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SUMMARY WITH CRITICAL APPRAISAL

Trastuzumab Combination and Monotherapy for HER2 Advanced or Recurrent Uterine or Endometrial Cancer: A Review of Clinical Effectiveness and Cost-Effectiveness

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Abbreviations

CP	carboplatin and paclitaxel
CP + T	carboplatin and paclitaxel + trastuzumab
CRD	Centre for Reviews and Dissemination
HER2	human epidermal growth factor receptor 2
MESH	Medical Subject Headings
RCT	Randomized Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours

Context and Policy Issues

Uterine cancer includes endometrial cancer and uterine serous carcinoma. Endometrial cancer is cancer of the inner lining of the uterus and consists of five histological types: adenocarcinoma, uterine carcinoma, squamous cell carcinoma, small cell carcinoma, transitional carcinoma, and serous carcinoma.[1] Uterine sarcoma is a second type of uterine cancer, which forms in the myometrium or connective tissue of the uterus.[1]

Uterine cancer was the most common female reproductive system cancer diagnosis in Canada in 2010.[2] With an incidence rate of 30.3 new cases per 100,000 women, uterine cancer represents 6.3% of all new cancers in women in this country.[2] The mortality rate for uterine cancer was 5.4 deaths per 100,000 women in 2010. Uterine serous carcinoma is a rare, aggressive sub-type of endometrial cancer that accounts for 10% of new cases and is associated with 80% of endometrial cancer deaths.[3]

The treatment of endometrial cancer varies depending on several factors, including severity and stage of disease and involvement of the human epidermal growth factor receptor 2 (HER2).[4] Overall, the prognosis for endometrial cancer is good. Patients with advanced or recurrent endometrial cancer are commonly treated with systemic chemotherapy (typically cisplatin plus doxorubicin with or without paclitaxel) or hormonal therapy, with varying response rates, ranging from 10 to 78%.[5] The current standard of care for uterine serous carcinoma begins with comprehensive surgical staging followed by adjuvant chemotherapy with six cycles of carboplatin and paclitaxel, followed by vaginal cuff brachytherapy.[6] Standard treatment for advanced or recurrent HER2-positive uterine serous carcinoma involves hysterectomy and surgical staging, followed by chemotherapy with carboplatin and paclitaxel.[7]

Targeting treatment toward the HER2 protein in patients with HER2-positive breast cancer has led to improved survival rates in that population.[7] Specifically, the antibody trastuzumab is frequently used in combination with chemotherapy to treat HER2 overexpressing breast cancers. It has been estimated that between fourteen and eighty percent of uterine serous carcinomas are HER2 positive.[7]

While trastuzumab and biosimilars of trastuzumab (e.g., Ogivri, Trazimera and Herzuma) are indicated for early breast cancer, metastatic breast cancer, and metastatic gastric cancer, a Health Canada Notice of Compliance (NOC) does not exist for trastuzumab for patients with HER2-positive advanced or recurrent uterine or endometrial cancer. In addition, the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee

(pERC) has not reviewed trastuzumab monotherapy or trastuzumab combination therapy in patients with HER2-positive advanced or recurrent uterine or endometrial cancer. In order to support decision-making on the use of trastuzumab monotherapy or trastuzumab combination therapy in patients with HER2-positive advanced or recurrent uterine or endometrial cancer, the purpose of this report is to summarize and critically appraise the relevant evidence regarding the clinical effectiveness and cost-effectiveness of trastuzumab combination therapy or trastuzumab monotherapy for HER2 positive advanced or recurrent uterine or endometrial cancer.

Research Questions

1. What is the clinical effectiveness of trastuzumab combination therapy or trastuzumab monotherapy for human epidermal growth factor receptor 2 positive advanced or recurrent uterine or endometrial cancer?
2. What is the cost-effectiveness of trastuzumab combination therapy or trastuzumab monotherapy for human epidermal growth factor receptor 2 positive advanced or recurrent uterine or endometrial cancer?

Key Findings

One moderate quality randomized controlled trial (two publications) regarding the clinical effectiveness of trastuzumab combined with carboplatin and paclitaxel compared with carboplatin and paclitaxel alone in patients with HER2 positive uterine serous carcinoma was identified. The trial showed that trastuzumab combined with carboplatin and paclitaxel significantly improved progression-free survival and improved overall survival in patients with advanced and recurrent HER2 positive uterine serous carcinoma compared with carboplatin and paclitaxel alone. High-grade adverse events during and following treatment were not significantly different between the treatment groups. Objective response rate did not differ between groups. No clinical evidence regarding trastuzumab monotherapy or other types of trastuzumab combination therapies (e.g., trastuzumab in combination with cisplatin and paclitaxel or docetaxel), patients with non-serous uterine cancer, other comparators (e.g., docetaxel), or data on quality of life were identified. No studies were identified regarding the cost-effectiveness of trastuzumab.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline and EMBASE via OVID, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were trastuzumab and uterine or endometrial cancers. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and October 13, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients aged 18 years and older with stage III to IV or recurrent (any previous stage) human epidermal growth factor receptor 2 (HER2) positive uterine or endometrial cancer
Intervention	Trastuzumab combination therapy (e.g., Trastuzumab in combination with: carboplatin and paclitaxel, carboplatin and docetaxel, cisplatin and paclitaxel, cisplatin and docetaxel) or trastuzumab monotherapy (e.g., after discontinuation of chemotherapy)
Comparator	Alternative treatments or no treatment, including: • Carboplatin with paclitaxel or docetaxel; • Cisplatin with paclitaxel or docetaxel; • Liposomal doxorubicin; • Best supportive care (e.g., managing symptoms, no active systemic treatment for cancer, palliative care); • Immunotherapy (e.g., pembrolizumab); • No treatment
Outcomes	Q1: Progression free survival, overall survival, objective response, quality of life, adverse events, treatment discontinuation Q2: Cost-effectiveness outcomes (e.g., incremental cost-effectiveness ratio, cost per quality adjusted life year gained)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, non-randomized studies

HER2 = human epidermal growth factor receptor 2.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews.

Critical Appraisal of Individual Studies

The included publications from the randomized controlled trial (RCT) were critically appraised by one reviewer using the Downs and Black checklist.[8] Summary scores were not calculated for the included study; rather, the strengths and limitations of the included publications were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 182 citations were identified in the literature search. Following screening of titles and abstracts, 163 citations were excluded and 19 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant

articles, 18 publications were excluded for various reasons, and two publications from one clinical RCT met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[9] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two publications from the "Randomized Phase II Evaluation of Carboplatin / Paclitaxel With and Without Trastuzumab (Herceptin) in HER2/Neu+ Patients With Advance / Recurrent Uterine Serous Papillary Carcinoma" trial are included in this report.[7,10] The first publication was a report on preliminary data and was published in 2018.[7] The second publication followed in 2020 and provided an updated overall survival analysis (data cut off not provided).

Study Design

The RCT used a randomized, open-label, phase II design.[7,10] Participants were randomized 1:1 by the lead institution. Minimization was used to balance groups by study site, disease status (advanced-stage primary versus recurrent disease), and residual tumor after primary surgical cytoreduction (for patients with advanced-stage disease).[7]

Country of Origin

The RCT was conducted at eleven sites across the United States.[7,10]

Patient Population

Sixty-one patients with uterine serous carcinoma from eleven academic medical centres across the United States were enrolled in the RCT.[7,10] One patient withdrew consent prior to randomization and two patients were removed from the study for not meeting eligibility criteria, leaving 58 patients in the "evaluable" sample. Adult patients were eligible if they were within eight weeks of surgery or recurrence diagnosis for advanced (stage III or IV) or recurrent histologically confirmed uterine serous papillary carcinoma with measurable disease and a measurable HER2/neu positive tumor.[7,10]

Patients with a history of other invasive malignancies were excluded with a few exceptions, which are listed in Table 2.

Enrolled patients had a mean age of 69 years; patients in the intervention group were significantly younger than their counterparts in the comparator group (median 66 years versus 73 years, P = 0.006).[7,10] Seventy-one percent of patients had advanced disease and 29% had recurrent disease.[7,10]

Interventions and Comparators

The intervention (carboplatin and paclitaxel + trastuzumab; CP + T) and comparator (CP) groups both received the chemotherapy drugs paclitaxel and carboplatin every 21 days for six cycles. Paclitaxel (175 mg/m^2) and carboplatin (area under the curve 5) were administered intravenously every 21 days for six cycles.[7,10]

In the CP +T intervention group, participants received the same paclitaxel and carboplatin treatment, with the addition of trastuzumab as follows. Participants first received an 8 mg/kg loading dose of trastuzumab administered over a 90-minute period on day one of treatment. On day 21, 6 mg/kg of trastuzumab was administered intravenously. This was repeated every 21 days and continued indefinitely after 6 cycles of cytotoxic therapy (i.e., carboplatin

and paclitaxel) were completed and until progression of the disease or prohibitive toxicities occurred.

Outcomes

Progression-free survival was the primary endpoint. It was defined as "length of time from randomization to disease recurrence, disease progression, or death for any reason, whichever occurred first (p. 2).[7]" Progression was defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and computed tomography of the chest, abdomen, and pelvis every three months or upon suspicion of progression. Analyses were conducted overall and by disease state (advanced or recurrent).

Secondary endpoints were objective response, overall survival, and safety. Objective response was a composite of complete response plus partial response. Safety was assessed as high-grade adverse events (i.e., grade of 3, 4, or 5) using the Common Terminology for Adverse Events. A composite of complete response, partial response, and stable disease labelled as "clinical benefit" was also reported.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Randomized Controlled Trial

There were several strengths and limitations of the included RCT.[7,10] The study objective, treatments, and main findings were clearly described. This included transparent and precise reporting of statistics. Specifically, confidence intervals described the variability around the primary outcome and actual probability values were reported for main study endpoints. HER2 status was detected using standard diagnostic methods (i.e., fluorescence in situ hybridization and/or immunohistochemistry). Adverse events were assessed according to Common Terminology Criteria for Adverse Events. Although the characteristics of patients lost to follow-up were not described, fewer than five percent of enrolled participants were lost to follow up and the reasons they were removed (n = 2) or withdrew (n = 1) were not related to outcomes of interest.

The study had elements of good internal validity. Randomization was performed by minimization. Survival analysis was used to account for different lengths of follow up and survival outcomes were appropriately assessed using Kaplan-Meier curves. Compliance with interventions was similar for the intervention and comparator groups Eighty-two percent of participants in the trastuzumab intervention group and 86% in the comparator group received all six cycles of the prescribed carboplatin-paclitaxel chemotherapy.[7] The assessment tools used to evaluate response and disease progression (RECIST[11]) and adverse events (Common Terminology Criteria for Adverse Events[12]) had been validated in previous research. The trial was adequately powered to detect significance for the primary endpoint. Although these elements support the trustworthiness of the findings, there are reasons for caution in interpreting study findings. Participants were not blinded to the intervention received in this open-label trial, and it is not clear whether outcome assessors were blinded. The study protocol referred to by Fader et al.[7,10] did not include a detailed account of patient recruitment, randomization, or enrollment procedures, leaving questions

about study rigour. For instance, it was not clear if randomized intervention assignment was concealed until recruitment was complete and irrevocable. It is likely that some results were based on data-dredging, as there were additional outcomes assessed and subgroup analyses performed (e.g., analyses were performed by recurrent or advanced disease state and type of advanced disease) than were listed in the clinical trials registry or study protocol. Further, study authors used 90% confidence intervals rather than the conventional 95% confidence intervals, which raises questions about whether statistical tests were appropriate. Readers were referred to a study protocol for a rationale however a rationale was not provided within the protocol.[13]

As a result of the limited methodology detail provided in the published articles or study protocol,[7,10,13] the external validity of the study findings is questionable with several study elements unknown at the time of this critical appraisal. Specifically, it was unclear whether the staff, places, and facilities where study participants received their treatment were representative of the care the majority of patients receive, or whether participants asked to participate - or those prepared to participate – were representative of the entire population from which they were recruited.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Trastuzumab

Progression Free Survival

Progression-free survival was the primary endpoint of the RCT.[7,10] For the total evaluable sample, the trastuzumab plus chemotherapy (i.e., carboplatin and paclitaxel) intervention group had nearly five more months median progression-free survival compared with the comparator group of carboplatin and paclitaxel alone.[10] The results favoured CP + T when sub-analyses were conducted for patients with advanced disease (stage III and IV) and for individuals with recurrent disease.[10] Sub-analysis of patients with stage IIIC or IV advanced disease did not show a difference between groups for progression-free survival in the original analysis,[7] but with the passage of time and additional events to include, the CP + T group had improved progression free survival versus the CP group in the 2020 publication.[10]

Overall Survival

In the preliminary analysis, there were no significant differences between the CP+T and CP groups in terms of overall survival.[7] In the updated analysis, patients in the CP + T intervention group fared significantly better than the CP comparator group in terms of median overall survival for the total sample and the advanced disease sub-analyses, but not for the recurrent disease sub-analysis.[10] The authors suggested that the greatest benefit was achieved by the patients with stage IIC and IV advanced disease, however formal comparisons between subgroups of patients based on recurrence or disease stage (IIC and IV or III or IV) were not conducted.

Safety

In the preliminary analysis, study participants experienced 78 high-grade (level three or greater) adverse events.[7] Of those, 51 occurred in the CP + T intervention group and 27 occurred in the CP comparator group. There were no significant differences between groups in the number of occurrences of any specific adverse event.[7] In the updated

analysis, 42 additional high-grade toxicities were identified.[10] For the CP + T intervention group, 10 adverse events occurred during treatment and 13 occurred following treatment. In contrast, the CP comparator group reported one adverse event at the end of treatment and 13 events post-treatment.[10]

Overall Response

Overall response was reported in the 2018 publication.[7] Differences between groups for the following outcomes were not examined statistically: complete response, partial response, stable disease, and progressive disease. A composite of complete response, partial response, and stable disease was labelled as “clinical benefit”, and there was no statistically significant difference between the CP + T intervention group and the CP comparator group for this outcome. A second composite variable consisting of complete response and partial response was labelled “objective response”, for which there was no statistically significant difference between groups.[7]

Cost-Effectiveness of Trastuzumab

No relevant evidence regarding the cost-effectiveness of trastuzumab combination or monotherapy for HER2 positive advanced or recurrent uterine or endometrial cancer was identified; therefore, no summary can be provided.

Limitations

The main limitation of the evidence for this report was the limited quantity of research on trastuzumab for the treatment of patients with HER2 positive uterine cancer. Two publications were included that reported the findings of one RCT regarding the use of trastuzumab in combination with cisplatin and paclitaxel chemotherapy for patients with HER2 positive uterine serous cancer.[7,10] The trial was stopped early due to slow enrollment, despite interim futility analysis showing benefit of trastuzumab plus chemotherapy. It is not clear whether, or how, continuing to enroll the planned number of patients would have affected the results. No relevant clinical evidence was identified regarding patients with stage III to IV or recurrent uterine cancer that was not of the uterine serous carcinoma sub-type. Furthermore, no evidence was identified regarding intervention with trastuzumab monotherapy, alternative comparators, or the outcome, quality of life. Finally, there was no evidence identified regarding the cost-effectiveness of trastuzumab monotherapy or combination therapy.[7,10]

The included RCT was conducted in the United States.[7,10] It is not known whether studies conducted outside of Canada are generalizable to clinical practice in Canada.

Conclusions and Implications for Decision or Policy Making

Two publications from one RCT of moderate quality were included to address the research question on clinical effectiveness of trastuzumab combination therapy in patients with advanced or recurrent HER2 positive uterine serous carcinomas.[7,10] Overall median progression free survival was significantly greater in patients with advanced or recurrent HER2 positive uterine serous carcinoma that were randomized to receive trastuzumab in combination with carboplatin and paclitaxel compared with carboplatin and paclitaxel alone, with no significant increase in high-grade toxicities.[7,10] While these findings suggest trastuzumab may be a promising treatment option for patients with HER2 positive uterine serous carcinoma, the effect of trastuzumab on quality of life remains an important gap in the literature. The study was conducted in the US, and findings may be generalizable to the

Canadian setting, however it is unclear If there are differences in care pathways or other factors that might limit generalizability. Furthermore, the comparator in the trial was limited to carboplatin and paclitaxel, and additional alternative treatments are used in Canada including cisplatin with paclitaxel or docetaxel, liposomal doxorubicin, or immunotherapy (e.g., pembrolizumab) therapy. Information on these alternative comparators was not identified for inclusion in this report. In addition to the lack of evidence on other comparators for patient with uterine serous carcinoma, there was also no evidence was identified regarding the clinical effectiveness of trastuzumab monotherapy or other types of trastuzumab combination therapies for patients with HER2 positive advanced or recurrent uterine or endometrial cancer.

Future research investigating the clinical effectiveness of trastuzumab monotherapy or combination therapy with Canadian representation and information regarding safety (data on serious and treatment-related adverse events), and quality of life would provide additional information for clinicians providing care to patients with HER2 positive advanced or recurrent uterine or endometrial cancer.

Finally, studies on the cost-effectiveness of trastuzumab for the treatment of HER2 positive uterine cancer were not identified for this report. The authors of the included RCT discussed the expense of treatment and high drug acquisition cost of trastuzumab, and discussed plans for a cost-effectiveness study to be conducted in women with primary, advanced HER2-positive.[10] The authors further cited evidence to support the cost-effectiveness of trastuzumab in palliative breast cancer settings,[14] however whether trastuzumab is cost-effective for the treatment of HER2 positive uterine or endometrial cancer remains unknown.[10] Economic evaluations investigating the cost-effectiveness of trastuzumab monotherapy or trastuzumab combination therapy versus alternative treatment options in patients with advanced or recurrent HER2 positive uterine or endometrial cancer would help stakeholders in decision making on the use of trastuzumab treatment.

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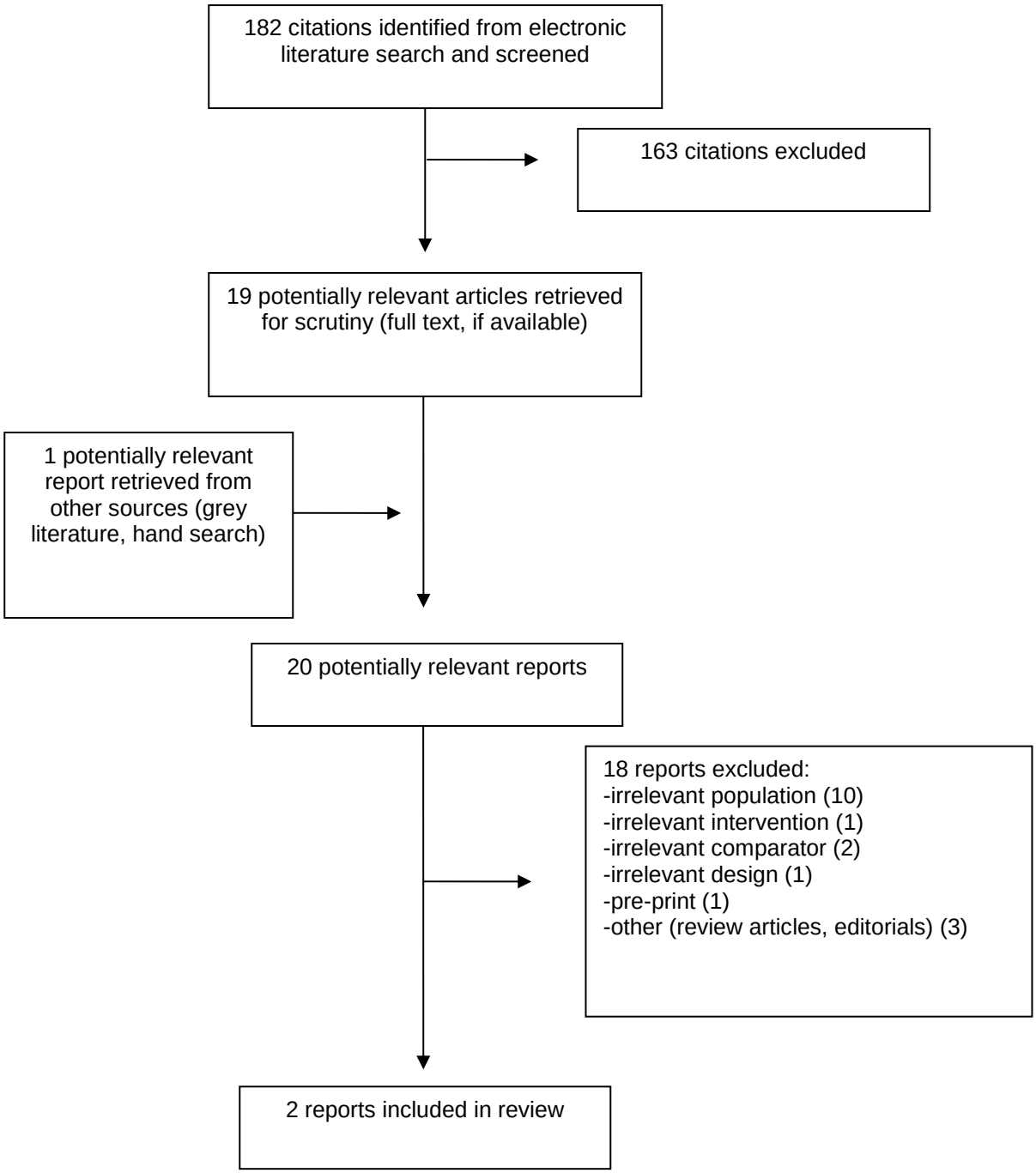
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized Controlled Trial				

Fader et al., 2020[10] and 2018[7]
 	
Trial name: Randomized Phase II Evaluation of Carboplatin / Paclitaxel With and Without Trastuzumab (Herceptin) in HER2/Neu+ Patients With Advance / Recurrent Uterine Serous Papillary Carcinoma
 	
United States
 	
Funding Source: Genetech Inc. provided study drugs
	Randomized, open-label phase II trial
	
	Randomization:
	• 1:1 by the lead institution
	• Minimization used to balance groups by study site, disease status (advanced-stage primary vs. recurrent disease), and residual tumor after primary surgical cytoreduction (for those with advanced stage disease
	
	Enrollment:
	August 2011 to January 2017
		Number of participants:
		61 enrolled
		3 excluded
		= 58
		
		Intervention, n = 30
		
		Comparator, n = 28
		
		Mean age: 69 years
		
		Median age (IQR):
		Intervention: 66 years (64-69);
		Comparator: 73 years (68-78)
		
		Sex: female
		
		Stage of disease:
		71% advanced
		29% recurrent
		
		Inclusion criteria:
		• Advanced or recurrent histologically confirmed uterine serous papillary carcinoma with measurable disease;
		• HER2/neu+ tumor based on IHC staining score of 3+ or 2+ with confirmed gene amplification by FISH
		
		Exclusion criteria:
		• a history of other invasive malignancies, except:
		  ○ non-melanoma skin cancers,
		  ○ significant history of cardiac disease,
			Intervention:
			CP + T
			
			Paclitaxel 175 mg/m^2 administered intravenously every 21 days for 6 cycles.
			
			Carboplatin AUC 5 administered intravenously every 21 days for 6 cycles.
			
			From day 1, an 8 mg/kg loading dose of trastuzumab was administered over a 90 minute period. Beginning on day 21, patients received 6 mg/kg of trastuzumab, administered intravenously every 21 days and continued indefinitely every 21 days after 6 cycles of cytotoxic therapy were completed and until progression of the disease or prohibitive toxicities occurred.
			
			Comparator:
			CP
			
			Paclitaxel 175 mg/m^2 administered intravenously every 21 days for 6 cycles.
			
			Carboplatin AUC 5 administered intravenously every 21 days for 6 cycles.
				Primary endpoint:
				• PFS i.e., "length of time from randomization to disease recurrence, disease progression, or death for any reason, whichever occurred first" (p. 2)
				
				Secondary endpoints:
				• Objective response
				• OS
				• Safety assessed according to CTCAE
				
				Follow-up: until PFS (disease recurrence, progression, or death)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		○ uncontrolled hypertension, ○ unstable medical issue, ○ brain leptomeningeal, ○ prior therapy with trastuzumab, ○ uncontrolled seizure disorder, ○ seropositive for HIV, ○ active hepatitis, ○ hemorrhagic diathesis ○ requiring supplemental oxygen		

AUC = area under the curve; CP = carboplatin-paclitaxel; CP + T = carboplatin and paclitaxel + trastuzumab; CTCAE = Common Terminology Criteria for Adverse Events; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; NR = not reported; OS = overall survival; PFS = progression free survival.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[8]

Strengths	Limitations
Fader et al., 2018[7] and 2020[10]	
• Study objective was clearly described. • Main outcomes clearly described in methods. • Patient inclusion and exclusion criteria were clearly described. • Interventions of interest were clearly described. • Main findings of the study were clearly described. • Estimates of random variability (i.e., confidence intervals) in the data were provided for the main outcome. • Adverse events were systematically assessed and reported. • Characteristics of patients lost to follow-up were not described, however <5% of enrolled participants were lost to follow up and reasons were not related to outcomes of interest. • Actual probability values were reported for main study endpoints. • Analyses were adjusted for different lengths of follow up (i.e., survival analysis). • Compliance with the interventions was reliable – 18% received <6 cycles of CP in the comparator group; 13% received <6 cycles of CP + T in the intervention group. • Main outcome measures were accurate and reliable; response and disease progression were defined by RECIST 1.1, and CTCAE version 4.0 was used to describe adverse events. • Patients in different intervention groups were recruited from the same population. • Patients in different intervention groups were recruited over the same period of time. • Participants were randomized to intervention groups 1:1. • Minimization was used to stratify patients on important characteristics (i.e., study site, disease status, and residual tumour after surgical cytoreduction (within the advanced-disease group). • The trial was adequately powered to detect significance for the primary endpoint.	• Staff, places, and facilities where participants were treated were representative of the treatment the majority of patients receive (i.e., 11 academic medical centres) • Unable to determine if participants asked to participate were representative of the entire population from which they were recruited. • Unable to determine if participants who were prepared to participate were representative of the entire population from which they were recruited. • Participants were not blinded to the intervention received. • Unable to determine if outcome assessors were blinded to the main outcomes. • Some results may have been based data-dredging. The clinical trials registry lists PFS and safety as the only outcome measures of interest, the protocol also lists objective response rate and overall survival, however others were also included. Sub-analyses performed were not explicitly described in the statistical analyses section of the study methods or the study protocol. • Unable to determine if statistical tests used to assess the main outcomes were appropriate. A 90% CI was used with the only rationale being, “as described in the study protocol.” However, rationale was not provided in the study protocol. • Unable to determine if randomized intervention assignment was concealed from both patients and healthcare staff until recruitment was complete and irrevocable. • Intention to treat analysis was not used. • The trial was stopped early before enrolling the planned number of participants for low enrollment, despite interim futility analysis showing benefit of trastuzumab. • Potential conflicts of interest were disclosed and there was no indication of how they were addressed. • Distributions of principal confounders in each group of participants to be compared were clearly described. Participants in the intervention group were significantly older than the comparison group (median 66 years vs. 73 years, P = 0.006). This may have biased outcomes in favour of the intervention. Statistics Canada reported that the age structure of a population with endometrial cancer will strongly influence the mortality rates observed and recommend controlling for differences in age in uterine cancer research. Study authors indicated that research suggests that age is not a prognostic factor for recurrence in patients with similar stages of cancer who are using similar treatments. It is not clear how these differing positions relate to uterine serous carcinoma, specifically.

CP = carboplatin-paclitaxel; CP + T = carboplatin-paclitaxel + trastuzumab; CTCAE = Common Terminology for Adverse Events; RECIST = Response evaluation criteria in solid tumors.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Fader et al., 2020[10]	
Intervention (CP + T) vs. Comparator (CP) **<u>Primary Endpoint: Median PFS</u>** 58 patients experienced 44 events (43 progressions and 38 deaths) during a total follow-up of 1,865 months (median: 25.9 months; range: 0.33 to 91.5 months) **Total Sample** CP + T, 12.9 months vs. CP, 8.0 months HR = 0.46; 90% CI, 0.28 to 0.76; P = 0.005 **Subgroups**: **Advanced disease (stage III and IV) undergoing primary treatment** CP + T, 17.7 months vs. CP, 9.3 months HR = 0.44; 90% CI, 0.23 to 0.83; P = 0.015 **Recurrent disease** CP + T, 9.2 months vs. CP, 7.0 months HR = 0.13; 90% CI, 0.33 to 0.48; P = 0.0035 **Advanced disease (stage IIIC or IV only - IIIA and IIIB excluded)** CP + T (n = 17) vs. CP (n = 19) 14.8 months vs. 9.0 months HR = 0.40; 90% CI, 0.20 to 0.76; P = 0.008 **<u>Secondary Endpoint: Median OS</u>** **Total Sample** CP + T, 29.9 months vs. CP, 24.4 months HR = 0.58; 90% CI, 0.34 to 0.99; P = 0.046 Subgroups: **Advanced disease (stage III and IV) undergoing primary treatment** CP + T, OS not reached vs. CP, 25.4 months HR = 0.49; 90% CI, 0.25 to 0.97; P = 0.041 **Advanced disease (stage IIIC or IV only – IIIA and IIIB excluded)** CP + T, 31.9 months vs. CP, 21.3 months HR = 0.44; 90% CI. 0.22 to 0.88; P = 0.023 **Recurrent disease** CP + T, 25.0 months vs. CP, 22.5 months HR = 0.0864; 90% CI, 0.36 to 2.10; P = 0.39	"…the addition of trastuzumab to carboplatin/paclitaxel resulted in significantly improved PFS and OS, with the greatest benefit in both survival categories observed in women with stage III/IV disease undergoing primary therapy after surgery. Updated median-PFS continued to favor the trastuzumab arm by approximately 5 months in the entire cohort, with a >8-month improvement for women with stage III to IV disease undergoing primary treatment. OS was also significantly higher in the trastuzumab arm by 5 months, with a particular benefit again noted in those with stage III to IV disease treated upfront (median OS not reached in the trastuzumab arm vs... 25.4 months in the control arm). The addition of trastuzumab was well tolerated by patients, with few high-grade adverse events. In fact, 20% of patients on the trastuzumab arm remain on the drug without evidence of disease recurrence (*p3933*)."

Main study findings	Authors' conclusion
Secondary Endpoint: Safety **42 high grade [CTCAE grade ≥ 3] toxicities identified since Feder et al. 2018.**[7] 57 of 60 patients had an evaluable CTCAE event No patients required discontinuation of trastuzumab for toxicity 5 AEs *before treatment assignment* – all grade 1 **CP + T** 10 AEs *during CP +T:* included 1 pruritus (grade 3) and 1 neutropenia (grade 3) 13 *post CP + T*: included 1 leukopenia (grade 3) **CP** 1 *at the end of CP*: alopecia of unknown grade 13 *post-CP*: included abdominal pain (grade 3) and nausea (grade 3) in the same patient	
Fader et al., 2018[7]	
Intervention (CP + T) vs. Comparator (CP) **Primary Endpoint: Median PFS** **Total Sample** CP + T, 12.6 months vs. CP, 8.0 months HR = 0.40; 90% CI, 2.0 to 0.76; P = 0.005 **Subgroups:** **Advanced disease (stage III and IV) undergoing primary treatment** CP + T, 17.9 months vs. CP, 9.3 months HR = 0.40; 90% CI, 2.0 to 0.80; P = 0.013 **Recurrent disease** CP + T, 9.2 months vs. CP, 6.0 months HR = 0.14; 90% CI, 0.05 to 0.54; P = 0.003 **Advanced disease (stage IIIC or IV only - IIIA and IIIB excluded)** CP + T, 14.0 months vs. CP, 8.9 months HR = 0.368; 90% CI, 0.181 to 0.750 **Secondary Outcome: Overall Response** **Recurrent disease, n (%)** Complete response = 1 (11%) vs. 2 (25%) Partial response = 3 (33%) vs. 4 (50%) Stable disease = 5 (56%) vs. 1 (12.5%) Progressive disease = 0 (0%) vs. 1 (12.5%) -Clinical benefit = 100% vs. 87.5%; P = 0.47 -Objective response (complete + partial) = 44% and 75%; P = 0.33	"In summary, novel therapeutic strategies must be developed for USC. Outcomes for women with this malignancy remain dismal. Our study demonstrates that the addition of trastuzumab to carboplatin-paclitaxel improves PFS by 4.6 months in women with advanced-stage or recurrent USC and achieves a meaningful clinical benefit rate without increasing toxicity. The greatest benefit may be observed when trastuzumab is used with carboplatin-paclitaxel in the up-front setting and in those with stage IIIC or IV disease (*p2050*)."

Main study findings	Authors' conclusion
Secondary Outcome: Safety High grade [CTCAE grade ≥ 3] toxicities, CP + T vs. CP, n (%) • Neutrophil count decreased, 4 (13%) vs. 5 (18%) • Anemia, 6 (19%) vs. 2 (7%) • Blood and lymphatic system disorders – other (neutropenia), 5 (16%) vs. 1 (4%) • Hypertension, 5 (16%) vs. 0 (0%) • Hyperglycemia, 3 (9%) vs. 1 (4%) • WBC decreased, 3 (9%) vs. 1 (4%) • Diarrhea, colitis, and enterocolitis, 3 (9%) vs. 1 (4%) • Thromboembolic event, 1 (3%) vs. 2 (7%) • Abdominal pain, 2 (6%) vs. 0 (0%) • Dehydration, 1 (3%) vs. 1 (4%) • Febrile neutropenia, 1 (3%) vs. 1 (4%) • Hyponatremia, 0 (0%) vs. 2 (7%) • Hypoxia, 2 (6%) vs. 0 (0%) • Small intestinal obstruction, 1 (3%) vs. 1 (4%) • Acute kidney injury, 0 (0%) vs. 1 (4%) • Aspiration, 1 (3%) vs. 0 (0%) • Bone pain, 1 (3%) vs. 0 (0%) • Cognitive disturbance, 1 (3%) vs. 0 (0%) • Constipation, 1 (3%) vs. 0 (0%) • Creatinine increased, 0 (0%) vs. 1 (4%) • Dyspnea, 1 (3%) vs. 0 (0%) • Fatigue, 1 (3%) vs. 0 (0%) • Gastroparesis, 0 (0%) vs. 1 (4%) • Hematuria, 1 (3%) vs. 0 (0%) • Hypokalemia, 1 (3%) vs. 0 (0%) • Left ventricular systolic dysfunction, 1 (3%) vs. 0 (0%) • Lymphocyte count decreased, 1 (3%) vs. 0 (0%) • Peripheral sensory neuropathy, 0 (0%) vs. 1 (4%) • Platelet count decreased, 1 (3%) vs. 0 (0%) • Pleural effusion, 0 (0%) vs. 1 (4%) • Psychiatric disorders – other (depressed consciousness level), 0 (0%) vs. 1 (4%) • Renal and urinary disorders – other (UTI), 0 (0%) vs. 1 (4%) • Respiratory, thoracic and mediastinal disorders – other (URI), 1 (3%) vs. 0 (0%) • Sepsis, 1 (3%) vs. 0 (0%) • UTI, 0 (0%) vs. 1 (4%) • Vomiting, 1 (3%) vs. 0 (0%) • Wound infection, 0 (0%) vs. 1 (4%) Total = 51 vs. 27 high-grade AEs Ps = not significant (values NR) **Secondary Outcome: OS (preliminary analysis)** **Subgroups:** **Advanced disease**, n = 41, deaths = 14 59% reduced mortality for CP + T vs. CP, HR = 0.41, 90% CI, 0.16 to 1.03, P = 0.05	

Main study findings	Authors' conclusion
Recurrent disease, n = 17, deaths = 9 68% reduced mortality for CP + T vs. CP, HR = 0.32, 90% CI, 0.07 to 1.46, P = 0.097 **Advanced disease, excluding stage IIIA or IIIB disease, n = 36 (14 deaths)** 66% mortality reduction for CP + T vs. CP, HR =0.34, 90% CI, 0.14 to 0.86, P = 0.23	

AE = adverse event; CP = carboplatin-paclitaxel; CP + T = carboplatin-paclitaxel + trastuzumab; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; OS = overall survival; PFS = progression free survival; NR = not reported; URI = upper respiratory infection; USC = uterine serous carcinoma; UTI = urinary tract infection; WBC = white blood cells.

CADTH

Appendix 5: Further Information

Scoping Review

Garcia-Sanchez J, Torregrosa MD, Cauli O. Cognitive functions under Anti-HER2 targeted therapy in cancer patients: a scoping review. *Endocr Metab Immune Disord Drug Targets*. 2020 Jul;29.