conference abstract and 17/22 trial registry database records). Zn-c3 is

Table 1

Study characteristics of included full text articles (above grey bar) and included conference abstracts/study registries [b]ORR: Objective response ratio (either by RECIST or laboratory parameters; CBR: Clinical benefit ratio; MTD: Maximal tolerated dose; RP2D: Recommended phase 2 dose; Safety: safety and tolerability including incidence of (serious) adverse events, (dose-limiting) toxicity (DLTs) etc; DoR: Duration of response; PFS: Progression free survival; PK: Pharmacokinetics; A: Adavosertib The rows with a grey background color are trials with gynecological cancers, non-marked is solid tumor trial.

Title	Author	Trial registration id	Cancer type	Cancer type	Wee1 inhibitor	Monotherapy (M) or combined with	Schedule	Randomized?	Placebo controlled (P)	Phase	Primary endpoints	Number of patients treated with	Age	ECOG	number of previous therapies
Phase II study of WEE1 inhibitor AZD1775 plus carboplatin in patients with tp53-mutated ovarian cancer refractory or resistant to first-line therapy within 3 months [12]	Leijen, S., et al.	NCT01164995.	Gyn	Ovarian	Adavosertib	C	Carboplatin	A: 225mg BID on 2.5 days & carboplatin (AUC 5) every 21-day cycles	-	O	II	ORR, DoR and safety	23	Median 58, range 25-74	n.a.	One previous line of therapy n=23 (100%)
Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial [13]	Lheureux, S., et al.	NCT02151292	Gyn	Ovarian	Adavosertib	C	Gemcitabine	A: 175mg QD or Placebo on days 1, 2, 8, 9, 15, and 16 & gemcitabine 1000 mg/m² on days 1, 8, and 15 all in in 28-day cycles	+	P	II	PFS	90	Median age for all included (n=119) was 62 years (IQR 54–67).	total population ECOG 0: n=33 ECOG 1: n=81 ECOG 2: n=5	Cohort A ada + gem: median 3 (2-4) Cohort B pcb + gem: median 3 (2-4) Exploratory cohort: median 3 (2-5)
Phase II Study of the WEE1 Inhibitor Adavosertib in Recurrent Uterine Serous Carcinoma. [20]	Liu, J., et al.	NCT03668340	Gyn	Uterine	Adavosertib	M		A: 300mg QD days 1-5 and 8-12 of a 21-day cycles	-	O	II	ORR, PFS	35	Median age in years (range) 70.2 (58.9-88.5)	ECOG 0: n=11 (32.4%) ECOG 1: n=23 (67.6%)	Median 3, range 1-8
Adavosertib with Chemotherapy in Patients with Primary Platinum-Resistant Ovarian, Fallopian Tube, or Peritoneal Cancer: an Open-Label, Four-Arm, Phase II Study [21]	Moore, K. N., et al.	NCT02272790 & EudraCT2015-000886-30	Gyn	Ovarian	Adavosertib	C	Gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin.	A: 175mg QD to 225mg BID 2 days on/5 days off or 3 days on/4 days off in six cohorts, all combined with gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin	-	O	II	ORR	94	Overall median age 60 (34–85)	ECOG 0: 45 (47.9%) ECOG 1: 49 (52.1%)	Median 2 lines of prior systemic therapy (1-4)
A Biomarker-enriched, Randomized Phase II Trial of Adavosertib (AZD1775) plus Paclitaxel and Carboplatin for Women with Platinum-sensitive TP53-mutant Ovarian Cancer [22]	Oza, A. M., et al.	NCT01357161	Gyn	Ovarian	Adavosertib	C	Carboplatin & Paclitaxel	A: 225mg BID for 2.5 days/21-day cycle or placebo, & carboplatin(AUC5) and paclitaxel (175 mg/m2)	+	P	II	PFS, Safety (DLTs)	59	Cohort A+C: median 58 (range: 42–77) Cohort P+C: median 60 (range: 40–80)	ECOG 0: A: n=38 (64%) P: n=35 (57%) ECOG 1: A: n=21 (36%) P: n=27 (44%)	Median 1 line of platinum-based therapy.
Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT): A Randomized Multicenter Phase II Trial [42]	Chen, A., et al.	NCT01827384	Solid		Adavosertib**	C	Carboplatin	A: 225mg BID Days 1-5 & Carboplatin AUC 5 on Day 1, 21-day cycles	+	O	II	ORR	24	Median 54.5 (overall) median 55.5 (Intervention) 46 (control)	Karnofsky PS 100% n=10; 90% n=114 80% n=65; 0% n=9	median 4 lines (intervention) median 3,5 lines (control) median4 lines (overall)
Phase I study of single-agent AZD1775 (MK-1775), a wee1 kinase inhibitor, in patients with refractory solid tumors [9]	Do, K., et al.	NCT01748825	Solid		Adavosertib	M		A: 225 mg BID, 2.5 days for 1 week of a 21-day cycle (DL1), 225mg(DL2) or 300mg(DL3) BID for 2.5 days per week for 2 weeks of a 21-day cycle.	-	O	I	Safety, MTD	25	Median 52 years (range 22-78) (overall)	n.a.	mean 5 Range 1-9
Safety, Pharmacokinetics, and Clinical Activity of Adavosertib in Combination with Chemotherapy in Asian Patients with Advanced Solid Tumors: Phase Ib Study [24]	Kato, H., et al.	NCT02341456	Solid		Adavosertib	M&C	carboplatin and paclitaxel	C1 (A175PC): A175mg BID 2.5 day & paclitaxel 175 mg/m² & carboplatin AUC 5 C1a: (A175C): A 175mg BID 2.5 day & carboplatin AUC 5 C2 (A225PC): A 225mg BID 2.5 day & paclitaxel 175 mg/m² & carboplatin AUC 5 all-in 21 day cycles for max. 6 cycles, followed by A monotherapy	-	O	Ib	Safety	19	Median (range) C1 55.0 (46-62) C2 57.0 (34-66) C1a 49.5 (19-56)	n.a.	Median ≥ 5
Phase I study evaluating WEE1 inhibitor AZD1775 as monotherapy and in combination with gemcitabine, cisplatin, or carboplatin in patients with advanced solid tumors [25]	Leijen, S., et al.	NCT00648648	Solid		Adavosertib	M&C	Gemcitabine, cisplatin or carboplatin	A: once 325-1300mg (part 1); A: 100-325 once a cycle of 21 days (Part 2a); A: 25-325mg BID for 2.5 days with gemcitabine (1,000 mg/m2), or cisplatin (75 mg/m2), or carboplatin (AUC 5) or A 100-200QD for 2 days combined with gemcitabine (Part 2b)	-	O	I	Safety (DLT), PK/PD	202	mean 57.7 SD 12.0, range 31-78	ECOG 0: n=73 (36%) ECOG 1: n=128 (64%)	1: n=108 (54%); 2: n=51 (25%); 3: n=24 (12%); 4 or more lines n=18 (9%)
Effect of food on the pharmacokinetics of the WEE1 inhibitor adavosertib (AZD1775) in patients with advanced solid tumors [41]	Någård, M., et al.	NCT03315091	Solid		Adavosertib	M		A: once 300mg	+	O	I	PK	31	Mean 61.5 (9.1 SD) Median 61.0 (42–77 range)	ECOG 0: n=12 (38.7%) ECOG 1: n=19 (61.3%)	Median 4 (range 1-8)
Safety, antitumor activity, and biomarker analysis in a phase I trial of the once-daily wee1 inhibitor adavosertib (AZD1775) in patients with advanced solid tumors [26]	Takebe, N., et al.	NCT01748825	Solid		Adavosertib	M		A: 200mg QD with escalations to 225, 250, 300, and 400mg QD on days 1-5 and 8-12 in 21-day cycles	-	O	I	Safety, PK	42	Median age 64 (range, 26–83)	ECOG 0: n=4 ECOG 1: n=38	median 5.5 lines of prior therapy (range, 0–15).
Patient self-reporting of tolerability using PRO-CTCAE: a randomized double-blind placebo controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in women with platinum resistant epithelial ovarian cancer [23]	Madariaga, A., et al.	NCT02151292	Gyn	Ovarian	Adavosertib	C	Gemcitabine	A: 175mg QD or Placebo on days 1, 2, 8, 9, 15, and 16 & gemcitabine 1000 mg/m² on days 1, 8, and 15 all in in 28-day cycles	+	P	II	PFS	28	n.a.	ECOG status was ≤1 in 44/47pts.	intervention median 5 (1-16) control median 2 (1-16)
EFFORT: eFficacy Of adavosertib in parp ResisTance: a randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer [28]	Westin S. N. et al.	NCT03579316	Gyn	Ovarian	Adavosertib	C	Olaparib	Cohort 1: A: 300mg QD days 1-5 and 8-12 of a 21-day cycle. Cohort 2: A 150mg BID days 1-3 and 8-10 and Olaparib 200mg BID days 1-21 of a 21-day cycle.	+	O	II	ORR	80	60 years (range 36-76)	n.a.	median of 4 (range 1-11)
A Study of MK-1775 in Combination With Topotecan/Cisplatin in Participants With Cervical Cancer (MK-1775-008) [46]	-	NCT01076400	Gyn	Cervical	Adavosertib	C	Topotecan/Cisplatin	Part 1: A: once 50mg of adavosertib Part 2: A: 50mg BID Days 1-4, once on Day 5, Topotecan 0.75 mg/m^2 on Days 1-3 of each cycle. Cisplatin 50 mg/m^2 on Day 1 of each cycle. 21-day cycles	-	O	I/IIa	ORR, DLTs, PFS (for part 2)	7	Mean 50.3 (SD 3.5)	n.a.	n.a.
Open-label, multicenter, Phase Ib study to assess safety, tolerability and efficacy of adavosertib monotherapy in patients with advanced solid tumors: Expansion cohorts [43]	Bauer, T. M., et al.	NCT02482311	Solid		Adavosertib	M		A: 175mg BID days 1–3 and 8–10 per 21-day cycle	-	O	Ib	Safety	80	Overall: median 60 (35 - 83)	ECOG 0: n=26 (33%) ECOG 1: n=54 (68%)	overall: median 5, (range 1 to >6
A Phase Ib study of Wee1 inhibitor adavosertib in patients with advanced solid tumors [44]	Falchook, G. S., et al.	NCT02610075	Solid		Adavosertib	M		A: 200-300mg (QD) or 125-150mg BID for 5 days on, 9 days off (5/9) in 14-day cycles, or 5 days on, 2 days off; weekly or 2 out of 3 weeks in 21-day cycles	-	O	Ib	Safety (DLTs)	62	median age, 61.5 years	n.a.	0
Phase II trial of the Wee1 inhibitor adavosertib in advanced refractory solid tumors with CCNE1 amplification [47]	Fu, S., et al.	NCT03253679***	Solid		Adavosertib	M		A: 300mg QD days 1-5 and 8-12 of a 21-day cycle.	-	O	II	ORR	29	n.a.	n.a.	The median line of prior systemic therapy was 4 (range 1-8)
Phase Ib study of adavosertib in combination with olaparib in patients with refractory solid tumors: Dose escalation [29]	Hamilton, E., et al.	NCT02511795	Solid		Adavosertib	C	Olaparib	A: 125-175mg BID or 200-300mg QD for 3 days on, 4 days off treatment (3/4), or 5 days on, 2 days off (5/2), plus olaparib (BID) for 14 days of a 21-day cycle	-	O	Ib	Safety (DLTs)	119	median age 59;	n.a.	n.a.
Model based analysis of the effect of AZD1775, a WEE1 kinase inhibitor on olaparib exposure [45]	Johnson, M., et al.	?	Solid		Adavosertib	C	Olaparib	A: Dose unknown, with Olaparib, dose unknown	?	?	?	PK	n.a	n.a.	n.a.	n.a.
NCI-MATCH EAY131 -Z1I: Phase II study of AZD1775, a wee-1 kinase inhibitor, in patients with tumors containing BRCA1 and BRCA2 mutations [52]	Kummar, S., et al.	NCT02465060	Solid		Adavosertib	M		A: 300mg QD for 5 days on, 2 days off, 2 weeks on and 1 week off; 21-day cycles.	-	O	II	ORR	31	range 36-79 yrs.	ECOG 0: (n=5) ECOG 1: (n=26)	n.a.
Clinical pharmacokinetics of adavosertib in the presence or absence of PD-L1 inhibitor durvalumab in patients with refractory solid tumors [48]	Miah, K., et al.	NCT02617277	Solid		Adavosertib	C	Durvalumab	A: 125–175 mgBID or 200–300 mg QD & Durvalumab 1500mg once every cycle of 28-days	-	O	I	Safety (DLTs)	n.a.	n.a.	n.a.	n.a.
Phase I study to assess the effect of adavosertib (AZD1775) on the pharmacokinetics of substrates of CYP1A2, CYP2C19 and CYP3A4 in patients with advanced solid tumors [27]	Någård, M., et al.	NCT03333824	Solid		Adavosertib	C	cocktail of Caffeine Omeprazole, Midazolam (all single dose)	A: 225mg BID on days 1–3 (5 doses), with a a cocktail of Caffeine 200mg, Omeprazole 20mg, Midazolam 2mg (all single dose) on day 3.	-	O	I	PK/PD	30	median age, 60.0 years, range 41-83	n.a.	n.a.
Adavosertib (AZD1775) does not prolong QT interval in patients with advanced solid tumors: A Phase I open-label study. [40]	Någård, M., et al.	NCT03333824	Solid		Adavosertib	M		A: 225mg BID for 2.5 days	-	O	I	PK/PD	21	median age, 60.0 years, range 41-83	n.a.	n.a.
Open-label, multicenter, phase I study to assess safety and tolerability of adavosertib plus durvalumab in patients with advanced solid tumors [49]	Patel, M. R., et al.	NCT02617277	Solid		Adavosertib	C	Durvalumab	A: 125–175mg BID or 200–300mg QD for 4 different schedules & Durvalumab 1500mg once every cycle of 28-days	-	O	I	Safety (DLTs)	54	n.a.	n.a.	n.a.
Clinical activity of single-agent ZN-c3, an oral WEE1 inhibitor, in a phase 1 dose-escalation trial in patients with advanced solid tumors. [50]	Tolcher, A. W., et al.	NCT04158336	Solid		Zn-c3	M		ZN-c3: 25mg to 450mg orally QD	-	O	I/II	Safety (DLTs), MTD, RP2D, ORR	39	n.a.	n.a.	n.a.
A Dose Escalation Study of MK1775 in Combination With 5-FU or 5-FU/CDDP in Patients With Advanced Solid Tumor (1775-005) [51]	-	NCT01047007	Solid		Adavosertib	C	5-FU or SFU with cisplatin	Part 1: A 65mg BID Days 1-5 of a 21-day cycle. Part 2: A 20mg BID Days 1-5 with 5-FU 1000mg/m^2/d on days 1-4 /21-d cycle. Part 3: A 20mg QD Days 1-5 with 5-FU 1000 mg/m^2/d / days 1-4 /21-d cycle.	-	O	I	Safety (DLTs), MTD	11	mean 62.1 (SD 6.4)	ECOG 0: n=7 ECOG 1: n=4	mean 3.1 (SD 0.9) Chemotherapy regimes

the only other WEE1i with published results (conference abstract) [42]. Although different (pre-)clinical trials with other WEE1i (e.g. IMP7068, SC0191, Debio0123, SDGR2, NUV569, CJM061, PD0407824, PD0166285 are ongoing (Appendix) no results are in the public domain yet.

Risk of bias (RoB) assessment

The RoB of all full-text articles was assessed, using ROBINS-I for the 7 non-randomized articles [8,18,21–24,28] and RoB v2.0 tool for the remaining 4 randomized studies [19,20,40,41]. The RoB is visualized in Appendix-4, including evaluation per domain. The overall RoB was serious in all non-randomized articles, mainly due to confounding. All four randomized trials had a low RoB.

Primary outcome: Effectiveness

Efficacy outcomes were reported in 18 records (Table 2), eight records did not report any results about efficacy [36–38,41,43–46] of whom five conference abstracts [38,43–46], one full-text article on food effects on adavosertib pharmacokinetics [41] and two 2 trial registries providing limited results of early terminated trials (clinicaltrials.gov, NCT01047007 and NCT01076400) [36,37]. Objective response rates ranged from 0 to 67% and were reported in ten full-text and seven conference abstract records.

Disease Control Rate (DCR) or CBR was reported or could be calculated in nine full-text and seven conference abstracts and ranged 33–89%. Median PFS ranged 1.7–12.0 months and was reported in five full-text [18–22] and four conference abstract records [39,47–49]. Median overall survival (mOS) was reported in three full-text articles [19,21,22] and ranged and 6.2–19.2 months, although immature data indicate a mOS of > 35.4 months in another study [20]. The extensive ranges in the outcome measures reflects heterogeneity between the studies (e.g. study population, treatment regimens, previous therapies; presented in Table 1 highlights this heterogeneity). Specific subtypes of gynecological cancer and the undifferentiated solid tumor studies are summarized hereafter.

Ovarian cancer

The subtype ovarian cancer also includes both fallopian tube and peritoneal cancer as it constitutes one single disease entity. Therefore, in the rest of the paper, "ovarian cancer" (OC) is used for ovarian, fallopian tube and/or peritoneal cancer. Important clinical differences exist between histologic subtypes (i.e. serous and non-serous) and biologic behavior (i.e. low- and high-grade) subtypes of ovarian cancer. Driver mutations of *TP53* are a hallmark feature of high grade (serous) ovarian cancer, and although not all trials specifically described *TP53* mutation and disease grade, these characteristics are thus interchangeable. The addition of a WEE1i for patients with ovarian cancer was reported in four full-text records [19–22] and in one conference abstract [39]. In these trials, different stages/settings were included, (e.g. platinum sensitive and platinum resistant/refractory). Patients with ovarian cancer were enrolled in different solid tumor trials. Due to lack of subgroup analyses in these trials, these results are not described separately.

Platinum sensitive ovarian cancer (PSOC)

For platinum sensitive ovarian cancer (PSOC), a randomized, placebo controlled phase-II trial evaluated effectiveness of adavosertib plus

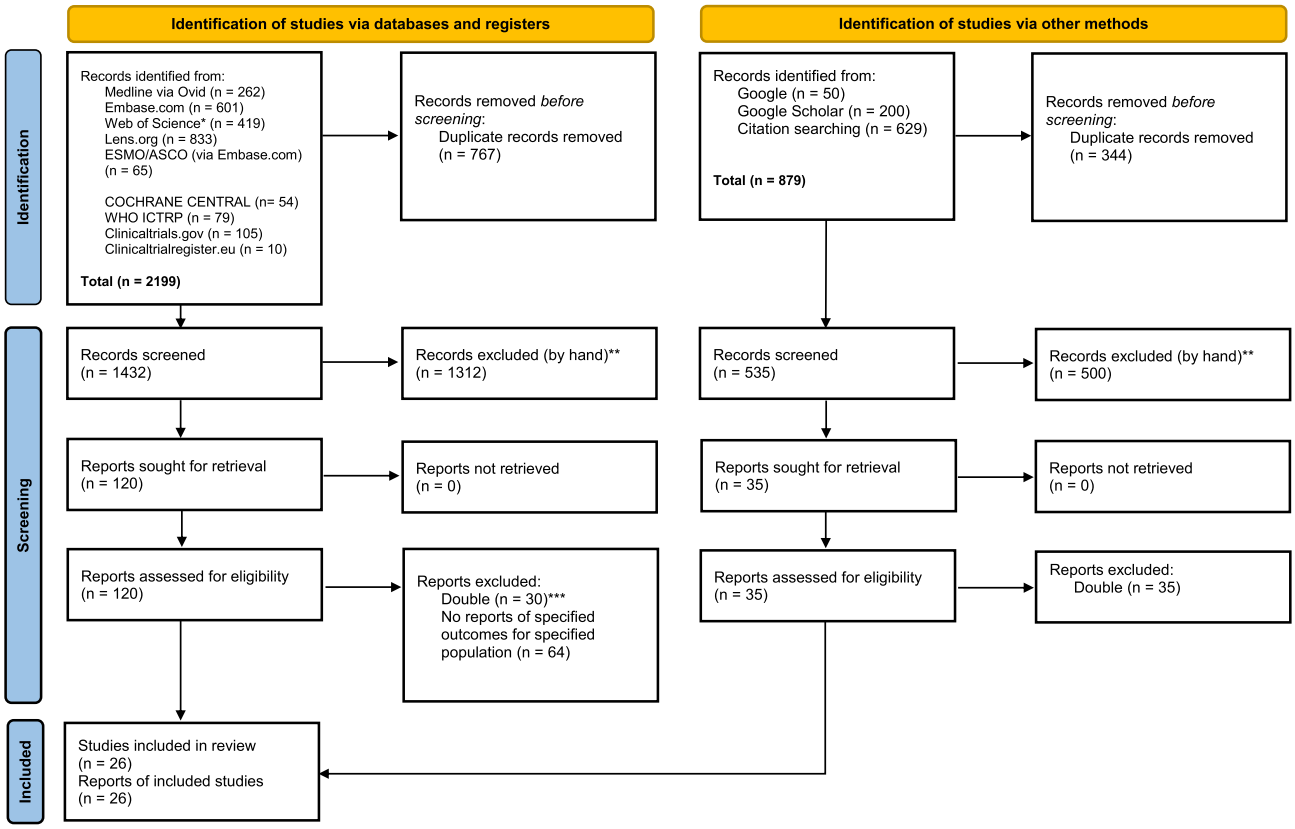

Fig. 2. The PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. A small adaptation to the original diagram included the addition of a de-duplication before screening and a screening step/box before the retrieval step, this to make the procedure for the "other methods " equivalent to those of the regular database. * Web of science: Web of Science Core Collection including SCI-EXPANDED, SSCIO, AHCI and ESCI. **For screening we used the Rayyan application which allowed us (TS & AE) to individually screen by hand (blinded from each other). For the regular search, a total of 36 conflicts (36/2199 = 2.5% conflict ratio) emerged after de-blinding, which were promptly resolved after a discussion between the screening authors. The large majority (34/36) of conflicts were resolved by including the disputed report. For the google scholar search a single conflict was also promptly resolved after a discussion (1/79 1.3% conflict ratio). *** Doubles include trial registries with reported results in trial registry database (n = 7) which results have also been published as conference abstract or full-article, if included.

paclitaxel and carboplatin for women with *TP53*-mutant, non-low-grade PSOC [20]. In this trial, >70% of patients had a serous histology and previous treatments included a median of one previous line of platinum-based therapy. The median PFS (mPFS) was 1.9 months longer with adavosertib vs placebo (9.9 vs 8.0 months, p = 0.030) [20]. There was no significant difference in OS between the two groups.

Platinum resistant (PROC) or refractory ovarian cancer

Three trials evaluated the addition of adavosertib in patients with PROC [19,21,22]. One phase-II trial with adavosertib plus carboplatin in patients with *TP53*-mutated PROC or resistant to first-line therapy demonstrated an 43% ORR (95%CI, 22–66%), CBR of 76%, mPFS of 5.3 months (95%CI 2.3–9.0) and median OS of 12.6 months (95% CI, 4.9–19.7) [22]. The investigators included an additional cohort of *TP53*-mutated PROC patients to gain more safety, efficacy and translational data of the combination carboplatin plus adavosertib. The results of this cohort are expected soon. Another, larger phase-II trial of 94 patients with PROC assessed the effect of adavosertib with either gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin [21]. In this trial, patients had a median two lines of prior therapy. The results showed an 32% ORR, 5.5 months mPFS (95%CI 3.9–7.2) and median OS of 19.2 months (95%CI 12.4–19.2) which are somewhat longer than the previous mentioned smaller phase-II trial [22].

The third trial of adavosertib in patients with ovarian cancer who were progressive on previous platinum based therapy was a double-blind randomized placebo-controlled phase-II trial assessing the value of adding adavosertib to gemcitabine [19]. This study demonstrated a significant better ORR of 23% for the adavosertib-gemcitabine cohort, compared to 6% in the placebo-gemcitabine cohort (p = 0.038). This ORR resulted in a significant benefit in mPFS of 1.6 months (HR 0.55 [95%CI 0.35–0.90]; p = 0.015) and OS benefit of 4.2 months HR 0.56 (95%CI 0.35–0.91); p = 0.017) [19](Table 2). Ongoing trials for patients with PROC include a phase-Ib trial to evaluate safety and efficacy of ZN-c3 in an estimated number of 140 patients with PROC (Appendix-3).

Other specific sub-groups of ovarian cancer

In one conference abstract reporting on the (preliminary) results of a randomized phase-II trial of adavosertib with or without olaparib in women with PARP-resistant OC (EFFORT, NCT03579316) [39], patients received either adavosertib monotherapy or adavosertib with olaparib (cycle details/doses, Table 2). This conference abstract reports on the first 70 evaluable patients with an ORR of adavosertib monotherapy of 23% (90%CI 12–38) and an ORR of the adavosertib and olaparib combination of 29% (90%CI 16–44) [39]. The reported mPFS were 5.5 months (90%CI 3.9–6.9) and 6.8 months (90%CI 4.3–8.3) for the adavosertib monotherapy and in combination with olaparib respectively [39]. This study is ongoing and full results are expected soon. Another large ongoing phase-II trial is the IGNITE-trial (ACTRN12619 001185156) evaluating adavosertib in cyclin E1 altered high grade serous ovarian cancer and intends to enroll 96 patients. The use of WEE1i as neo-adjuvant treatment is evaluated in a phase-I trial for 30 patients with advanced high grade OC, who will be treated with adavosertib monotherapy prior to tumor reductive surgery (NCT02659241).

Table 2

Outcomes of effectiveness for the different included records. Outcomes of effectiveness of WEE1i reported in the full text articles (above grey bar) and in conference abstracts (below grey bar), records not reporting on outcomes of effectiveness were not displayed in this table [36–38,41,43–46].N.a.: not available. DCR / CBR defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease;

Author	Analysed population. n(%)	Objective response rate (months)	Duration of response (DoR)	PFS	Disease Control Rate (DCR) and Clinical Benefit Rate (CBR)	Overall survival
Chen, A., et al. [40]	overall: 24/198 enrolled = 12,1% Intervention n=18	n=0 = 0%	n.a.	4m PFS 30.8% in experimental Adavosertib-carboplatin cohort, not significantly different from the 25% standard (P = .32; 95% CI, 13.2% to 71.9%)	DCR 12/24 (50%) overall group, matched 8/18 =44,4%	n.a.
Do, K., et al. [4]	21/25 (84%)	2/21 = 9.5%	n.a.	n.a.	n.a.	n.a.
Kato, H., et al. [38]	Cohort 1 (Ada175PaclCarbo) N = 6 Cohort 2 (A225PC) N = 6 Cohort 1a (A175C) N = 6	Cohort 1: n=1 (16.7%) Cohort 2: n=3 (50.0%) Cohort 1a: n=1 (16.7%)	Cohort 1: 18.1 (NE, NE) Cohort 2: 20.7 (NE, NE) Cohort 1a: NE (NE, NE)	n.a.	Cohort 1: n=3 (50.0%) Cohort 2: n=5 (83.3%) Cohort 3: n=3 (50.0%)	n.a.
Leijen, S., et al. [23]	Overall 176/202 (87%) Cohort 2A: n=63 Gem n=14; CDDP n=13; Carbo n=16 Cohort 2B: n=158 Gem n=67; CDDP n=45 ; Carbo n=46	Overall n=17/176 (10%) Cohort 2A Gem n=1 (8%); CDDP n=2 (17%); Carbo n=2 (13%) Cohort 2B Gem n=3 (5%); CDDP n=7 (18%); Carbo n=2 (5%)	n.a.	n.a.	Overall CBR n=111/176 (63%) PR 17/176 pts (10%) SD 94/176 pts (53%)	n.a.
Leijen, S., et al. [22]	21/24 (87.5%)	n=9/21 = 43% (95% CI, 22-66%) 41% in the intent-to-treat population.	n.a.	mPFS: 5.3 months (95% CI 2.3 - 9.0)	Overall CBR n=16/21 (76%) SD: n=7 (33%); PR: n=8 (38%); CR: n=1 (5%)	Median OS 12.6 months (95% CI, 4.9-19.7)
Lheureux, S., et al. [39]	Randomized cohort:94/ 99 (95%) Exploratory cohort 25/25 (100%)	Cohort ada + gem: n=14/61 (23%) Cohort pcb + gem: n=2/33 (6%) Exploratory cohort ada + gem: n=4/25 (16%)	Cohort ada + gem: Median PFS 4.6 months (95% CI 3.6–6.4) Cohort pcb + gem: Median PFS 3.0 months (95% CI 1.8–3.8)	Cohort ada + gem (n=14): median DoR: 3.7 months (IQR 3.5–9.6) Cohort pcb + gem (n=2): DoR: 5.8 months and 12.9 months	ada + gem CBR: n= 49 (80%) pcb + gem CBR: n= 26 (79%) Exploratory cohort CBR: n=13 (52%)	ada + gem: 11.4 months (95% CI 8.2–16.5) pcb + gem: 7.2 months (95% CI 5.2–13.2)
Liu, J., et al. [18]	34/35 (97%)	n=10/34 (29.4%) (95% CI 15.1-47.5)	median DoR 9.0 months (95% CI, 5.3-NA)	n=16 progression-free at 6 months PFS6 rate of 47.1% (95% CI, 29.8-64.9). Median PFS was 6.1 months (95% CI, 4.21-9.92)	n=7 SD for at least 6 months; Overall CBR was 50% (95% CI 32.4-67.6). Overall SD n=9 Overall DCR: n=19/34 (55.9%)	n.a.
Moore, K. N., et al. [21]	94/94 (100%)	Overall: n=30/94 (31.9%) Ada + Gem: 1/9 (11.1%) Ada + Pacli: 11/38 (28.9%) Ada + Carbo: 7/23 (30.4%) Ada + Carbo: 8/12 (66.7%) Ada + PLD1: 2/6 (33.3%) Ada + PLD2: 1/6 (16.7)	n.a.	mPFS (95% CI) - Overall 5.5 months (3.9–7.2) Ada + Gem: 1.7 (0.3–5.5) Ada + Pacli: 5.5 (3.7–7.4) Ada + Carbo: 4.2 (2.8–8.9) Ada + Carbo: 12.0 (2.7–NC) Ada + PLD1: 2.7 (0.5–NC) Ada + PLD2: NC	Overall: n=69/94 (73.4) Ada + Gem: 3/9 (33.3%) Ada + Pacli: 27/38 (71.1%) Ada + Carbo: 19/23 (82.6%) Ada + Carbo: 12/12 (100.0%) Ada + PLD1: 3/6 (50.0%) Ada + PLD2: 5/6 (83.3)	Overall median OS 19.2 (12.4–19.2) Ada + Gem: 16.0 (2.2–NC) Ada + Pacli: NC (11.6–NC) Ada + Carbo: 8.9 (6.5–NC) Ada + Carbo: 19.2 (12.4–19.2) Ada + PLD1: 6.2 (2.0–NC) Ada + PLD2: NC (NC–NC)
Oza, A. M., et al. [20]	121/121 (100%)	ORR (95% CI) cohort Ada + Carbo: 66.1% (52.6–77.9%) cohort Pcb + Carbo: 51.6% (38.6–64.5%)	n.a	mPFS Ada + Carbo 9.9 months Pcb + Carbo 8.0 months	enhanced RECIST 1.1 & CA-125 (CR/PR/SD) cohort Ada + Carbo: (11.9%/62.7%/5.1%) n=47/59 (79.7%) cohort Pcb + Carbo: (8.9%/61.3%/4.8%) n=46/62 (74.2%)	median OS Ada + Carbo not calculable Pcb + Carbo 35.4 months
Takebe, N., et al. [19]	35/42 (83%)	n=6/42 (itt) (14%): (90% CI 6%– 26%) Ovarian: 4/10 (40%) Endometrial : 2/3 (67%)	median DoR 4.9 months (range, 4.3–23.3),	n.a.	overall: PR 6; SD 20 = 26/42 (62%)	n.a.
Bauer, T. M., et al. [48]	80	Overall: n=3 (4%) cohort A: n=1 (6%) cohort B: n=1 (3%)	n.a.	Overall: mPFS 3.0 Months Cohort A: 4.5 months Cohort B: 3.9 months	Overall: n=51 (64%) (CR: 0 PR: n=3 (4%) SD ≥5 weeks n=48 (60%)) cohort A: n=11 (69%) cohort B: n=23 (77%)	n.a.
Falchook, G. S., et al. [49]	59/62 (95%)	Total population 2/59= 3.4% (n=2 [thymoma; anal])	n.a.	mPFS is 2.7 months	DCR 30/59 (48.4%)	n.a.
Fu, S., et al. [47]	27/29 (93%)	7/27 =25.9% (95% CI 15.1-47.5%).	n.a.	mPFS: 4.0 months	n.a.	one-year overall survival was 55%
Hamilton, E., et al. [53]	98/119 (82.4%)	total population 11.1% MTD/RP2D BID 30.8% MTD/RP2D QD 0%	n.a.	n.a.	total population 55.7% @ MTD/RP2D BID 76.9% @ MTD/RP2D QD 53.8%	n.a.
Kummar, S., et al.[57]	31/33 (94%)	3.2% (90% CI 0.15%-14.4%)		6-month PFS rate 19% (90% CI 10%-36%)	CBR = 5/31= 16%	n.a.
Patel, M. R., et al. [54]		n.a.	n.a.	n.a.	DCR total cohort: 36%	n.a.
Tolcher, A. W., et al. [42]	16	ORR 2/16 PR = 12,5%	n.a.	n.a.	CBR 7/16 = 44%	n.a.
Westin, S.N. et al. [46]	Total 70 Cohort Ada: 35; Cohort Ada/Ola: 35	ORR (90% CI) Ada: 23% (12–38) Ada/Ola: 29% (16–44)	DoR in months (95% CI) Ada: 5.5 (2.8–NE) Ada/Ola: 6.4 (2.8–14.6)	mPFS, months (90%CI) Ada: 5.5 (3.9–6.9) Ada/Ola: 6.8 (4.3–8.3)	CBR (90% CI) Ada: 63% (48–76) Ada/Ola: 89% (76–96)	n.a.

Ada: Adavosertib; Ola: Olaparib; PLD: pegylated liposomal doxorubicin; Pcb: Placebo; Gem: Gemcitabine; CDDP: Cisplatin; Carbo: Carboplatin; Pacli: paclitaxel; PFS: progression free survival; mPFS: median progression free survival; OS Overall survival; mOS: median overall survival. The rows with a grey background color are trials with gynaecological cancers, non-marked is solid tumor trial.

Uterine and endometrial cancer

One phase-II study investigated adavosertib monotherapy in recurrent uterine serous carcinoma [18]. A large majority of patients had a serous histology (82%), the remainder had a mixed phenotype, with a serous component. The overall CBR was 50% (95%CI 32.4–67.6) and the median duration of response was 9.0 months (95%CI, 5.3-NA). The PFS at 6 months (PFS6) was 47.1% (95%CI, 29.8–64.9) and mPFS was 6.1 months (95%CI, 4.21–9.92) [18]. In three phase-I trials for patients with solid tumors, five individual patients with uterine cancer were treated, however no individual effectiveness data could be extracted [24,28,41].

None of the trials evaluated WEE1i in endometrial cancer specifically. In a phase-I trial evaluating the safety and antitumor activity of adavosertib monotherapy, three patients with endometrial carcinoma and one with endometrial carcinosarcoma were included [24]. Of these three patients, two had a partial response and one had an unconfirmed partial response [24]. In one conference abstract for patients with solid tumors, two patients with endometrial cancer were treated, however no individual effectiveness data could be extracted [47].

Three ongoing studies in patients with uterine cancer are registered in trial databases (Appendix-3). One is a phase-IIb study assessing the efficacy and safety of adavosertib for recurrent/persistent uterine serous carcinoma (ADAGIO trial), a sequel to the above mentioned phase-II trial [18]. The ADAGIO trial protocol has been published, however excluded for this review as it did not report outcomes [50,51]. One other ongoing and registered phase-I trial evaluates safety and RP2D of adavosertib combined with cisplatin and radiotherapy in gynecological cancers including uterine and endometrial cancer. The third and last registered ongoing study is a phase-II study with WEE1i ZN-c3 in 110 women with recurrent/persistent uterine serous carcinoma (NCT04814108).

Cervical cancer

One phase I-IIa trial evaluated the addition of adavosertib to cisplatin and topotecan as initial or adjuvant treatment for advanced, metastatic, and recurrent squamous cell, adenosquamous, or adeno-carcinoma of the uterine cervix [36]. This trial was prematurely terminated after the enrollment of 7 participants and no efficacy/effectiveness data and only limited safety results are available in the trial registry [36]. The sponsor declared this was not related to safety concerns. In another phase-I trial evaluating the safety and antitumor activity of adavosertib monotherapy for patients with solid tumors for which all standard therapies had failed, one patient with cervical carcinoma was included [24]. This patient had stable disease as best overall response [24]. In two other phase-I/phase-Ib trials evaluating adavosertib for patients with advanced solid tumors, three patients with cervical cancer were included, however no individual effectiveness data could be extracted [28,41]. An ongoing phase-I trial evaluates safety and RP2D of adavosertib combined with cisplatin and radiotherapy for cervical (and other gynecological) cancers for which the results are expected soon (Appendix-3).

Vaginal and other specific gynecological cancers

None of the trials evaluated WEE1i in vaginal or other specific gynecological cancers specifically, and in the solid tumor trials no individual patient data for vaginal or other specific gynecological cancer patients were reported. One ongoing phase-I trial includes patients with vaginal and other specific gynecological cancers and evaluates safety and RP2D of the combination of adavosertib, cisplatin and radiotherapy (Appendix-3).

Solid tumor studies

Eighteen studies included patients with solid malignancies, of whom six full-texts [8,23,24,28,40,41], eleven conference abstracts and one trial registry [37]. The large majority of these trials were phase-I or phase-Ib studies, three studies were described as phase-II [40,47,52] and one combined phase-I/II [42]. These three phase-II trials for patient with solid tumors are all based on molecular profiling [40,47,52], see also the *''Pharmacodynamics and biomarkers for response to WEE1i'* section. Effectiveness outcomes were described in 5/6 full-text records [8,23,24,28,40] and 7/11 conference abstracts [42,47–49,52–54]. The ORR ranged between 0 [40] to ≥ 50% [24,28] in (sub)populations of these studies, although populations and treatments were highly heterogeneous (Table 1). DCR or CBR ranged from 16% [52] to 83% [28]. Median PFS was reported in four studies, ranging 2.7–4.0 months with a

median of 3.5 [40,47–49]. For ongoing trials with WEE1i in patients with solid tumors see Appendix-3.

Secondary outcomes

Safety

Nearly all included records reported safety outcomes (except two conference abstracts [43,44]), although the quality and quantity of reported data varied. No subgroup analyses for safety outcomes were described. Therefore, this section will include safety information reported in all abovementioned records, even if no data about patients with gynecological cancers is described separately.

The most common adverse events of adavosertib monotherapy or in combination with other anticancer agents were bone marrow toxicity, diarrhea, vomiting and fatigue. The frequencies of these (treatment) related adverse events are shown in Table 3. Patients receiving ZN-c3 experienced comparable adverse events [42]. One trial compared the safety of adavosertib in combination with several cytotoxic agents in different dose schedules in patients with PROC [21]. A higher incidence of bone marrow suppression in patients receiving weekly adavosertib in combination with carboplatin has been observed. All patients in this cohort experienced Grade $\geq$ 3 adverse events (mainly neutropenia, thrombocytopenia and anemia, in 75%, 83% and 58% of the patients, respectively).

The Patient-Reported Outcomes version of The Common Terminology Criteria for Adverse Events (PRO-CTCAE) was used to determine self-reported symptomatic adverse events in the study population of Lheureux et al [19,38]. A total of 119 patients with PROC received either gemcitabine with adavosertib (n = 86) or placebo (n = 33). Patients treated with gemcitabine and adavosertib experienced more fatigue, diarrhea, mucositis and dysphagia compared to patients treated with gemcitabine and placebo. A higher score for fatigue was reported on day 15 of the first treatment cycle.

Reported adavosertib related SAEs were bone marrow toxicity, gastrointestinal symptoms, septic shock, liver abscess and pulmonary embolism. Other SAEs are shown in Table 3 and were not treatment related in all cases. The incidence and description of SAEs in patients receiving ZN-c3 were not reported.

The most common reason for dose reductions and dose discontinuations was hematological toxicity. Approximately a quarter of patients randomized to gemcitabine plus adavosertib discontinued treatment due to adverse events vs. no patients in the placebo plus gemcitabine cohort in the study of Lheureux [19]. Moore and colleagues described dose reductions in all treatment arms, except patients treated with adavosertib with pegylated liposomal doxorubicin [21]. The highest rate was observed in the adavosertib plus carboplatin arm, (92% experienced AEs resulting in dose reductions).

The MTD and RP2D of adavosertib as monotherapy and as part of different combinational regimens is shown in Table 3 (if reported). The RP2D for ZN-c3 was 300 mg QD, given in a continuous schedule [42].

Pharmacodynamics and biomarkers for response to WEE1i

Pharmacodynamic outcomes of WEE1i were reported in four studies, all with adavosertib as WEE1i [8,22–24]. Levels of phosphorylated CDK1/2 (also pY15-CDK) as marker of WEE1 inhibition and γH2AX as marker for DNA damage response were assessed using paired tumor biopsies in two studies [8,24]. A decrease in pY15-CDK and increase in γH2AX levels was observed after treatment with adavosertib monotherapy. Leijen et al. used pre- and post-dose skin biopsies for determination of the ratio phosphorylated CDK1 (pCDK1):CDK1 in their studies [22,23]. A 50% decrease of this ratio was used as threshold for target inhibition. In the ovarian cancer cohort, with combined adavosertib and carboplatin treatment, target inhibition was achieved in 65% of the evaluable patients (n = 13) [22]. These results indicate adequate target engagement and molecular drug responses [8,22–24].

Gynecological malignancies often harbor genetic alterations resulting in genomic instability making them susceptible to drugs affecting the G2/M checkpoint such as WEE1i [18,19]. These alterations could act as potential biomarkers for response to or resistance against WEE1i. The association between the anti-tumor effect of WEE1i and specific genetic features has been investigated in several studies [8,18–24,40,47,48,52]. In addition to *TP53*-mutation (*TP53*m), genomic analyses of interest concerned: WEE1 related genes, homologous recombination deficiency status (HRD), oncogenes involved in replications stress such as *KRAS* and *MYC*, and other cell cycle related genes such as *CCNE1* and *CDKN2A*. In four studies, selection of the patient population was based on biomarker status, twice *TP53*m [20,22], and once *CCNE1*-amplification (*CCNE1*amp) [47] or the presence of a *BRCA1/2*-mutation [52]. The (preliminary) efficacy in these trials has been discussed above. In other trials discussing the results of genomic data in gynecologic malignancies, it has been found that *TP53*m is the most common genetic aberration in this population [18,19,21]. Although most studies did not report significant associations between any specific alterations and clinical outcomes, some interesting findings have been highlighted. Leijen et al. found a higher ORR in *TP53m* versus *TP53 wild-type (TP53*wt*)* tumors (21% vs. 12%) [23]. They concluded that alterations in *BRCA1*, *CCNE1* and *MYC* may also contribute to a better response to adavosertib when combined with carboplatin. *CCNE1*amp is a potential biomarker for response, as *CCNE1*amp tumors were significantly more responsive when adavosertib was added to gemcitabine (ORR 62% in *CCNE1*amp vs. 13% in non-*CCNE1*amp tumors, p = 0.013) [19]. Other studies also reported *CCNE1*amp in patients with long responses with an PFS > 2 years [20,22], and demonstrated clinical benefit in subgroups carrying this alteration [21,24,47]. Takebe et al. rationalized the value of *CCNE1* mRNA overexpression analysis in ovarian and endometrial cancers [24]. The results of a retrospective dataset analysis suggest that a subset of these tumors could show *CCNE1* overexpression without having *CCNE1*amp and vice versa [24].

Pharmacokinetics

Pharmacokinetic properties of WEE1i were reported in nine full-text articles [8,19–24,28,41] and six conference abstracts [43–46,49,54], eleven records did not report on pharmacokinetics [18,36–40,42,47,48,52,53]. In all studies reporting on pharmacokinetics of WEE1i, adavosertib was used as WEE1i. Adavosertib is steadily absorbed after oral administration. Pharmacokinetic parameters of absorption including C_{max} depended on dose and schedule and T_{max} was in general within hours (Appendix-5). The C_{max} is not substantially influenced by a fastened of fed state and concomitant intake with food has no clinical meaningful effects on adavosertib systemic exposure (AUC, AUC_{0-t}) [41]. Adavosertib itself is metabolized via CYP3A4 and significant and clinical relevant increase in adavosertib exposure (+40%) has been described in patients treated with aprepitant (CYP3A4 inhibitor) [23]. Nowadays trials with adavosertib exclude patients treated with (strong) CYP3A4 inhibitors or inducers. Another clinically relevant interaction have been described with pegylated liposomal doxorubicin (PLD). Concentrations (mean C_{max} and AUC_{0-t}) of adavosertib plus PLD were +/- 40-fold higher than after other chemotherapy [21]. Further research on bioanalytical interference, in vitro metabolism and liposome binding did not reveal a plausible mechanism [21]. No significant interactions have been described in combination with paclitaxel [21,28], cisplatin [23], carboplatin [21,23,28] or gemcitabine [19,21,23]. Although not formally assessed, similar adavosertib exposure combined with or without durvalumab (IgG1-monoclonal antibody targeting PD-L1) suggests lack of a significant interaction [44,54]. Adavosertib itself is a weak inhibitor of CYP1A2, CYP2C19 and CYP3A4 and can thereby influence concentrations of other drugs and/or metabolites [45]. Interaction effects of adavosertib has been described for olaparib, as olaparib AUCs are higher when combined with adavosertib [53]. Simulations indicate that intermittent dosing of adavosertib and continuous dosing of olaparib 200 mg BID (instead of regular 300 mg

Table 3

Outcomes of safety for the different included records..N.a.: is not available (either data not reported or not applicable). AE: Adverse event. TRAE: Treatment-related Adverse Event. SAE: Serious Adverse Event. DLT: Dose Limiting Toxicity. MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose, DR: Dose reduction. Ada: Adavosertib PLD: pegylated liposomal doxorubicin; Gem: Gemcitabine; CDDP: Cisplatin; Carbo: Carboplatin; Pacli: paclitaxel;

Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
Chen, A., et al. 2021	Solid tumors, no subgroup analysis	Treatment regimen according to actionable mutation of interest One of the treatment arms: Ada 225 mg BID for 5 doses + carbo AUC 5 in a 21-day cycle	N = 28 received Ada + carboplatin Genitourinary tumors in Ada arm: n = 8	N.a.	N.a.	Anemia: n = 10/18 (56%) Diarrhea: n = 4/18 (22%) Febrile neutropenia: n = 3/18 (17%)	N.a.	N.a.
Do, K., et al. 2015	Refractory solid tumors, no subgroup analysis	DL1: Ada 225 mg BID for 2.5 days for 1 week of a 21-day cycle (n = 3) DL2: Ada 225 mg BID for 2.5 days for 2 weeks of a 21-day cycle (n = 19) DL3: Ada 300 mg BID for 2.5 days for 2 weeks of a 21-day cycle (n = 3)	N = 25, (at least) n = 4 with ovarian cancer, one patient with fallopian tube carcinoma	DL1: n = 1 (grade 4 myelosuppression) DL3: n = 2 (grade 4 myelosuppression and supraventricular tachyarrhythmia) MTD = DLT2: Ada 225 mg BID over 2.5 days for 2 weeks of a 21-day cycle	Total all dose levels: Nausea (72%), vomiting (72%), diarrhea (68%), lymphopenia (64%), leucopenia (60%), anemia (52%), thrombocytopenia (48%), neutropenia (40%)	In all dose levels: leucopenia, lymphopenia, anemia, thrombocytopenia, neutropenia, mostly n = 1 to 2	1 SAE reported: death due to sepsis caused by aspiration pneumonia	N.a.
Kato, H., et al. 2020	Advanced solid tumors, no subgroup analysis	Single dose of Ada followed by: Cohort 1: Ada 175 BID for 2.5 days + paclitaxel 175 mg/m2 + carboplatin AUC 5 in a 21-day cycle Cohort 1a: Ada 175 mg BID for 2.5 days per cycle + carbo AUC 5 in a 21-day cycle Cohort 2 (dose-escalation): Ada 225 mg BID for 2.5 days + pacli 175 mg/m2 + carbo AUC 5 in a 21-day cycle	Cohort 1: n = 7, 43% gynecological malignancies (3/7) Cohort 1a: n = 6, 33% gynecological malignancies (2/6) Cohort 2: n = 6, 17% cervical cancer (1/6)	Cohort 1 and cohort 1a: n = 2 (grade 4 thrombocytopenia) Cohort 2: n = 2 (grade 4 sepsis and grade 5 ARDS)	Single dose A: nausea (15.8%), constipation (5.3%), diarrhea (5.3%) hypersensitivity (5.3%) In cohorts 1 vs. 2 vs. 1a: nausea (85.7% vs. 83.3% vs. 50%) diarrhea (71.4% vs. 83.3% vs. 33%), vomiting (71.4% vs. 66.7% vs. 33.3%), anemia (71.4% vs. 66.7% vs. 33.3%), decreased WBC count (71.4% vs. 83.3% vs. 50%), decreased platelet count (57.1% vs. 50% vs. 33.3%)	Total incidence: Cohort 1: n = 6/7 (85.7%) Cohort 2: n = 6/6 (100%) Cohort 1a: n = 4/6 (66.7%) In cohorts 1 vs. 2 vs. 1a respectively: anemia (57.1% vs. 83.3% vs. 33.3%) decreased WBC count (71.4% vs. 83.3% vs. 33.3%) decreased platelet count (57.1% vs. 50% vs. 33.3%) decreased neutrophil count (42.9% vs. 50% vs. 33.3%)	Total n = 7 Cohort 1: n = 3/7 (43%, nausea and vomiting, thrombocytopenia, febrile neutropenia) Cohort 2: 4/6 (66.7%, neutropenia, diarrhea, ARDS and interstitial pneumonia in one patient)	Discontinuation of adavosertib in n = 1 in cohort 1 and n = 2 in cohort 2 Discontinuation of paclitaxel in n = 1 in cohort 1 and n = 2 in cohort 2 Discontinuation of carboplatin in n = 1 2 from cohort 2
Leijen, S., et al. 2016	Advanced solid tumors, no subgroup analysis	Part 1: Ada single dose 325–1300 mg Part 2A: Gem 1000 mg/m2 on days 1,8, 15 of 28-cycle OR CDDP 75 mg/m2 on	N = 201, 12% ovarian cancer (25/201)	Part 1: 0% Parts 2A: Gem/Ada: n = 3/14 (21%), CDDP/Ada: n = 2/13 (15%), Carbo/Ada: n = 2/16 (13%)	Part 1: diarrhea (22%) and fatigue (22%) Part 2: nausea (67%), vomiting (35%), diarrhea (41%), fatigue (58%), thrombocytopenia (44%),	Incidence per treatment arm: Gem/Ada single dose: n = 7/14 (50%) Gem/Ada multiple dose: n = 45/67 (67%)	Part 2: N = 38/201 (19%)	N.a.

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Table 3 (*continued*)

Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
		day 1 of 21-day cycle OR carbo AUC 5 on day 1 of 21-day cycle + single dose Ada 100–325 mg Part 2B: same as Part 2A but 5x Ada (25–325 mg) instead of single dose		Part 2B: Gem/Ada: n = 8/67 (12%), CDDP/Ada: n = 7/45 (16%), Carbo/Ada: n = 13/46 (28%)	neutropenia (32%), anemia (32%)	CDDP/Ada single dose: n = 4/13 (31%) CDDP/Ada multiple dose: n = 21/45 (47%) Carbo/Ada single dose: n = 2/16 (13%) Carbo/Ada multiple dose: n = 31/46 (67%) Most common: anemia: n = 24/201 (12%), neutropenia: n = 45/201 (22%), GI disorders: n = 20/201 (12%)		
Leijen, S., et al. 2016	Platinum-resistant or platinum-refractory TP53-Mutated ovarian cancer	Ada 225 mg BID 5for 2.5 days + carbo AUC 5 on day 1 of a 21-cycle	N = 23	N.a.	Fatigue (87%), nausea (78%), diarrhea (70%), thrombocytopenia (70%), anemia (61%), vomiting (48%), neutropenia (43%)	Grade 3 neutropenia: n = 4/23 (17%), grade 4 thrombocytopenia and neutropenia: n = 11/23 (48%) and n = 5/23 (22%), respectively	N.a.	Dose reductions in n = 11/23 (48%) due to grade 4 thrombocytopenia and/or grade 2–4 neutropenia
Lheureux, S., et al. 2021	Platinum-resistant or platinum-refractory recurrent ovarian cancer	Arm A: Gem 1000 mg/m2 on days 1,8 and 15 + Ada 175 mg on days 1,2,8,9,15 and 16. Arm B: Gem 1000 mg/m2 on days 1,8 and 15 + placebo	Arm A: N = 86 Arm B: N = 33	N.a.	Arm A vs. Arm B Fatigue (92% vs. 97%), anemia (92% vs. 91%), thrombocytopenia (85% vs. 67%), neutropenia (85% vs. 67%), nausea (80% vs. 73%), abdominal pain (76% vs. 67%)	neutropenia n = 56/86 (65%), thrombocytopenia n = 28/86 (35%)	N.a., no treatment related deaths	Arm A: Ada dose modifications in n = 77/86 (90%), Gem dose modifications in n = 81/86 (94%) Arm B: Gem dose modifications in n = 23/33 (70%) Treatment discontinuation due to AEs n = 21/86 (24%) in Arm A vs. n = 0/33 (0%) in Arm B
Moore, K.N., et al. 2021	Primary platinum-resistant ovarian, fallopian tube of peritoneal cancer	Arm A: Ada 175 mg QD for 2 days + Gem 800–1000 mg/m2 in 28-day cycle Arm B: Ada 225 mg BID for 2.5 days + Pacli 80 mg/m2 in 28-day cycle Arm C + C2: Ada 225 mg BID for 2.5 days + Carbo AUC 5 in 21-day cycle (C2 weekly Ada) Arm D + D2: Ada 175–225 mg BID for 2.5 days + PLD 40 mg/m2 in 28-day cycle	Total: N = 94 Arm A: N = 9 Arm B: N = 38 Arm C: N = 23 Arm C2: N = 12 Arm D: N = 6 Arm D2: N = 6	Arm A: n = 2 due to grade 4 neutropenia Arm B: n = 1 due to grade 4 neutropenia Arm C: n = 2 due to grade 2 diarrhea and grade 3 nausea and vomiting in one patient Arm C2, Arm D and Arm D2: no DLTs reported	Overall vs. highest percentage: nausea (69.1% vs. 83% in arms C and C2), diarrhea (66% vs. > 80% in arms B and D2), fatigue (62.8% vs. 83.3% in arm D2), anemia and neutropenia (58.5% and 75% vs. 91.7% in arm C2, thrombocytopenia (48.9% vs. 91.7% in arm C2), vomiting (47.9% vs. 56.5% in arm C)	neutropenia: n = 43/94 (47.7%, in arm A 77.8%, in arm C2 75%), thrombocytopenia: n = 29/94 (30.9%, in arm C2 83.3%), anemia: n = 28/94 (29.8%, in arm C2 58.3%) Incidence arm C2: 100%	SAEs in 46.8% of all patients, 27.7% patients experienced ADA-related SAEs (bone marrow toxicity, GI-symptoms, septic shock, liver abscess, pulmonary embolism)	Arm A: DR Ada n = 2 (22.2%), DR Gem n = 6 (66.7%) Arm B: DR Ada n = 18 (47.2%), DR Pacli n = 19 (50%) Arm C: DR Ada n = 5 (21.7%), DR Carbo n = 8 (34.8%) Arm C2: DR Ada n = 11 (91.7%), DR Carbo n = 11 (91.7%) Arm D and D2: no dose reductions

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Table 3 (*continued*)

Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
Liu, J., et al. 2021	Recurrent uterine serous carcinoma	Ada monotherapy: 300 mg QD on days 1–5 and 8–12 of a 21-day cycle	N = 34	N.a.	anemia (67.6%), thrombocytopenia (61.8%), neutropenia (44.1%), diarrhea (76.5%), fatigue (64.7%), nausea (61.8%), vomiting (35.3%), anorexia (29.4%, rises in ALT (29.4%) and AST (26.5%)	Total incidence: 61.8% anemia (23.5%), thrombocytopenia (17.6%), neutropenia (32.4%), fatigue (23.5%)	N.a.	Dose holds in n = 26 (76.5%), dose reductions in n = 20 (58.8%), treatment discontinuations in n = 2 (5.9%)
Någård, M., et al. 2020	Advanced solid tumors, no subgroup analysis	Single dose of Ada 300 mg in two treatment sequences (Fasted + T and Fed + T)	N = 31. Total gynecologic malignancies n = 9/31 (29%, cervix uteri n = 1, ovary n = 6, uterus n = 2)	N.a.	Total: Nausea (38.7%), vomiting (35.5%) and diarrhea (16.1%) Common in fasted state: vomiting (27.6% vs. 20.0%), headache (10.3 vs. 3.3%), fatigue (6.9% vs. 3.3%) and abdominal pain (6.9% vs. 0%). Common in fed state: nausea (33.3% vs. 24.1%) and diarrhea (13.3% vs. 6.9%)	n = 2 (6.5%) Diarrhea and headache (n = 1 fasted state), hypokalemia (n = 1 fed state)	0% related to adavosertib	N.a.
Oza, A. M., et al. 2020	Platinum-sensitive *TP53* mutant ovarian cancer	Part 1: Ada 225 mg BID for 2.5 day/21-day cycle + Pacli 175 mg/m2 + Carbo AUC 5 on day 1 Part 2: Ada/Pacli/Carbo or Placebo/Pacli/Carbo	Part 1: N = 13 Part 2: Ada/Pacli/Carbo: n = 59, Placebo/Pacli/Carbo: n = 60	Part 1: Grade 3 febrile neutropenia (n = 1), grade 4 neutropenia (n = 1) and grade 4 thrombocytopenia (n = 1)	Part 1: diarrhea (85%), nausea, vomiting and fatigue (77%) Part 2: adavosertib/Pacli/Carbo vs. Placebo/Pacli/Carbo: nausea (78% vs. 60%), diarrhea (75% vs. 37%) and vomiting (63% vs. 27%)	n = 59 Most common = 12/59 (20%), neutropenia n = 21/59 (36%), thrombocytopenia n = 12/59 (20%)	n = 24/59 (41%), one death from SAE neutropenia (related to chemotherapy) and malignant neoplasm progression	Ada/Pacli/Carbo: Dose interruptions n = 12/59 (20%), dose reductions n = 26/59 (44%) Placebo/Pacli/Carbo: dose interruptions n = 11/60 (18%), dose reductions n = 19/60 (31%)
Takebe, N., et al. 2021	Advanced solid tumors, no subgroup analysis	Ada monotherapy: 200 mg QD on days 1–5 and 8–12 of 21-day cycle with dose escalations to 225, 250, 300 and 400 mg	Total: N = 42, 33% gynecological malignancies (13/42, n = 10 ovarian, n = 3 endometrial carcinoma, n = 1 cervical cancer)	3 DLTs at dose level 400 mg QD: grade 3 fatigue, grade 4 pancytopenia, grade 4 neutropenia MTD and RP2D: 300 mg QD on days 1–5 nd 8–12 of each 21-day cycle	nausea (81%), vomiting (69%), lymphopenia (71%), anemia (69%), leucopenia (50%)	lymphopenia (29%), anemia (21%), leucopenia (22%), neutropenia (22%), vomiting (12%), hypophosphatemia (14%)	N.a.	Dose reductions in n = 13 due to non-DLT toxicities (mostly at dose level 300 mg QD)
Bauer, T. M., et al. 2019	Advanced solid tumors, (efficacy) results per subgroup	Ada 175 mg BID on days 1–3 and 8–10 in a 21-day cycle	N = 80, 58% ovarian cancer (46/80) n = 16 BRCAwt n = 30 BRCAm, PARPi failure	N.a.	diarrhea (61%), nausea (50%), fatigue (43%)	Diarrhea (7.5%), nausea (6%), fatigue (6%), small intestine obstruction (6%)	N.a.	Dose interruptions (22.5%), dose reductions (11.3%), discontinuations (16.3%) due to AEs
Falchook, G. S., et al. 2019	Advanced solid tumors, no subgroup analysis	Ada QD or BID (125–300 mg) in a 5/9 day schedule in 14-day cycles or 5/2 dosing schedules	N = 62, 21% ovarian cancer 59 patients evaluable	12 DLTs: some patients > 1 DLT 150 mg BID: diarrhea, nausea, deydration	Incidence all grade AEs not reported	n = 39 (62.9%) Most common: Anemia and neutropenia, both n = 9/62 (14.5%), diarrhea n = 8/62 (12.9%)	N.a.	Dose interruptions (40.3%), dose reductions (27.4%), discontinuations (6.5%) due to AEs

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Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
		(weekly or 2 out of 3 weeks) in 21-day cycles		250 mg QD (5/2 weekly): thrombocytopenia, neutropenia 300 mg QD (5/2 weekly): nausea, weight loss, pneumonia 300 mg QD (5/2 weekly): 2/2 thrombocytopenia, nausea, vomiting MTD 125 mg (BID 5/9) and 300 mg (QD 5/2 and 5/9) for 2/3 week; RP2D 300 mg (QD 5/2)				
Fu, S., et al. 2021	Refractory solid tumors with CCNE1 amp, no subgroups	Ada 300 mg QD on days 1–5 and 8–12 on 21-day cycle	N = 29. Total gynecological malignancies n = 16/29 (55%, ovarian n = 14, endometrial n = 2)	N.a.	Incidence all grade AEs not reported	n = 15 (52%) neutropenia (24%), thrombocytopenia (17%), anemia (14%), nausea (17%), diarrhea (17%), fatigue (17%)	N.a.	Dose reductions in n = 16/29 (55%, from 300 mg to 250 mg) Twice in 7 patients: from 250 mg to 200 mg
Hamilton, E., et al. 2019	Refractory solid tumors, no subgroup analysis	Ada (250–300 mg QD/ 125–175 mg BID) in 3/4 or 5/2 schedule + olaparib 100–300 mg BID for 14 or 21 days in a 21 -day cycle	N = 119, 21% ovarian cancer	Thrombocytopenia (n = 4), neutropenia (n = 4) MTD/RP2D for BID schedule 175 mg (3/4) for 2/3 weeks + olaparib 200 mg BID RP2D for QD schedule adavosertib 200 mg (3/4) for 2/3 weeks + olaparib 200 mg BID	Incidence all grade AEs not reported	anemia n = 28/119 (23.5%), neutropenia n = 26/119 (21.8%), thrombocytopenia n = 20/119 (16.8%)	N = 4, one treatment related death	N.a.
Kummar, S., et al. 2019	Tumors with BRCA1 and BRCA2 mutations	Ada 300 mg QD 5/2 days, 2 weeks on, 1 week off in a 21-day cycle	N = 31. Total gynecologic malignancies n = 7/31 (23%, ovarian n = 5, fallopian tube n = 1, mixed n = 1)	N.a.	Incidence all grade AEs not reported, most common AEs: myelosuppression, fatigue, nausea, vomiting and diarrhea	N.a.	N.a.	N.a.
Madariaga, A., et al. 2021 (Self-reporting of tolerability)	Population of Lheureux et al. platinum-resistant or platinum-refractory recurrent ovarian cancer	Arm A: Gem 1000 mg/m2 on days 1,8 and 15 + Ada 175 mg on days 1,2,8,9,15 and 16. Arm B: Gem 1000 mg/m2 on days 1,8 and 15 + placebo	See Lheureux et al. N = 47 evaluable (n = 28 in arm A, n = 19 in arm B)	N.a.	AUC12w calculated for both groups: Fatigue severity (A: 152 vs. B 112, p = 0.005) Diarrhea frequency (A 70 vs. B 33, p = 0.014), mucositis (A: 23 vs. B: 6, p = 0.012) No significant differences for gastrointestinal symptoms.	N.a.	N.a.	N.a.
Någård, M., et al. 2020	Advanced solid tumors, no	Period 1: single dose of caffeine 200 mg, omeprazole 20 mg,	N = 33. No tumor types described	N.a.	diarrhea (53%), vomiting (30%), nausea (27%)	n = 6 (20%), no description given	N.a.	N.a.

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Table 3 (*continued*)

Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
	subgroup analysis	midazolam 2 mg Period 2 (after a 7–14 day washout): Ada 225 mg BID on days 1–3 with C, O and M on day 3	Received Ada: n = 31					
Någård, M., et al. 2020	Advanced solid tumors, no subgroup analysis	Ada 225 mg BID 5 doses on days 1–3 (after a 7–14 day washout period)	N = 21. No tumor types described	N.a.	diarrhea (33%), nausea (33%), vomiting (24%)	N = 2 (10%), no description given	N.a.	N.a.
Patel, M. R., et al. 2019	Advanced solid tumors, no subgroup analysis	Ada + Durvalumab 1500 mg on day 1 of four different 28-day schedules, Ada doses: A: 125 mg BID (5/9)/ (3/4) B: 150 mg BID (3/4)/ 175 mg BID (3/4) C: 125 mg BID (3/4)/ 200 mg QD (5/2) D: 250 mg QD (5/2)/ 300 mg QD (5/2)	N = 54. Number of gynecological malignancies not reported	nausea (n = 2), diarrhea (n = 1) MTD/RP2D: Ada 150 mg BID (3/4) + durvalumab 1500 mg on d1 Q4W	Incidence all grade AEs not reported	Fatigue (15%), diarrhea (11%) and nausea (9%)	n = 7/54 (13%), not all reported. 2 patients reversible drug-induced liver injury (Sch B 125 mg and Sch C)	A:125 mg BID (5/9) n = 1/6 (DR and discontinuation each) B: 150 mg BID (3/4) n = 1/12 DR, 175 mg BID (3/4) n = 1/7 discontinuation and n = 2/7 DR C: 125 mg BID (3/4) n = 1/7 discontinuation D: 250 mg QD (5/2) = 1/6 (DR and discontinuation each), 300 mg QD (5/2): n = 1/3 DR
Tolcher, A. W., et al. 2021	Advanced solid tumors, no subgroup analysis	ZN-c3 dose escalation schedule from 25 mg − 450 mg QD	N = 39. Number of gynecological malignancies not reported (at least one)	DLT: not reported RP2D: for ZN-c3: 300 mg QD continuous schedule	Incidence all grade AEs not reported, most common AEs: nausea, diarrhea, vomiting and fatigue	N.a.	N.a.	N.a.
Westin, S. N., et al. 2021	PARP-resistant ovarian cancer	Arm A: Ada 300 mg QD on days 1–5 and 8–12 of a 21-day cycle Arm A/O: Ada 150 mg BID on days 1–3 and 8–10 + Olaparib 200 mg BID on days 1–21 of a 21-day cycle	Arm A: n = 39 Arm A/O: n = 41	Not reported	Incidence all grade AEs not reported	Arm A: 51%, most common: neutropenia (13%), thrombocytopenia (10%), diarrhea (8%) Arm A/O: 76%, most common thrombocytopenia (20%), neutropenia (15%), diarrhea (12%), fatigue (12%), anemia (10%)	N.a.	Arm A: dose interruptions in n = 28 (72%), dose reductions in n = 20 (51%) Arm A/O: dose interruptions in n = 36 (88%), dose reductions in n = 29 (71%), n = 4 (10%) did not restart due to toxicity
N.a. NCT01047007	Advanced solid tumors, no subgroup analysis	Part 1: Ada 65 mg BID on days 1–5 of a 21-day cycle Part 2 A1: Ada 20 mg BID (same schedule) + 5-FU 1000 mg/m2 on days 1–4 Part 2 A2: Ada 20 mg	Part 1: N = 3 Part 2 A1: N = 6 Part 2 A2: N = 2 Part 2B + 3: N = 0	N.a.	Part 1: diarrhea and stomatitis (both 66.7%), nausea, constipation, fatigue and alterations in liver function tests (33.3%) Part 2A1: Anemia (66.7%), lymphopenia (50%), vomiting, nausea and fatigue	N.a.	Part 2 A1: n = 2/6; encephalopathy and pulmonary fistula Part 2 A2: n = 1/2; gastric cancer	N.a.

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Table 3 (*continued*)

Author and year of publication	Tumor type	Treatment arms	Number of patients received treatment	Incidence and description of DLTs	Incidence and description of most common (TR)AEs in WEE1 group compared with other treatment arms	Incidence and description of most common (TR)AEs Grade ≥ 3 in WEE1 group	Incidence and description of SAEs in WEE1 group	Dose modifications
		QD + 5-FU 1000 mg/m2 (same schedule) Part 2B + 3 Ada 20 mg/65 mg BID/QD + 5-FU 1000 mg /m2 + CDDP 60–100 mg/m2 on day 1			(66.7%), alterations in liver function tests (16.7%) Part 2 A2: Lymphopenia, nausea, stomatitis and fatigue (50%)			
N.a.	Cervical Cancer	Part 1: Ada 50 mg BID on days 1–5 (9 doses) + Topotecan 0.75 mg/m2 on days 1–3 /Cisplatin 50 mg/m2 on day 1 of a 21-cycle Part 2: Ada/placebo + Topotecan/CDDP (same dose schedule)	Part 1: N = 7 Part 2: N = 0	N.a.	Part 1: Anemia (85.7%), neutropenia (85.7%), thrombocytopenia (71.43%), nausea (57.1%), abdominal pain (42.86%)	N.a.	Part 1: n = 5/7; febrile neutropenia, thrombocytopenia, vomiting, Escherichia bacteraemia, ALT increase, urinary tract obstruction, dyspnoea	N.a.
NCT01076400								

BID) maintains adequate olaparib exposure [43]. In general, the elimination of adavosertib is slow and concentrations steadily decrease in the hours after reaching C_{max}. The geometric mean plasma concentrations 8 h post-dose were 56% of the C_{max} geometric mean after multiple dosing [21]. Adavosertib concentrations decline in a mono-exponential manner for most patients after T_{max} [20]. The terminal half-life $t_{1/2}$ of adavosertib is reported in 6 records [8,19,23,24,41,49] with mean reported $t_{1/2}$ ranging 7.8–12.3 [19,41] and overall quite some variability between patients [23,41]. A formal (pre-registration) human pharmacokinetics study of [14C]Adavosertib is ongoing (NCT05008913)(Appendix-2). Also refer Appendix-5.

Discussion

As far as we know, this is the first SLR on the clinical development of WEE1i in gynecological malignancies. We found promising signals of effectiveness of the first-in-class WEE1i adavosertib as monotherapy and in combination with standard chemotherapy regimens in this patient population. This concept is mainly studied in ovarian cancer and uterine carcinoma. No conclusions can be drawn on the anti-tumor activity of WEE1i in other gynecological cancers since no studies reported on this. To date, no clinical data of other WEE1i than adavosertib and ZN-c3 have been published, although clinical trials with Debio-0123 are ongoing. The use of different WEE1i in several tumor types including gynecological malignancies is currently being investigated.

Among the gynecological cancers, WEE1 inhibition has been best studied in ovarian cancer. Evaluating the safety of adavosertib and ZN-c3 we observed a comparable toxicity profile of both WEE1i when it comes to the incidence of gastrointestinal toxicities. Bone marrow toxicity was the most common reason for dose reductions of regimens containing adavosertib. This was not reported as common adverse event of ZN-c3 [42]. Yet, the exact incidence of treatment related events after ZN-c3 exposure are unpublished and should be interpreted carefully. Moreover, the variety of studies and limited data availability do not permit effective comparisons of the safety profiles of the different treatment regimens. In the study of Moore et al., a drug-drug interaction of adavosertib and pegylated liposomal doxorubicin (PLD) has been shown resulting in a higher C_{max} and $AUC_{0\text{-}t}$ [21]). The higher incidence of diarrhea and fatigue in the PLD dose-escalated group (both 83.3%) makes this interaction clinically relevant. One should be aware of this in future studies combining PLD and adavosertib. In the same study, the highest incidence of toxicity was reported when adavosertib was dosed weekly. Although an exposure-toxicity relationship of adavosertib has not been described yet, it is persuasive that the incidence of toxicity is dose-related and that frequent dosing is associated with more adverse events.

Comparing effectiveness across studies, different settings and stages are challenging and introduces selection bias regarding pretreatment and genetic tumor characteristics. However, it is still necessary to interpret uncontrolled studies or treatment combinations not evaluated in individual randomized controlled studies. Appendix-6 provides an overview of landmark studies within ovarian cancer with/without the WEE1i adavosertib and the reported mPFS and mOS. Overall adavosertib combinations seem effective on mPFS although mOS data were immature for most described phase-II studies. Nevertheless, the landmark phase-II study of Lheureux et al. reported an improved OS after gemcitabine plus adavosertib compared with gemcitabine plus placebo (11.4 vs. 7.2 months) [19], confirming efficacy signals of other studies [20–22].

Nearly all records reported results of genomic analyses in order to identify biomarkers for response to WEE1i. *TP53*m has been identified as main driver in studies of adavosertib in gynecological malignancies. [18–23] Though, adavosertib was also effective in patients with *TP53*wt tumors. An explanation for this could be that adavosertib not only stimulates premature entry into mitosis, but also affects DNA damage response (S-phase defects), resulting in cytotoxicity independent of

TP53 status [8], as shown in tumor cell lines [9].

Besides *TP53*m, *CCNE1*amp and *BRCA1/2*-mutations seem to be potential genetic biomarkers for response to adavosertib, plausibly contributing to better responses and longer progression-free intervals [18,19,21,22,24,47,52]. This is currently being investigated in biomarker-driven studies [47,52]. One explanation for better responses in *CCNE1*amp tumors is that cyclin E1 overexpression, adversely affects G1/S checkpoint function, making survival of tumor cells dependent on the G2/M checkpoint [55]. These effects are strengthened in case of *TP53*m as explained in Fig. 1.

Studies of adavosertib in PROC have shown that the addition of adavosertib to platinum containing therapy can reverse resistance [21,22]. WEE1i are also assumed to overcome PARP-inhibitor (PARPi) resistance in OC, since overexpression of WEE1 is one of the potential mechanisms of PARPi-resistance [56]. Moreover, the combination of PARPi and WEE1i revokes G2 arrest and induces mitotic catastrophe, resulting in cell death and thus tumor response [57]. This concept is studied with promising preliminary results [39].

Strengths of this SLR are the systematic search approach, inclusion of all clinical trials and conference abstracts, the independent assessment and the structured reporting of the results. Previous narrative reviews on WEE1i evaluated one specific WEE1i, only focused on ongoing clinical trials, and none specifically focused on the clinical development in gynecological cancers [11,58,59]. The lack of subgroup analyses is a limitation of this SLR, in particular for the evaluation of efficacy outcomes. The majority of the extracted studies were non-randomized with different dosing schedules. No *meta*-analysis was performed because the included records were too heterogeneous.

The risk of bias in the non-randomized articles was considered high, although this could be expected in phase-I and II trials. Nevertheless, these trials all have their merits and provide substantial basis for further research. Notwithstanding, this SLR provides a comprehensive analysis of the (early) clinical development of WEE1i of gynecological malignancies. Given the abovementioned results and considerations, we believe that the anti-tumor activity of WEE1i in ovarian, uterine and cervical cancer is promising. Based on our present overview of the literature we cannot provide guidance on the best combination strategies or dosing schedules of adavosertib. Follow-up studies are needed to further optimize the therapeutic area of WEE1i in and beyond gynecological malignancies.

Ethical considerations

This systematic literature review is a secondary analysis of data and document analysis. Therefore no ethical approval was deemed applicable.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be seen as a potential conflict of interest to the presented work. Each author provided a detailed conflict of interest statement according to the Journals policy. N Steeghs received research grants (All outside the submitted work, all payment to the Netherlands Cancer Institute) from: Abbvie, Actuate Therapeutics, Amgen, Array, Ascendis Pharma, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, BridgeBio, Bristol-Myers Squibb, Cantargia, CellCentric, Cogent Biosciences, Cresecendo Biologics, Cytovation, Deciphera, Dragonfly, Eli Lilly, Exelixis, Genentech, GlaxoSmithKline, IDRx, Immunocore, Incyte, InteRNA, Janssen, Kinnate Biopharma, Kling Biotherapeutics, Luszana, Merck, Merck Sharp & Dohme, Merus, Molecular Partners, Navire Pharma, Novartis, Numab Therapeutics, Pfizer, Relay Pharmaceuticals, Revolution Medicin, Roche, Sanofi, Seattle Genetics, Taiho, Takeda. N. Steeghs received consulting fees (All outside the submitted work, all payment to the Netherlands Cancer Institute) from Boehringer Ingelheim, Cogent Biosciences, Ellipses Pharma, Luszana.

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Appendix A. Supplementary data

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