Uitgangsvraag 3
3a. Bij welke patiënten met een recidief, locally advanced of gemetastaseerd endometriumcarcinoom is systemische therapie geïndiceerd voor een betere overleving en/of kwaliteit van leven?
3b. Welke systemische therapie heeft op welk moment in de behandeling de voorkeur?

Study (trial) ID	Study type	Source of funding/Conflicts of interest	Setting	Country	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up
1 Humber et al., 2007 (1)	Meta-analysis	Not reported	NA	UK	To evaluate both the benefits and adverse effects of cytotoxic chemotherapy for advanced, recurrent or metastatic endometrial cancer	Meta-analysis updated to 2005 *Inclusion* Only RCTs comparing cytotoxic chemotherapy (single agent or combination) versus placebo, best supportive care, alternative chemotherapy or endocrine (hormonal) therapy were considered. They should have aimed to randomly assign women with advanced, recurrent or metastatic endometrial adenocarcinoma that was not amenable to potentially curative surgery or radical radiotherapy *Exclusion* Trials of adjuvant chemotherapy or which included women with uterine carcinosarcoma or sarcoma	*Sample size* - 11 eligible RCTs, of which 6 trials were included (2-7) - 68 phase II studied (not reported in this table)
2 Decruze et al., 2007 (8)	Review	Not reported	NA	UK	Which populations should be considered for hormone therapy?	*Inclusion* Electronic databases from 1951 to date, trials registers, and reference lists of journals were searched for RCTs in advanced or recurrent endometrial carcinoma treated with a hormonal intervention. It became clear that the number of RCTs was limited and the search was extended to phase II studies in the English language *Exclusion* - Trials of adjuvant chemotherapy and trials comprising patients with uterine sarcomas including carcinosarcomas - Phase II studies of combinations of hormone treatments together with cytotoxic drug(s) - Retrospective analyses of series	*Sample size* - 5 RCTs (of which 1 RCT was excluded) (9-12) and 29 phase II studies (not reported in this table) were identified comprising a total of 2,471 patients
3 Carey et al., 2006 (13)	Review	Not reported	NA	Canada	What are the chemotherapeutic and hormonal therapy options for women with advanced or recurrent adenocarcinoma of	- Medline: 1966-March 2005 - Embase: 1980-March 2005 - Cochrane Library: 2005, Issue 1	*Sample size* 17 RCTs: - 13 RCTs compared

					the endometrium?	- Proceedings of 1997-2004 ASCO meetings *Inclusion* - RCTs or meta-analyses comparing regimens of systemic chemotherapy or hormonal therapy for advanced or recurrent endometrial cancer reporting at least one of the following outcomes: survival, quality of life, response rate or toxicity - Patients had measurable or evaluable disease and/or response rates were reported	chemotherapy regimens (2, 3, 6, 7, 14-22) - 3 RCTs compared hormonal therapies (9-11) - 1 RCT compared chemotherapy to chemotherapy plus hormonal therapy (23), 43 patients eligible, (all stage III), 60% recurrent disease
4 Polyzos et al.,2006 (24)	Review	None declared	NA	Greece (RCT from USA, Canada and Europe)	- Examination whether there is evidence for superior survival outcomes with specific chemotherapeutic or hormonal regimens against others - To provide insights for helping guide future clinical research in this field	- Medline, Embase and the Central Library of Controlled Trials of the Cochrane Library until April 2005 (RCTs) - All previous reviews of RCTs in this field were identified and their references were perused - Cross-searches were performed in MEDLINE using the names of investigators who were lead authors in at least one eligible trial *Inclusion* - All RCTs that compared at least 2 arms of different chemotherapy or hormonal therapy regimens in patients with advanced endometrial cancer (stage IIIB or IV, unresectable, or recurrent) with at least 5 patients per arm - Focus on the eligible patient subgroups for trials that had included also some patients with non-advanced disease or other malignancies - RCTs comparing different dosing schemes and schedules of the same agent or combination of agents. For completeness, also trials comparing chemotherapy or hormone therapy against best supportive care without any systemic treatment were recorded *Exclusion* - Non-randomized trials or pseudo-randomized trials with alternate allocation of subjects, trials limited to non-advanced disease and those limited to cancer of the uterine cervix - Meeting abstracts, as they provide insufficient information for appraisal of a study and its results	*Sample size* -34 eligible RCTs, of which 17 were included (2, 3, 6, 7, 9-11, 14-16, 18, 20-23, 25, 26) - A total of 2,964 subjects were randomized and 2,771 were considered eligible for survival analyses
5 Thigpen et	RCT Phase III	*Funding* - National Cancer Institute	- GOG member	USA	Evaluation of whether there is increased response rate when combining	*Inclusion* - Histologically documented stage III, IV, or	*Sample size* n=281

al., 2004 (16)		Grants *Conflicts* - Thigpen consultant at Bristol-Myers Squibb Co	institutions - Healthcare setting		doxorubicin and cisplatin versus doxorubicin alone in stage III, IV or recurrent endometrial carcinoma	recurrent endometrial carcinoma after prior surgery and/or radiotherapy - Disease measurable and no prior cytotoxic chemotherapy (except hormonal or one prior biologic therapy) - Several pretreatment laboratory assessment, GOG performance status of 0 to 2, no contraindication cisplatin, no history of congestive heart failure or abnormal cardiac compensation, no history of previous invasive malignancy other than skin cancer (excluding melanoma). Multiplegated acquisition scans required to document normal ejection fraction before study entry	-Doxorubicin: n=150 -Doxorubicin + Cisplatin: n=131 *Lost to Follow-up* - Present, but number of lost to follow up not mentioned
6 Fleming et al., 2004 (15)	RCT Phase III	*Funding* - National Cancer Institute grants *Conflicts* - Authors (or family) indicated financial interest - No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation - Fleming consultant at Bristol-Myers Squibb Co	- Healthcare setting	USA	To compare three drug (TAP) combination with the two drug (AP) combination in terms of RR, PFS, and OS	*Inclusion* Chemotherapy-naıve women with histologically documented measurable stage III, stage IV, recurrent endometrial carcinoma of any cell type, and a GOG performance status (PS) of 0 to 2. Patients with a second malignancy other than nonmelanoma skin cancer only if disease-free > 5 years *Exclusion* Patients with serious concomitant medical illnesses such as uncontrolled infection or angina, or serious neuropathy	*Sample size* - n=273 patients enrolled (n=10 ineligible; AP: n=7; TAP: n=3) - n=263 (AP: n=129; TAP: n=134) deemed eligible and included in primary survival analysis - n=260 (AP: n=129; TAP: n=131) at least 1 cycle and assessable for toxicity
7 Gallion et al., 2003 (2)	RCT prospective, multicenter GOG study	*Funding* - National Cancer Institute grants *Conflicts* - Authors indicated no potential conflicts of interest	- Multicenter - Healthcare setting	USA	To determine if circadian timed (CT) chemotherapy results in improved response, progression-free survival, overall survival, and lower toxicity, when compared with standard timed (ST) chemotherapy	*Inclusion* Stage III, IV, or recurrent endometrial cancer with poor potential for cure by radiation therapy or surgery; measurable disease; no prior chemotherapy, prior hormonal therapy or biologic response modifiers *Exclusion (n=10)* Prior cytotoxic therapy, > 1 prior biologic therapy, prior radiotherapy within 3 months of study entry to only area of known disease	*Sample size* - n=342 - Standard time (n=175, final included n=169) - Circadian time (n=177, final included n=173) *Lost to Follow-up* - Not reported
8 Aapro et al., 2003 (14)	RCT Multi-centre prospective randomised trial	Not reported	- 35 institutions - Healthcare setting	Several EU countries (not specified in article, affiliations from: CH, BE, IT, ES, NL,	- Do the reported differences in the efficacy and toxicity of monotherapy with doxorubicin (DOX) versus combination therapy with cisplatin (CDDP) in endometrial adenocarcinoma lead to significant advantage in favour of the combination? - Is there difference in toxicity of both treatment arms in comparable patients?	*Inclusion* Histologically-proven advanced and/or recurrent endometrial adenocarcinoma and chemo-naïve *Exclusion* Prior chemotherapy, radiotherapy or hormone therapy within 4 weeks of trial entry; unresolved toxic manifestations of their prior treatment; a concomitant or prior second	- 177 patients (35 institutions) with advanced inoperable or recurrent endometrial cancer

				FR, PL, AT, PT, UK)		cancer, other than adequately-treated basal or squamous cell carcinoma of the skin; brain or leptomeningeal involvement; pleural effusion, ascites, bone lesions detectable only by bone scan or sclerotic bone metastases as the single tumour response parameter; poor medical risk due to non-malignant disease, such as active bacterial or other infection, heart failure or uncontrolled hypertension; and expected difficulty with follow-up	

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/Comparator (including duration, dose)
1	NA	NA	Women with advanced, recurrent or metastatic endometrial adenocarcinoma that was not amenable to potentially curative surgery or radical radiotherapy	- 4 trials were identified that compared a single agent with the same agent in combination (3, 5, 7) - 2 trials compared doxorubicin and cisplatin with doxorubicin and cisplatin combined with other drugs (4, 6)	NA
2	NA	NA	Advanced and recurrent endometrial cancer	Megestrol acetate (MA), medroxyprogesterone acetate (MPA), tamoxifen (TAM), aminogluthetimide (AMINO)	NA
3	NA	NA	Women with advanced or recurrent adenocarcinoma of the endometrium	NA	NA
4	NA	NA	Patients with advanced endometrial cancer (stage IIIB or IV, unresectable, or recurrent) who received different chemotherapy or hormonal therapy in at least two arms	- Overall, 7 monotherapies and 14 combinations of different agents had been tested - 3 trials (5 arms) assessed medroxyprogesterone acetate (MPA) - 5 trials (6 arms) assessed cisplatin + doxorubicin. 4 arms used doxorubicin monotherapy and 2 arms used cyclophosphamide monotherapy, otherwise all other 17 regimens had been involved only once in a single arm of a single published RCT - 2 trials compared doxorubicin vs. doxorubicin + cisplatin - 5 trials involved comparison of monotherapy against combinations, 5 compared monotherapies only and 7 compared at least 2 different combinations of agents. 21 arms used only chemotherapeutic regimens (containing paclitaxel n=2; doxorubicin n=6; doxorubicin + cisplatin n=7; other n=6), 8 arms used only hormonal regimens, and 5 arms used both hormonal and chemotherapeutic regimens - Paclitaxel-containing regimens had been used only in the most recent trials published in 2004, and the doxorubicin + cisplatin combination regimen had also been used mainly after 2000 (only 1 arm in a trial prior to 2000)	NA
5	48 months (derived from survival curve)	- Randomized study treatment not revealed until complete registration - Study regimens sequentially drawn from preallocated lists of treatments randomly permuted and balanced within blocks - Separate treatment allocation lists were maintained for each GOG member institution	*Median age* - Single 66.9 years vs. combi: 64.4 years *Histologic grade* Doxo (n=150) Doxo+cis (n=131) 1 27 (18%) 29 (22%) 2 51 (34%) 35 (27%) 3 72 (47%) 67 (51%)	**Combi** Doxorubicin 60 mg/m^2 (IV) + Cisplatin 50 mg/m^2 (IV) *Compliance* Only 3 eligible patients did not receive any of their assigned study treatment	**Single** Doxorubicin 60 mg/m^2 (i.v.)

			Cell type Doxo (n=150) Doxo+cis (n=131) Endometriod 74 (49%) 61 (47%) Serous 23 (15%) 22 (17%) Adenosquamous 24 (16%) 17 (13%) Adenoca 14 (9%) 17 (13%) Clear cell 9 (6%) 6 (5%) Other 6 (4%) 8 (6%) - Most patients (65%) had prior radiotherapy and 32% had prior hormonal therapy		
6	*Inclusion* December 28,1998-August 14, 2000 *Follow-up* 46 months	The GOG Statistical and Data Center (SDC) randomly assigned therapy to each patient, with equal probability of assignment to each treatment regimen. The sequence of treatment assignments was concealed from institutions and patients until registration. Patient entry was accomplished by telephone registration with verification of eligibility	*Age (in years)* AP (n=129) TAP (n=134) ≤ 50 12 (9.3%) 10 (7.5%) 51-60 35 (27.1%) 37 (27.6%) 61-70 54 (41.9%) 56 (41.8%) 71-80 24 (18.6%) 30 (22.4%) ≥ 81 4 (3.1%) 1 (0.7%) *Tumor grade* AP (n=129) TAP (n=134) 1 24 (18.6%) 20 (14.9%) 2 46 (35.7%) 43 (32.1%) 3 59 (45.7%) 71 (53.0%) - The 2 arms were fairly well-balanced with respect to baseline characteristics, though the AP arm contained fewer African American patients and fewer patients with stage III disease, PS 0, and grade 3 histology	**AP** - Doxorubicin 60 mg/m^2 - Followed immediately by Cisplatin 50 mg/m^2 - Cisplatin was diluted in 250 ml 0.9% sodium chloride and infused over 1 hour	**TAP** - Doxorubicin 45 mg/m^2 - Followed immediately by Cisplatin 50 mg/m^2 on day 1 - Paclitaxel 160 mg/m^2 as a 3-hour infusion on day 2 - Filgrastim administered at a dose of 5 μg/kg subcutaneously on days 3 to 12 - Cisplatin dose was decreased to 50 mg/m^2, with the expectation of decreasing incidence of neurotoxicity, providing the same starting cisplatin dose in the 2 study arms
7	60 months (derived from survival curve)	Randomization with equal probabilities, balancing sequence of assigned regimens within institutions only using permuted balanced block design. Sequence generated by computerized random number generator and block length of 4 treatment assignments. Concealed sequence of treatment assignments	*Median age* - 65 years *Tumor grade* ST (n=169) CT (n=173) 1 22 (13%) 32 (19%) 2 59 (35%) 51 (30%) 3 88 (52%) 90 (52%) - Groups well balanced for pre-treatment characteristics, including	**Circadian timed (CT) chemotherapy** - Doxorubicin 60 mg/m^2 IV during the course of 30 minutes scheduled at 6:00 AM - Cisplatin 60 mg/m^2 IV during the course of 30 minutes given at 6:00 PM - Cycles were repeated every 3 weeks to a maximum of 8 cycles *Compliance*	**Standard timed (ST) chemotherapy** - At any convenient time, doxorubicin 60 mg/m^2 intravenously (IV) during the course of 30 minutes - Followed immediately by cisplatin 60 mg/m^2 IV

			performance status, cell type, and tumor grade - Slight imbalances for age and race	- Completed 8 cycles: 74 patients (43%)	during the course of 30 minutes *Compliance* Completed 8 cycles: 67 patients (40%)
8	*Inclusion* September 1988-June 1994 *Median follow-up* 7.1 years (exact duration unclear, survival curves end after ≈ 9 years)	Minimisation technique; patients stratified: - Institution - Degree of differentiation - Type of disease - Performance status	*Median age* - 63 years (range 40-76 years) *Type of disease* - Advanced primary: DOX-CDDP: n=36; DOX: n=36 - Recurrent: DOX-CDDP: n=54; DOX: n=51 *Tumor differentiation* - Well: DOX-CDDP: n=18; DOX: n=16 - Moderately/poor: DOX-CDDP: n=72; DOX: n=71 - Baseline characteristics similar in both treatment arms	**Single-agent DOX (n=87)** - Doxorubicin 60 mg/m^2 every 4 weeks	**DOX–CDDP combination (n=90)** - Doxorubicin 60 mg/m^2 + Cisplatin 50 mg/m^2 every 4 weeks

ID	Primary Outcome Measure(s) Secondary outcome(s)	Effect size-Primary Outcome(s) Effect size-Secondary outcome(s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
1	- Objective response rate - Progression free survival - Overall survival - Treatment-related deaths - Toxicity	*Objective response rate* - In all 6 trials, the objective response rate appeared greater when more was compared with less chemotherapy (30-69% versus 17-34%). Differences statistically significant in 2 of these trials (4, 5) *Progression free survival* - Progression free survival data were available for all 6 trials (1,132 patients and 1,014 events), although only as time to progression in 2 of these (2, 6) - Pooled HR=0.80 (95% CI 0.71-0.90) showing significant 20% relative improvement in PFS (p=0.0004) with more intensive regimens: absolute improvement in the median PFS of ≈ 1 month - Effect more pronounced in group trials comparing doxorubicin and cisplatin plus other drugs with doxorubicin and cisplatin alone: HR= 0.64 (95% CI 0.49-0.82, p=0.0004) *Overall survival* - Data on OS were available for all 6 trials (2-7), including 1,135 patients and 1,034 events and the results of these trials of various types of chemotherapy are very consistent (I^2=18.6%) - No OS benefit for more compared with less chemotherapy HR=0.91 (95% CI 0.80-1.03; p=0.12) - Doxorubicin and cisplatin in combination with other drugs offer a survival benefit when compared with doxorubicin and cisplatin alone. The HR of 0.75 (95% CI 0.58-0.97) indicates a 25% reduction in the relative risk of death with more intense chemotherapy equivalent to a 3-month improvement in survival - These results are largely driven by the results of the one trial (4) evaluating the addition of paclitaxel that individually had a statistically significant result (HR=0.75, 95% CI 0.57-0.988; p=0.037, adjusted for performance status) → Meta-analysis of 6 trials indicates that more intense chemotherapy significantly improves the median PFS, but not OS. This is, however, at the expense of increased grade 3/4 toxicity. Across these 6 trials, the results are fairly consistent and no one regimen appears superior to another in improving PFS and OS. The only RCT that reported a significant improvement in PFS and OS was that of doxorubicin, cisplatin and paclitaxel versus doxorubicin and cisplatin with the benefit associated with the paclitaxel-containing arm (4). Grade 3 or 4 thrombocytopenia and neurological toxicity, however, were also significantly greater	*Treatment-related deaths* - 7 possible treatment-related deaths (1.8%) in one trial, but it is not clear whether these relate to one or other treatment (7) - 5 treatment-related deaths were attributable to the doxorubicin, cisplatin and paclitaxel arm but there were none on the doxorubicin and cisplatin arm (4) - In another trial 10% of patients stopped treatment in the doxorubicin and cisplatin arm compared with 2% of patients receiving cisplatin alone (14) *Toxicity* - Data on grade 3 or 4 nausea and vomiting, diarrhoea/other GI toxicity, leucopenia, thrombocytopenia and neurological toxicity were available in sufficient detail for 5 out of 6 trials, including 761 patients. Across trials, serious nausea and vomiting was increased almost threefold with the more intense regimens (OR=2.73, 95% CI 1.76-4.23; p< 0.00001) - There were few grade 3 or 4 diarrhoea/other GI events overall (n=29), there still seemed to be an excess with more compared with less chemotherapy (OR=2.48, 95% CI 1.19-5.17) - Serious leucopenia much more variable from trial to trial (I^2= 89.5%), with no statistically significant increase with more intense chemotherapy (OR=1.30, 95% CI 0.98-1.73; p=0.07) - Grade 3 or 4 thrombocytopenia increased more than four-fold with more chemotherapy (OR=4.44, 95% CI 2.67-7.38; p<0.00001) - Serious neurological toxicity was very rare, except in the trial of doxorubicin, cisplatin and paclitaxel versus doxorubicin and cisplatin (4), where it was significantly increased in the arm including paclitaxel (p=0.0004) - Grade 3-4 alopecia, anaemia, cardiotoxicity, fever/infection, stomatitis/mucositis and renal/genitourinary toxicity were reported for fewer trials and also tended to be less frequent. The overall tendency for these types of toxicity was to be more frequent when more chemotherapy was given	- A number of these trials pre-date the routine use of the type 3 serotonin receptor (5-HT3) antagonists and the rate of grade 3 and 4 vomiting may be higher than what one would expect in current practice	A1

		and there were 5 treatment-related deaths with the paclitaxel arm			
2	- Response rates - Progression free survival - Overall survival	4 randomized phase studies included: 1. MPA 200 mg (n=145), MPA 1000 mg (n=154) (9) *Response* - MPA 200 mg: CR n=25, PR n=11, NR n=109 - MPA 1000 mg: CR n=14, PR n=10, NR n=130 *Progression free survival* - MPA 200 mg: 3.2 months - MPA 1000 mg: 2.5 months *Overall survival* - MPA 200 mg: 11.1 months - MPA 1000 mg: 7.0 months 2. TAM (n=45), MPA (n=48), combined to crossover at progression (10) *Response* - TAM: CR n=6, PR n=10, NR n=8 - MPA: CR n=8, PR n=14, NR n=5 - TAM and MPA: CR n=5, PR n=15, NR n=9 *Progression free survival* - TAM 9 months - MPA 14 months *Overall survival* - TAM 9 months - MPA 14 months 3. MA (n=20), TAM and MA (n= 42) (11) *Response* - MA: CR n=1, PR n=3, NR n=0 - TAM and MA: CR n=1, PR n=7, NR n=1 *Progression free survival* - Not specified *Overall survival* - MA: 12.0 months (11 days to 60.6 months) - TAM and MA: 8.6 months (48 days to 46.6 months) 4. TAM (n=6), AMINO (n=5) *(12)* *Response* - TAM: CR n=1, PR n=1, NR n=4; - AMINO: CR n=1, PR n=2, NR n=2 *Progression free survival* - TAM: responders 9.5 months; non-responders 8.0 months - AMINO: responders 6.0 months; non-responders 5.0 months *Overall survival* - No survival figures → Hormone therapy should be considered for the management	*Adverse events* **-** G3 and 4: thrombophlebitis n=6, pulmonary embolism n=3, anemia n=2 (9) **-** TAM: nausea 31%, gastralgia 20%, anorexia 38%, urticarial skin reaction 22%, thrombocytopenia 16% trans, tumor flare 91%; - MPA: weight gain due to fluid retention 70%, facies lunaris 16% tremors 14%, gluteal abscess 10%, vaginal bleeding 10% (10) - Mild to moderate toxicity in 40% MA alone and 57% of combined arm, of which hematologic toxicity is most frequent; severe to life-threatening toxicity in 5% combined arm (11) - AMINO lethargy common and 2 G3 dizziness; - TAM group, 2 cases of nausea (12) → The duration of remission is of the order of 3-6 months, which is comparable with that of cytotoxic chemotherapy. Occasionally, responses may be more durable. No direct evidence of a survival benefit or randomized comparison with chemotherapy	- Quality individual studies, especially phase II studies comprise the majority of the data and many are of poor quality (phase II not included in evidence table) - The 4 included RCTs showed extensive heterogeneity such that meta-analysis was not appropriate	B

		of all advanced and recurrent endometrial cancers and has llittle G3 or G4 toxicity			
3	- Progression free survival - Overall survival - Adverse events - Quality of life - Response rate - Toxicity	**Chemotherapy** *Progression-free and overall survival* - Range between 1.7 to 8.3 months and 4.2 to 15.3 months respectively in 10 RCTs (2, 3, 6, 7, 14-19) - Only 1 RCT detected a significant difference in both parameters between treatment groups (p<0.05) (15) - Remaining 9 RCTs did not detect any significant differences in either progression-free or median survival (2, 3, 6, 7, 14, 16-19) → In the absence of a proven survival advantage, short median survival times and the heterogeneity of patient populations, the decision to use combination chemotherapy rather than single agent chemotherapy must be individualized. Patients more likely to benefit from combination chemotherapy are those with a good performance status, those with recurrent disease outside the radiated field and those with longer anticipated survival times *Tumor response* - 3 RCTs detected statistically significant difference in response rates between treatment groups (14-16) - 1 RCT detected significant difference in tumor response when triple therapy with doxorubicin, cisplatin and paclitaxel was compared with doxorubicin and cisplatin alone (57% versus 34%; p<0.001) (15) -In 2 RCTs patients treated with combination doxorubicin and cisplatin significantly improved tumor response rates when compared to patients who had received doxorubicin alone (14, 16) - 10 RCTs failed to detect a significant difference between the treatments compared (2, 3, 6, 7, 17-22) **Homonal therapy** *Survival* - Survival difference of 4 months megestrol vs. megestrol + tamoxifen not statistically significant (trial was not adequately powered to detect) (11) - Overall median survival 11 months with 200 mg/day of medroxyprogesterone acetate (MPA) compared to 7 months with 1000 mg/day of MPA. Overall, difference not statistically significant, after adjusting for performance status, progesterone receptor level, tumor grade and age: risk of death was 31% greater for the high-dose group vs. lowdose group (p=0.026). Longer median survival was associated with patients who had well-differentiated tumors or those who with positive progesterone receptor status (9) *Tumor response*	**Chemotherapy** *Quality of life* Only one RCT (17), reported as abstract, assessed quality of life during chemotherapy. No specific details were reported *Adverse Events* - Hematological adverse events with grade 3/4 leukopenia in 55%-89% of patients (doxorubicin and cisplatin) (2, 7, 14-16, 18, 20, 21) - Triple therapy with doxorubicin, cisplatin and paclitaxel: lower rates of leukopenia, 59%-68%, higher rates of grades 3 and 4 thrombocytopenia (22% versus 3%) and neurotoxicity (12% versus <1%), slight increase gastrointestinal toxicity (12% versus 8%) (2, 7, 14-16, 18, 20, 21) - 30 deaths possibly related to treatment were reported across the eight studies: 7 deaths with doxorubicin either alone or with cyclophosphamide, 14 deaths with doxorubicin and cisplatin, 4 deaths with doxorubicin and paclitaxel and 5 deaths with paclitaxel, doxorubicin and cisplatin (2, 7, 14-16, 18, 20, 21) **Homonal therapy** *Adverse events* - 5% of patients on megestrol plus tamoxifen: life-threatening adverse events, including one case of pulmonary embolism (11) - Thrombophlebitis (5%), gastrointestinal upset, fatigue, edema, somnolescence (all less than 3%) and pulmonary embolus (1%) (9) **Chemotherapy versus chemotherapy + hormonal therapy** *Adverse events* - 5/23 women (22%) combined chemohormonal therapy experienced phlebitis. Toxicity data not separate for 2 treatment groups: overall 14% grade 3 or 4 hematologic adverse events and 12% grade 3 or 4 nausea or vomiting (23)	- Results not pooled as result of heterogeneity of study populations - Considerable variation in response rates from studies using hormonal therapy (15% to 46%) suggesting selection bias in patient populations studied	B

		- No significant differences were reported between treatment groups in the 3 trials - 1 RCT calculated response rates for subgroups of participants: grade I, or progesterone receptor-positive, or estrogen receptor-positive tumors had response rates of 37%, 37% and 26%, respectively and median survival of 18.8, 12.1 and 8.3 months, respectively. Participants with grade III, or progesterone receptor-negative, or estrogen receptor-negative tumors had response rates of 9%, 8% and 7%, respectively and survival of 6.9, 6.8 and 6.7 months, respectively, based on univariant analysis (9) **Chemotherapy versus chemotherapy + hormonal therapy** *Survival* - In 43 patients: median survival 11 months with chemotherapy alone (cyclophosphamide, doxorubicin and 5-fluorouracil) and 14 months with chemotherapy plus cyclical hormonal therapy (medroxyprogesterone followed by tamoxifen) (p>0.05) (23) *Tumor response* - Response rates were 15% with chemotherapy alone (1 complete and 2 partial, n=20) and 43% with chemotherapy plus hormonal therapy group (6 complete and 4 partial, n=23). Difference between groups was borderline significant (p=0.05) (23) → Combination chemotherapy with doxorubicin and cisplatin results in higher response rates than doxorubicin alone. The addition of paclitaxel to either of these regimens resulted in a small survival advantage in one trial using all three drugs. In light of the limited survival advantage associated with this regimen, the use of less toxic combinations of taxanes with carboplatin requires further study. Medroxyprogesterone acetate is useful in selected patients			
4	- Median survival per arm	*Median survival* - 1 trial found a statistically significant difference in survival for the comparison of DOX + CIS vs. DOX + CIS + paclitaxel + G-CSF (Filgastim) (15). The compared arms did not differ only in regards to the chemotherapy regimen, but also regarding the receipt or not of a haemopoetic growth factor which was deemed necessary to control the risk of neutropenia in the triple chemotherapy arm. The difference in median survival was 3 months (12.3 months vs. 15.3 months; p=0.032) - Absolute impact on median survival: differences between arms were very small and typically did not exceed 3.5 months, with the exception of the one trial mentioned above (9),where a difference of 4.1 months was observed, but this was in fact deleterious (against the experimental arm)	- 3 trials claimed survival differences in secondary analyses: 1. No difference between doxorubicin + cisplatin vs. doxorubicin alone in the main analysis (p=0.11 for log-rank test), but significance after adjusting for performance status (p=0.024) (14) 2. Median survival was worse by 4.1 months in the experimental arm of a trial comparing high-dose oral medroxyprogesterone against the traditional lower dose. No comment was made on the statistical significance of this difference, but it was stated that the risk of death was significantly greater (relative risk increase 31%; p=0.026) after adjusting for performance status, progesterone-receptor level, tumour grade, and age (9) 3. No difference was found in the main unadjusted analysis comparing doxorubicin + cyclophosphamide against	- One borderline statistically significant finding may be expected simply by chance among 17 trials. It is interesting that several other trials have claimed potential survival differences, not all of them in favour of the experimental regimens. However, these are based on adjusted analyses that may not be the most appropriate approach for properly RCTs (27) - Of great concern is the use of several adjusted secondary analyses that were employed to make sporadic survival benefit claims	B

			doxorubicin (difference in median survival 0.4 months; p=0.24 one-tailed), but a significant benefit was observed after adjusting for performance status, grade, liver metastasis, and other intra-abdominal metastasis. The adjusted 17% relative risk reduction was of borderline significance and it was based on a one-tailed p-value (p=0.048 one-tailed) (3) → This overview suggests that the evidence for the use of hormonal and chemotherapeutic regimens in women with advanced endometrial cancer remains fragmented and relatively weak. Neither hormonal treatment nor chemotherapy have ever been explicitly proven to offer any clear survival benefit against best supportive care in these patients	-We could not probe into the extent of potential publication bias and time lag bias in this field. Any publication bias would mean that the evidence is even more ‘‘negative’’ and definitively against the routine use of any of these regimens - Other outcomes, such as response rates or progression-free survival, were not examined	
5	- Progression free survival (PFS) - Overall survival (OS) - Adverse Effects - (Clinical) response	*Median progression free survival* - Combi: 5.7 months - Single: 3.8 months - The PFS hazard ratio: 0.736 (95% CI 0.577-0.939; p=0.014) *Median overall survival* - Combi: 9.0 months - Single: 9.2 months - Overall death rates were similar in the 2 groups: hazard ratio 0.928 (95% CI 0.727-1.185) *Complete response* - Combi: n=25 (19%) - Single: n=12 (8%) - p=0.008 *Partial response* - Combi: n=30 (23%) - Single: n=26 (17%) *Overall response rate* - Combi: 42% - Single: 25% - p=0.004 → Adding cisplatin to doxorubicin in advanced endometrial carcinoma improves RR and PFS with a negligible impact on OS and produces increased toxicity	*Toxicities* Common were nausea, vomiting, and hematologic toxicities Combi (versus single): more grade 3 to 4 - Leukopenia (62% vs. 40%) - Thrombocytopenia (14% vs. 2%) - Anemia (22% vs. 4%) - Nausea/vomiting (13% vs. 3%)	- No Blinding - Adequate power calculation - Intent-to-treat analysis: eligibles versus non-elegibles - Possible co-morbid, co-medications - Most patients started at lower doxorubicin dose per protocol because of age > 65 years or prior radiation therapy	B
6	*Primary end point* - Overall survival (OS) to compare the treatment regimens *Secondary end points* - Progression free	*Response rate* - RR TAP vs. AP: 57% vs. 34% (p< 0.01) - CR TAP vs. AP: 22% vs. 7% - Odds of objective response, adjusted for PS and recurrent disease status, in the TAP arm were 2.7 times the odds in the AP arm (95% CI 1.5-4.6) - Histologic subtype was not related to the probability of response	*Treatment-related deaths* - TAP: 5 deaths; 2 deaths were clearly treatment-related (neutropenic fever and AML) - AP: no treatment-related deaths *Toxicities* - Grade 4 neutropenia: TAP 50%; AP 36%	- Intent-to-treat analysis - Lost to follow up: - Completion protocol in AP: 47% - Completion protocol in TAP: 49%	B

	survival (PFS) - Response Rate (RR) - Toxicities	*Median progression free survival* - TAP vs. AP: 8.3 months vs. 5.3 months - 40% reduction in progression hazard, adjusted for PS, associated with TAP relative to AP (relative hazard 0.60; 95% CI 0.46-0.78; *p*< 0.01) *Median overall survival* - TAP vs. AP: 15.3 months vs. 12.3 months - Death hazard relative to the AP arm, stratified by PS, was 0.75 (95% CI 0.57-0.988; p=0.037) → TAP significantly improves RR, PFS, and OS compared with AP. Evaluation of this regimen in the high-risk adjuvant setting is warranted, but close attention should be paid to the increased risk of peripheral neuropathy	- Neutropenic fever: TAP 3%; AP 2% - Grade 3 and 4 thrombocytopenia: TAP 22%; AP 3% - No differences between TAP and AP in lesser grades of cardiac taxicity: Grade 1 17% and 15%; Grade 2 11% and 10% - Congestive heart failure: TAP 2%; AP 0% - Grade 3 peripheral neuropathy: TAP 12%; AP 1% - Grade 2 peripheral neuropathy: TAP 27%; AP 4% - Patient-reported neurotoxicity was significantly higher in the TAP arm following two cycles of therapy		
7	- Response rate (complete and partial) - Progression-free survival (PFS) - Overall survival (OS) - Toxicity	*Complete responses + partial responses (total)* - ST: 46% (15% CR; 31% PR) - CT: 49% (17% CR; 32% PR) - Odds of responding, stratified by performance status, slightly higher in the CT vs. ST group (relative odds of response, 1.13; 95% CI 0.72-1.77; p=0.33) *Median progression free survival and overall survival* - ST: 6.5 and 11.2 months, respectively - CT: 5.9 and 13.2 months, respectively - PFS: p=0.31; OS: p=0.21 (one tail) *Common death hazard (CT relative to ST)* - 1.07 (95% CI 0.85-1.33; p=0.28) - Adjusted for performance status *Common relative hazard of progression or death* - 1.06 (95% CI 0.85-1.31; p=0.31) - Adjusted for performance status → No significant benefit in terms of response rate, PFS or OS, or toxicity profile was observed with CT doxorubicin plus cisplatin in patients with advanced or recurrent endometrial carcinoma	*Treatment-related deaths* - ST n=5 - CT n=3 *Toxicities* - Grade 3 or 4 leukopenia: ST 75%; CT 65% (p=0.01) - Grade 3 or 4 AGC toxicity: ST 82%; CT 74% (p=0.04) - Grade 3 or 4 nausea or vomiting: ST 11%; CT 16% (p>0.05) - Grade 3 or 4 adverse cardiac effects: ST 4%; CT 5% (p>0.05) *Median total doses* - ST: 209 mg/m2 doxorubicin and 349 mg/m2 cisplatin - CT: 246 mg/m2 doxorubicin and 354 mg/m2 cisplatin	- Treatment assignment and individual patient results not blinded to SDC staff or study chair - Aggregated results only available to study statistician, results kept confidential when reported to GOG Data Monitoring Committee - Intention-to-treat principle applied in all treatment group comparisons after excluding ineligible	B
8	- Response rate - Efficacy - Toxicity - Progression-free survival (PFS) - Overall survival (OS)	*Response rate* - DOX-CDDP: 39 patients (13 CR; 26 PR); 43% (95% CI 33%-54%) - DOX: 15 patients (8 CR; 7 PR); 17% (95% CI 3%-15%) - DOX-CDDP vs. DOX significant higher response rate (p<0.001) - No correlation was seen between the type of disease and the response rate. Prior radiotherapy and hormonotherapy did not seem to influence the response rate in either arm, and there were no major differences in the response rate of the various tumour	*Treatment-related deaths* - DOX–CDDP n=1 (died of toxicity 2 weeks after start 1st cycle) - No fatal toxicities reported in the DOX arm - Extensive toxicity was more often the reason for stopping treatment in the DOX-CDDP arm than in the single-agent DOX arm (10% versus 2%) *Haematological toxicity*	- Preliminary stop as recruitment decreased dramatically after the publication of the Gynecologic Oncology Group results in 1993 - No concealment - Intention to treat	B

		sites between the treatment arms - Median duration of response: DOX-CDDP 9 months vs. 24 months in the DOX arm (p=0.008) *Median overall survival* - DOX-CDDP : 9 months - DOX: 7 months - Wilcoxon p=0.0654 *Progression-free survival* - DOX-CDDP : 8 months (95% CI 7-11 months) - DOX: 7 months (95% CI 6-10 months) *Performance status* - After taking account of age, WHO performance status, FIGO stage, extent of disease and degree of differentiation, only WHO performance status appeared an prognostic factor for survival - After stratification for this factor, treatment effect: HR=1.46 (95% CI 1.05-2.03); p=0.024 → In comparison to single-agent DOX, the combination of DOX-CDDP results in higher toxicity, but also a significantly higher response rate, and overall provides a moderate benefit in survival in patients with a good performance status	- White blood cell toxicity grade 3 and 4: DOX-CDDP 55%; DOX 30% - Thrombocytopenia grade 3 and 4: DOX-CDDP 13%; DOX 5% (only grade 3) *Non-haematological toxicity* - Grade 3 and 4 alopecia: DOX-CDDP 72%; DOX 65% - Nausea/vomiting: DOX-CDDP 36%; DOX 12% - Oral: DOX-CDDP 6%; DOX 0% - Infection: DOX-CDDP 2%; DOX 1% - Cardiac: DOX-CDDP 1%; DOX 1% - Level of consciousness: DOX-CDDP 0%; DOX 1% - Grade 1 and 2 neuropathy: DOX-CDDP 25%; DOX 4% - Non-haematological toxicities were not to be cumulative → Combination treatment was more toxic than DOX alone, with observed toxicity being mainly primarily haematological and gastrointestinal. However, in general, this was acceptable, and similar to that observed in earlier trials		

AMINO=Aminogluthetimide; AP=Two-drug combination; CDDP=Combination therapy with cisplatin; CI=Confidence Interval; CR=Complete Response; CT=Circadian timed chemotherapy; DOX=Doxorubicin; HR=Hazard Ratio; MA=Megestrol acetate ; MPA=Medroxyprogesterone acetate; NR=Non response; OS=Overall survival; PFS=Progression Free Survival; PR=Partial response; PS=Performance status; RR=Response rate; ST=Standard timed chemotherapy; TAM=Tamoxifen; TAP=Three-drug combination

Literature Cited

1. Humber, C. E., Tierney, J. F., Symonds, R. P., Collingwood, M., Kirwan, J., Williams, C. & Green, J. A. (2007) Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann. Oncol 18: 409-420.

2. Gallion, H. H., Brunetto, V. L., Cibull, M., Lentz, S. S., Reid, G., Soper, J. T., Burger, R. A. & Andersen, W. (2003) Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin. Oncol 21: 3808-3813.

3. Thigpen, J. T., Blessing, J. A., DiSaia, P. J., Yordan, E., Carson, L. F. & Evers, C. (1994) A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. J Clin. Oncol 12: 1408-1414.

4. Boadle, D. J. & Tattersall, M. H. (1987) Phase II study of mitoxantrone in advanced or metastatic endometrial carcinoma. Aust. N. Z. J Obstet Gynaecol 27: 341-342.

5. Runge, H. M., Meerpohl, H. G. & Pfleiderer, A. (1989) Mitoxantrone therapy of advanced adenocarcinoma of the endometrium. A phase II trial. Onkologie. 12: 102-103.

6. Edmonson, J. H., Krook, J. E., Hilton, J. F., Malkasian, G. D., Everson, L. K., Jefferies, J. A. & Mailliard, J. A. (1987) Randomized phase II studies of cisplatin and a combination of cyclophosphamide-doxorubicin-cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. Gynecol Oncol 28: 20-24.

7. Fleming, G. F., Filiaci, V. L., Bentley, R. C., Herzog, T., Sorosky, J., Vaccarello, L. & Gallion, H. (2004) Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: a Gynecologic Oncology Group study. Ann. Oncol 15: 1173-1178.

8. Decruze, S. B. & Green, J. A. (2007) Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int. J Gynecol Cancer 17: 964-978.

9. Thigpen, J. T., Brady, M. F., Alvarez, R. D., Adelson, M. D., Homesley, H. D., Manetta, A., Soper, J. T. & Given, F. T. (1999) Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin. Oncol 17: 1736-1744.

10. Rendina, G. M., Donadio, C., Fabri, M., Mazzoni, P. & Nazzicone, P. (1984) Tamoxifen and medroxyprogesterone therapy for advanced endometrial carcinoma. Eur. J Obstet Gynecol Reprod. Biol. 17: 285-291.

11. Pandya, K. J., Yeap, B. Y., Weiner, L. M., Krook, J. E., Erban, J. K., Schinella, R. A. & Davis, T. E. (2001) Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). Am. J Clin. Oncol 24: 43-46.

12. Quinn, M. A. & Campbell, J. J. (1989) Tamoxifen therapy in advanced/recurrent endometrial carcinoma. Gynecol Oncol 32: 1-3.

13. Carey, M. S., Gawlik, C., Fung-Kee-Fung, M., Chambers, A. & Oliver, T. (2006) Systematic review of systemic therapy for advanced or recurrent endometrial cancer. Gynecol Oncol 101: 158-167.

14. Aapro, M. S., van Wijk, F. H., Bolis, G., Chevallier, B., van der Burg, M. E., Poveda, A., de Oliveira, C. F., Tumolo, S., Scotto, d. P., V et al. (2003) Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann. Oncol 14: 441-448.

15. Fleming, G. F., Brunetto, V. L., Cella, D., Look, K. Y., Reid, G. C., Munkarah, A. R., Kline, R., Burger, R. A., Goodman, A. & Burks, R. T. (2004) Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin. Oncol 22: 2159-2166.

16. Thigpen, J. T., Brady, M. F., Homesley, H. D., Malfetano, J., DuBeshter, B., Burger, R. A. & Liao, S. (2004) Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. J Clin. Oncol 22: 3902-3908.

17. Weber, B., Mayer, F., Bougnoux, B., Lesimple, T., Joly, F., Fabbro, M. & et al. (2003) What is the best chemotherapy regimen in recurrent or advanced endometrial carcinoma? Preliminary results [abstract]. Proc Am Soc Clin Oncol 22: 453.

18. Pawinski, A., Tumolo, S., Hoesel, G., Cervantes, A., van Oosterom, A. T., Boes, G. H. & Pecorelli, S. (1999) Cyclophosphamide or ifosfamide in patients with advanced and/or recurrent endometrial carcinoma: a randomized phase II study of the EORTC Gynecological Cancer Cooperative Group. Eur. J Obstet Gynecol Reprod. Biol. 86: 179-183.

19. Long, H. J., Nelimark, R. A. & Cha, S. S. (1995) Comparison of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) vs doxorubicin and cisplatin (AC) in advanced endometrial carcinoma [abstract]. Proc Am Soc Clin Oncol 14: 282.

20. Cohen, C. J., Bruckner, H. W., Deppe, G., Blessing, J. A., Homesley, H., Lee, J. H. & Watring, W. (1984) Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Obstet Gynecol 63: 719-726.

21. Horton, J., Elson, P., Gordon, P., Hahn, R. & Creech, R. (1982) Combination chemotherapy for advanced endometrial cancer. An evaluation of three regimens. Cancer 49: 2441-2445.

22. Horton, J., Begg, C. B., Arseneault, J., Bruckner, H., Creech, R. & Hahn, R. G. (1978) Comparison of adriamycin with cyclophosphamide in patients with advanced endometrial cancer. Cancer Treat. Rep. 62: 159-161.

23. Ayoub, J., udet-Lapointe, P., Methot, Y., Hanley, J., Beaulieu, R., Chemaly, R., Cormier, A., Dery, J. P., Drouin, P. et al. (1988) Efficacy of sequential cyclical hormonal therapy in endometrial cancer and its correlation with steroid hormone receptor status. Gynecol Oncol 31: 327-337.

24. Polyzos, N. P., Pavlidis, N., Paraskevaidis, E. & Ioannidis, J. P. A. (2006) Randomized evidence on chemotherapy and hormonal therapy regimens for advanced endometrial cancer: An overview of survival data. Eur J Cancer 42: 319-326.

25. Piver, M. S., Lele, S. B., Patsner, B. & et al. (1986) 5-Fluorouracil and medroxyprogesterone acetate in metastatic endometrial carcinoma. Obstet Gynecol 67: 261-264.

26. Sall, S., DiSaia, P. J., Morrow, C. P. & et al. (1979) A comparison of medroxyprogesterone serum concentrations by the oral or intramuscular route in patients with persistent or recurrent endometrial carcinoma. Am J Obstet Gynecol 135: 647-650.

27. Altman, D. G., Schulz, K. F., Moher, D. & et al. (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 134: 663-694.