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Guideline 2-26 Version 3 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

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An assessment conducted in December 2023 indicated that Guideline 2-26 Version 3 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 2-26v3 consists of 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/366

Section 1: Recommendations
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Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To provide guidance on the optimal systemic therapies for the treatment of advanced gastric and gastro-esophageal junction (GEJ) carcinoma. Optimal systemic therapies were defined as those that provided improved overall survival and improved quality of life.

TARGET POPULATION

Adult patients (age ≥18 years) with advanced gastric carcinoma or advanced carcinoma of the GEJ. In this patient population, advanced disease is defined as non-resectable disease that is either locally advanced, recurrent, or metastatic.

INTENDED USERS

This guideline is intended for use by clinicians and health care providers involved in the management or referral of the target population.

RECOMMENDATIONS

Recommendation 1a
Medical oncologists should prescribe either a fluoropyrimidine-oxaliplatin doublet or a fluoropyrimidine-irinotecan doublet regimen in the first-line treatment of patients with locally advanced, recurrent, or metastatic gastric and GEJ carcinoma.
Qualifying Statements for Recommendation 1a
• Based on improved efficacy with fluoropyrimidine-oxaliplatin-taxane when compared with monotherapy, this triplet regimen may be discussed with selected patients as an alternative to a doublet regimen. • Medical oncologists should individualize treatment based on the different toxicities associated with the preferred regimens, patient characteristics, and patient preferences when choosing the appropriate therapy.
Recommendation 1b
In patients with metastatic gastric cancer or GEJ carcinoma not overexpressing human epidermal growth factor receptor 2 (HER2), medical oncologists should not prescribe a biological agent in addition to a first-line chemotherapy regimen

Recommendation 2
In patients with recurrent or metastatic gastric and GEJ carcinoma, medical oncologists should prescribe an immune checkpoint inhibitor (ICI) in addition to a fluoropyrimidine doublet chemotherapy regimen in the first-line setting.
Qualifying Statements for Recommendation 2

- A positive association was observed between programmed cell death ligand 1 (PD-L1) combined positive score (CPS) and the magnitude of treatment benefit. In Checkmate-649, the overall survival benefit of nivolumab was confined to patients with a CPS of ≥5. To aid clinicians in informed decision making and counseling, we recommend that the CPS score be obtained, and the recommendation for the use of nivolumab be restricted to those patients whose tumours have a CPS of ≥5.

Recommendation 3
In patients with HER2 overexpressing gastric or GEJ carcinoma, medical oncologists should prescribe the addition of trastuzumab to a fluoropyrimidine doublet chemotherapy regimen in the first-line setting.
Qualifying Statements for Recommendation 3
• Trastuzumab should be prescribed until disease progression or intolerance in HER2 overexpressing patients

Recommendation 4
In patients with gastric or GEJ adenocarcinoma being considered for second-line therapy, medical oncologists may prescribe paclitaxel plus ramucirumab.
Qualifying Statements for Recommendation 4
• Single agent irinotecan or taxane is a reasonable alternative for patients not eligible for paclitaxel plus ramucirumab

Recommendation 5
In patients with gastric or GEJ adenocarcinoma being considered for third-line therapy, medical oncologists may prescribe trifluride-tipiracil monotherapy.

Recommendation 6
In patients with gastric or GEJ carcinoma undergoing later lines of therapy, medical oncologists should not prescribe ICI in addition to standard of care.

IMPLEMENTATION CONSIDERATIONS

Although testing for PD-L1 CPS is available in Ontario through local laboratories or the industry funded access programs, CPS is not routinely included on the tumor pathology report. Medical oncologists will need to request CPS testing from available resources. Until reporting of the CPS is routine, requesting the score may result in treatment decision delays.

Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To provide guidance on the optimal systematic therapies for the treatment of advanced gastric and gastro-esophageal junction (GEJ) carcinoma. Optimal systemic therapies were defined as those that provided improved overall survival and improved quality of life.

TARGET POPULATION

Adult patients (age ≥18 years) with advanced gastric carcinoma or carcinoma of the GEJ. In this patient population, advanced disease is defined as non-resectable disease that is either locally advanced, recurrent, or metastatic.

INTENDED USERS

This guideline is intended for use by clinicians and health care providers involved in the management or referral of the target population.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1a
Medical oncologists should prescribe either a fluoropyrimidine-oxaliplatin doublet or a fluoropyrimidine-irinotecan doublet regimen in the first-line treatment of patients with locally advanced, recurrent, or metastatic gastric and GEJ carcinoma.
Qualifying Statements for Recommendation 1a
• Based on improved efficacy with fluoropyrimidine-oxaliplatin-taxane when compared with monotherapy, this triplet regimen may be discussed with selected patients as an alternative to a doublet regimen. • Medical oncologists should individualize treatment based on the different toxicities of the preferred regimens, patient characteristics, and patient preferences when choosing the appropriate therapy.
Recommendation 1b
In patients with metastatic gastric cancer or GEJ carcinoma not overexpressing human epidermal growth factor receptor 2 (HER2), medical oncologists should not prescribe a biological agent in addition to a first-line chemotherapy regimen
Key Evidence for Recommendation 1
Evidence from a large network meta-analysis has demonstrated improved survival when fluoropyrimidine doublet regimens are prescribed to patients in a first-line setting [1]. When comparing fluoropyrimidine doublets, the network meta-analysis reported improved overall survival with fluoropyrimidine-oxaliplatin and fluoropyrimidine-irinotecan doublets compared with fluoropyrimidine-cisplatin [1]. Additionally, pairwise comparison included in the network meta-analysis demonstrated increased toxicity with fluoropyrimidine-cisplatin when compared with fluoropyrimidine-oxaliplatin and fluoropyrimidine-irinotecan doublets [1]. A second meta-analysis that compared oxaliplatin-based regimens and cisplatin-based regimens reported no difference between the arms for overall survival [2]. In this meta-analysis, oxaliplatin-based doublet and triplet regimens included oxaliplatin paired with S-1, docetaxel, epirubicin, capecitabine, and fluoropyrimidine, while cisplatin was delivered as monotherapy or in doublet and triplet regimens paired with S-1, epirubicin, capecitabine, and fluoropyrimidine [2] and thus this meta-analysis does not reflect a clear comparison

between fluoropyrimidine paired with oxaliplatin and cisplatin. Although not a direct comparison of fluoropyrimidine doublets, the meta-analysis did provide a more in-depth assessment of adverse events for oxaliplatin- and cisplatin-based regimens and reported decreased neutropenia, anemia, nausea, and thromboembolism with oxaliplatin-based therapy [2]. In comparison, the oxaliplatin-based regimens increased neurosensory toxicity and thrombocytopenia [2]. Based on improved efficacy and reduced toxicity observed in the network meta-analysis, fluoropyrimidine paired with oxaliplatin or irinotecan are the preferred first-line regimens. The second meta-analysis also supports the use of an oxaliplatin-based regimen over cisplatin-based regimen and provides data on differential toxicities of regimens to inform a discussion between care providers and patients.

In patients not overexpressing HER2, studies report higher risk of adverse events with targeted therapies [3] and no significant improvement in survival in a first-line setting [3-6]. Therefore, there is no role for any of these agents to be added to chemotherapy as part of a first-line regimen.

Justification for Recommendation 1

The strength of evidence informing this recommendation is moderate. Based on the efficacy benefits with the use of fluoropyrimidine-oxaliplatin and fluoropyrimidine-irinotecan doublet chemotherapy regimens and reduced harms when compared with fluoropyrimidine-cisplatin, the Working Group members concluded that the benefits of these doublet regimens outweighed the harms. In many institutions, this therapy is already standard practice, and the Working Group expects the guidance to be acceptable to key stakeholders and feasible to implement. Additionally, the Working Group believes that this guidance will probably have no impact on health equity and resource requirements will be negligible in comparison with other first-line doublet therapies.

Recommendation 2

In patients with recurrent or metastatic gastric and GEJ carcinoma, medical oncologists should prescribe an immune checkpoint inhibitor (ICI) in addition to a fluoropyrimidine doublet chemotherapy regimen in the first-line setting.

Qualifying Statements for Recommendation 2

- A positive association was observed between programmed cell death ligand 1 (PD-L1) combined positive score (CPS) and the magnitude of treatment benefit. In Checkmate-649, the overall survival benefit of nivolumab was confined to patients with a CPS of ≥5. To aid clinicians in informed decision making and counseling, we recommend that the CPS score be obtained, and the recommendation for the use of nivolumab be restricted to those patients whose tumours have a CPS of ≥5.

Key Evidence for Recommendation 2

The phase III KEYNOTE-062 trial [9], JAVELIN Gastric 100 trial [8], and CheckMate-649 trial [7] have all been published since 2020. Both KEYNOTE-062 [9] and JAVELIN Gastric 100 [8] demonstrated no difference in overall survival rates when patients were treated with pembrolizumab (hazard ratio [HR], 0.91; 99.2% confidence interval [CI], 0.69 to 1.18) [9] or avelumab (HR, 0.72; 95%CI, 0.49 to 1.05) [8]. However, CheckMate-649 randomized patients to either nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone and reported improved overall survival with nivolumab plus chemotherapy treatment in the primary endpoint population of patients who had a PD-L1 CPS of at least 5 (HR, 0.71; 98.4%CI, 0.59 to 0.86) when compared to patients receiving only chemotherapy [7]. Based on a meta-analysis that combined Checkmate-649 [7], JAVELIN Gastric 100 [8], and KEYNOTE-062 [9], in a first-line setting, compared with standard of care, ICIs provide a significant overall survival benefit (HR, 0.77; 95%CI, 0.67 to 0.89; p=0.0006) in patients with tumours that

express PD-L1. Positive expression of PD-L1 in the primary endpoint population was defined as ≥1% CPS in JAVELIN Gastric 100 [8] and KEYNOTE-062 [9], and as ≥5% CPS in Checkmate-649 [7].

Treatment-related adverse events of grade 3 or 4 ranged from 16.9% through 59.0% for the ICI arms in the identified randomized controlled trials (RCTs), while events ranged from 32.8% through 69.3% in the control arms [7-9]. Treatment-related deaths occurred in 1.1% through 6.6% of patients in the ICI arms and in 0.5% to 5.5% of patients in the control arms [7-9].

Justification for Recommendation 2

The strength of evidence informing this recommendation is moderate for both overall survival and adverse events. In the identified RCTs, nivolumab, avelumab, and pembrolizumab, alone or in combination with chemotherapy, were compared with chemotherapy in the first-line setting. The meta-analysis of individual trials demonstrates a statistically significant overall survival benefit for ICIs. Despite the increased toxicity of treatment with the ICI therapy in CheckMate-649 and a similar rate of grade 3 and 4 treatment-related adverse events when compared with chemotherapy in all three RCTs, the Working Group members concluded the overall survival benefit of prescribing ICIs outweighed the harms of their use. However, the Working Group suggests that medical oncologists obtain the CPS to aid in treatment decision making. While CheckMate-649 demonstrated an overall survival benefit with nivolumab for patients with a CPS ≥1, but not for patients with CPS <1, and for patients with CPS ≥5 but not for those with a CPS <5, the publication does not include subgroup analysis of patients with CPS of 1-4. It is likely that the benefit for patients with CPS ≥1 was driven by patients with a CPS ≥5, as more than 75% of patients included in the CPS ≥1 subgroup did in fact express CPS ≥5. Further to this, a secondary analysis that sought to reconstruct unreported survival curves from CheckMate-649 demonstrated no difference in overall survival for patients with a CPS of 1-4 when comparing patients treated with nivolumab plus chemotherapy and patients treated with chemotherapy alone (HR, 0.950; 95%CI, 0.747 to 1.209; p=0.678) [10]. Although the addition of ICIs would increase resource requirements in the first-line setting, this guidance is expected to be acceptable to all stakeholders. Currently nivolumab is the only ICI approved by Health Canada for advanced or metastatic gastric and GEJ carcinoma [11]; until other agents are approved and funded, the feasibility of implementing this guidance will be reduced.

Recommendation 3

In patients with HER2 overexpressing advanced gastric or GEJ carcinoma, medical oncologists should prescribe trastuzumab in addition to a fluoropyrimidine doublet chemotherapy regimen in the first-line setting.

Qualifying Statements for Recommendation 3

- Trastuzumab should be prescribed until disease progression or intolerance in HER2 overexpressing patients

Key Evidence for Recommendation 3

The ToGA trial, which compared trastuzumab plus chemotherapy with chemotherapy alone in patients with HER2 overexpressing gastric or GEJ carcinoma, reported improved overall survival in the combination treatment arm (median 13.8 months vs. median 11.1 months; HR, 0.74; 95%CI, 0.60 to 0.91; p=0.0045) [12]. The 2010 iteration of this guideline issued a provisional recommendation on the routine addition of trastuzumab to the then recommended first-line chemotherapy regimen for HER2-positive patients. The provisional recommendation was based on an interim analysis of ToGA trial data. In 2014, based upon the final analysis of the ToGA trial [12], the Gastrointestinal Disease Site Group (DSG) endorsed the original recommendation. The current iteration of this guideline reaffirms the

addition of trastuzumab to a first-line regimen in patients with HER2 overexpressing advanced gastric and GEJ carcinoma.

Justification for Recommendation 3

The strength of evidence underpinning this recommendation is moderate. Although the chemotherapy regimens in the ToGA trial were capecitabine-cisplatin or fluorouracil-cisplatin [12], a meta-analysis of three observational studies that added trastuzumab to fluorouracil/cisplatin-oxaliplatin demonstrated that compared with the ToGA regimen, trastuzumab plus the oxaliplatin doublet significantly improved overall survival (median 20.7 months vs. median 13.8 months; HR, 0.75; 95% CI, 0.59 to 0.99; $p<0.05$) [13]. Based on this evidence and an understanding of the biological pathways being targeted by the therapy, the Working Group extrapolated the benefits of the ToGA trial to any recommended fluoropyrimidine doublet regimen. The Working Group concluded that the benefits of improved survival outweighed the minimal harms. Although resources would be increased with the additional of trastuzumab to a first-line therapy, the Working Group members believe this guidance is currently standard practice for many medical oncologists and will be both acceptable to key stakeholders and feasible to implement.

Recommendation 4

In patients with gastric or GEJ adenocarcinoma being considered for second-line therapy, medical oncologists may prescribe paclitaxel plus ramucirumab.

Qualifying Statements for Recommendation 4

- Single agent irinotecan or a taxane is a reasonable alternative for patients not eligible for paclitaxel plus ramucirumab

Key Evidence for Recommendation 4

The RAINBOW trial randomized previously treated patients with advanced gastric or GEJ adenocarcinoma to either ramucirumab plus paclitaxel or placebo plus paclitaxel. The phase III trial reported significantly improved overall survival (Median 9.6 months vs. 7.4 months; HR, 0.81; 95% CI, 0.68 to 0.96; $p=0.02$) in patients treated with the combination therapy [14]. Both the original publication that included adverse events [14] and a later publication that focused on quality of life [15] reported increases in certain toxicities with the combination therapy compared with paclitaxel plus placebo. However, the same studies also reported reductions in other toxicities and improved quality of life domains with the therapy [14,15]. Medical oncologists can use the available data on efficacy, toxicity and quality of life as part of an informed decision-making process about the use of paclitaxel and ramucirumab.

In patients who are not eligible for paclitaxel plus ramucirumab, meta-analyses have demonstrated improved survival in second-line settings when patients undergo treatment with either irinotecan or taxane monotherapy [16,17].

Justification for Recommendation 4

The strength of evidence informing this recommendation is moderate. Although the RAINBOW trial was a well-conducted RCT with low risk of bias, this recommendation is only informed by the single study in two publications with a modest overall survival benefit (median = 2.2 months). Based on patient performance status at this stage of treatment and the potential for poorly controlled comorbidities, a focus on a patient's quality of life and minimizing toxicity are key considerations when choosing the best therapy for any individual patient. The Working Group considered the potential harms of some increased toxicity with ramucirumab, but the benefits of a modest improvement in median survival outweighed the potential harms. Medical oncologists should discuss the risk of toxicity with potential patients to ensure the patient would also value the survival benefit over the potential toxicity. The

Working Group expects this guidance to be acceptable to key stakeholders and feasible to implement.

Recommendation 5

In patients with gastric or GEJ adenocarcinoma being considered for third-line therapy, medical oncologists may prescribe trifluride-tipiracil monotherapy.

Key Evidence for Recommendation 5

The TAGS trial randomized patients with advanced gastric and GEJ adenocarcinoma who had previously undergone at least two prior lines of therapy to trifluride-tipiracil or placebo [18]. The study reported a significantly improved overall survival in patients receiving trifluride-tipiracil (median 5.7 months vs. median 3.6 months; HR, 0.69; 95% CI, 0.56 to 0.86; p<0.01) [18]. Although the TAGS trial did not conduct statistical analysis on the frequency of grade 3/4 adverse events, the study did report an 80% frequency in the trifluride-tipiracil arm and a 58% frequency in the placebo arm [18]. Medical oncologists can use the available data on efficacy, toxicity and quality of life as part of an informed decision-making process about the use of trifluride-tipiracil.

Justification for Recommendation 5

The strength of evidence informing this recommendation is moderate. Although the TAGS trial was a well-conducted RCT with low risk of bias, this recommendation is only informed by the single study. Similar to second-line therapy, patient performance status at this stage of treatment, the potential for poorly controlled comorbidities, a focus on a patient's quality of life, and minimizing toxicity must be key considerations when choosing the best therapy for any individual patient. The potential for grade 3/4 adverse events with trifluride-tipiracil needs to be weighed against the benefits of a modest improvement in survival. Medical oncologists should discuss the risk of adverse events with potential patients and the option of no further treatment to ensure patients would equally value the survival benefits. The Working Group accepts that there will be some increased resource use associated with this guidance as it does add an additional agent to third-line therapy, but the Working Group expects this guidance to still be acceptable to key stakeholders. Currently trifluride-tipiracil has only received initial approval by Health Canada, until this therapy is fully approved and funded, the feasibility of implementing this guidance will be reduced.

Recommendation 6

In patients with gastric or GEJ carcinoma undergoing later lines of therapy, medical oncologists should not prescribe ICIs in addition to standard of care.

Key Evidence for Recommendation 6

Based on a meta-analysis of one RCT in a second-line setting (KEYNOTE 061, [19]), and two RCTs in a third-line setting (ATTRACTION-2 [20], JAVELIN Gastric 300 [21]), compared with standard of care, ICIs do not provide any survival benefit (HR, 0.82; 95%CI, 0.59 to 1.14). Additionally, ATTRACTION-2 RCT [22] and a systematic review of nine clinical trials [23] demonstrated increased toxicity with ICIs.

In the second-line setting, KEYNOTE 061 randomized 196 patients to pembrolizumab and 199 to paclitaxel [19]. All enrolled patients had tumours that expressed PD-L1 of at least 1% CPS and the overall survival between treatment arms was not significantly different (HR, 0.82; 95%CI, 0.66 to 1.03). In the third-line setting, ATTRACTION-2 [20] randomized unselected patients to nivolumab or placebo, and JAVELIN Gastric 300 [21] randomized unselected patients to either avelumab or a control arm. The most recent publication for ATTRACTION-2 reported on just over three years of follow-up (38.5 months) and demonstrated that the survival benefit with nivolumab was maintained (overall survival HR, 0.62; 95% CI, 0.50 to

0.75; p<0.0001; progression free survival HR, 0.60; 95% CI, 0.49 to 0.75; p<0.0001) [20]. The JAVELIN Gastric 300 RCT allowed for either chemotherapy or best supportive care in the control arm and reported no significant difference in overall survival when compared with patients who received avelumab (HR, 1.1; 95%CI, 0.9 to 1.4). An identified systematic review compared multiple anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents with placebo, paclitaxel, irinotecan and best supportive care for patients with advanced gastric or GEJ cancer in a second- and third-line setting [23]. The systematic review included KEYNOTE 012, 059, and 061, as well as CHECKMATE 032, ATTRACTION-2, and JAVELIN Gastric 300 trials. Patient populations across the nine included studies were unselected for PD-L1 expression. Additionally, the systematic review was limited in that both RCT data and cohort study data were combined. The study reported a significantly increased risk for all grades of adverse events using immunotherapies when compared with chemotherapy [23]. In a report on two-year follow-up of ATTRACTION-2, serious treatment-related adverse events were experienced by 11.5% of patients in the nivolumab arm and 5.0% of patients in the placebo arm [22].
Justification for Recommendation 6
The strength of evidence informing this recommendation is low for overall survival and moderate for adverse events. Based on no significant survival benefit in later lines of therapy and a large potential for adverse events in this patient population, the Working Group concluded that ICIs should not be prescribed in later lines of therapy.

IMPLEMENTATION CONSIDERATIONS

- Although testing for PD-L1 CPS is available in Ontario through local laboratories or the industry funded access programs, CPS is not routinely included on the tumor pathology report. Medical oncologists will need to request CPS testing from available resources. Until reporting of the CPS is routine, requesting the score may result in treatment decision delays.

RELATED GUIDELINES

- MacKenzie M, Spithoff K, Jonker D; Gastrointestinal Cancer Disease Site Group. Systemic therapy for advanced gastric cancer: a clinical practice guideline. Curr Oncol. 2011 Aug;18(4):e202–9.
- Cancer Care Ontario. Immune Checkpoint Inhibitor Toxicity Management. Toronto (ON): Cancer Care Ontario; *2018 March*. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/52976.

Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC and any associated Programs is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

This topic was selected as a priority topic by the PEBC Gastrointestinal (GI) DSG, GI Cancers Advisory Committee, and GI Drug Advisory Committee to help leverage and expand the use of evidence-based guidance to improve the appropriateness of care. The previous guideline was developed in 2010 and the search was updated in 2014. Since then, newer medications that were not included in the previous guideline have emerged.

GUIDELINE DEVELOPERS

This guideline was developed by the Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG (Appendix 1), which was convened at the request of the GI DSG.

The project was led by a small Working Group of the Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, surgical oncology, and health research methodology. Other members of the GI DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [24,25]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [26] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation according to GRADE's evidence-to-decision framework [27]). A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed at least one research question (Section 4) were included. Guidelines older than three years (published before 2017 and guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines on October 1, 2020 with the search terms gastric cancer or gastro-esophageal cancer: National Institute for Health and Care Excellence Evidence Search, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki.

Of 705 identified guidelines, none met the guideline inclusion criteria.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other

potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

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The Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG would like to thank the following individuals for their assistance in developing this report:

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- Sara Miller for copy editing.

Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

Section 4: Systematic Review

INTRODUCTION

Cancer is among the leading cause of death worldwide and gastric cancer represents 1.03 million cases and 783,000 deaths making it one of the top five causes of death due to cancer in the world [28]. Gastric adenocarcinoma is the most common type of gastric cancer accounting for over 90% of cases [28]. From 1984 through 2015, the annual percent change for age-standardized gastric cancer incidence decreased by 0.8%, while the mortality rate has fallen by 3.0% in Canada [29]. In 2020 the estimated age-standardized incidence rate for gastric cancer in Canada was 9.4% and the mortality rate was 4.5% [30]. In comparison, carcinomas that arise in the esophagus are comprised of predominately adenocarcinomas (70%), with squamous cell carcinoma representing a minority of histologies [31]. The incidence rate of GEJ carcinoma had been increasing since the 1930s [32] and is considered the most common location for gastro-esophageal cancers in Canada. Following an age-adjusted 3.5% incidence increase in 2006-2010, the incidence rate of esophagus cancer has now started to decline at a rate of 1.9% in 2010 through 2015 [29]. Based on data from 1999 through 2015, the mortality rate for esophagus cancer has also fallen by 0.2% [29]. In 2020 the estimated age-standardized incidence rate for esophagus cancer in Canada was 5.7% and the mortality rate was 5.1% [30].

Treatment options for patients with gastric and GEJ carcinoma depend on the stage of the disease and include surgical resection, chemotherapy, palliative radiation, and best supportive care. Despite the recent decrease in the incidence rate, there is still a considerable variation in the stage distribution at diagnosis. Surgical resection of early-stage disease is potentially curative. Unfortunately, 43.5% of gastric cancer and 39.9% of esophagus cancer are diagnosed at stage IV [33]. In patients with metastatic and recurrent disease, systemic therapy is considered the most effective modality. While chemotherapy is generally recognized as the optimal first-line therapy for these patients, there is ongoing debate on the optimal chemotherapy regimen. Additionally, real-world data in an Ontario cohort has demonstrated that patients receiving chemotherapy are experiencing inferior overall survival and disease-specific survival than that reported in the landmark clinical trials [34]. In patients who experience disease progression on or after treatment with chemotherapy, targeted agents and immune checkpoint inhibitors (ICIs) are of great interest and many new trials evaluating different agents have been published since the previous version of this guideline.

In the original evidence-based guideline on this topic in 2010, the OH (CCO) GI DSG had recommended that a platinum agent should be included in any combination chemotherapy regimen to improve survival in this population and also made statements about the preferred fluoropyrimidine and the alternatives in a combination chemotherapy regimen [35]. However, with the emergence of newer evidence around the optimal chemotherapy regimen, the Working Group developed this evidentiary base to inform newer recommendations as part of a clinical practice guideline in the Management of Advanced Gastric and Gastroesophageal Carcinoma. Based on the objectives of this guideline (Section 2), the Working Group derived the following research question.

RESEARCH QUESTIONS

What are the optimal systemic therapy regimens for the treatment of advanced gastric and GEJ carcinoma when considering survival, adverse events, and quality of life?

a. Based on the clinical outcomes, what is the optimal first-, second-, and third-line regimen for HER2 overexpressing and HER2 non-overexpressing patients with advanced gastric and GEJ carcinoma?
b. Compared with cisplatin or carboplatin, does a chemotherapy regimen containing oxaliplatin demonstrate superior clinical outcomes in patients with advanced gastric or GEJ carcinoma?
c. In patients with advanced gastric or GEJ carcinoma, does the addition of a targeted agent to chemotherapy improve clinical outcomes when compared with chemotherapy alone in any line of therapy?
d. Compared with chemotherapy or best supportive care, do ICIs improve clinical outcomes in any line of therapy?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

The Ovid interface was used to search MEDLINE, Embase and Cochrane Database of Systematic Review from October 2013 to July 2021 for existing systematic reviews on any aspect of systemic therapy for advanced gastric or gastro-esophageal cancer.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [36] tool.

Search for Primary Literature

For each outcome per research question, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed from the search cut-off date of the systematic review to July 2021. If any included systematic review was limited in scope, then an updated search of the systematic review and a new search for primary literature to address the limitation in scope were conducted.

Literature Search Strategy

A combination of recurrent/metastatic/advanced, stomach/gastric/gastroesophageal and cancer/carcinoma/neoplasia/malignancy were used to search for RCTs published from October 2013 to July 2021. Although the original guideline included studies published from 2004 through 2009, version 2 of the guideline incorporated studies published up to October 2013 [35]. Version 2 of the guideline endorsed the original recommendations. The search was conducted in EMBASE and Medline. Appendix 2 presents the details of the search strategy. The proceedings of the 2020-2021 meetings of the American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) were also searched for relevant abstracts of randomized controlled trials.

Study Selection Criteria and Process

A review of the titles and abstracts that resulted from the electronic searches was conducted by one reviewer (CA or LS). For studies that warranted full-text review, one reviewer (CA or LS) reviewed each study independently with a second reviewer (TA) if uncertainty existed. Studies were included if they were RCTs evaluating the use of systemic therapy in the management of adult patients with advanced gastric or gastro-esophageal

carcinoma including GEJ adenocarcinoma. Advanced disease is defined as non-resectable disease that is either locally advanced, recurrent, or metastatic. The studies had to report at least one of the following outcomes: overall survival rate, disease-free survival rate, progression-free survival, adverse events, or quality of life. Both full-text peer-reviewed studies and recent abstracts were included. Articles were excluded if they were published in the form of letters or editorials or published in a language other than English due to unavailability of translation services; if they were not truly randomized or designed to assess secondary tumour resectability only; if they included intraperitoneal or intra-arterial chemotherapy or presented only preliminary data.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by LS independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios (HRs) and relative risks, were expressed with a ratio of <1.0 indicating reduced mortality or adverse event risk for the intervention group.

Risk of bias per outcome for each included full-text study was assessed using the Cochrane Risk of Bias tool [37]. Additional quality features including whether analyses were statistically powered, reporting of funding, and industry funding, were recorded.

Synthesizing the Evidence

For time-to-event outcomes, when clinically and methodologically homogeneous results from two or more studies were available, a meta-analysis was conducted using Review Manager software provided by the Cochrane Collaboration [38]. HR, rather than the number of events at a specific time, were the preferred statistic for meta-analysis, and were used as reported. If the HR and/or its standard error were not reported, they were derived from other information reported in the study if available, using the methods described by Parmar et al. [39]. The generic inverse variance model with random effects was used.

The chi-squared (X^2) test was used to test the null hypothesis of homogeneity, and a probability level less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity. If heterogeneity was detected, then the I^2 index was used to quantify the percentage of the variability in the effect estimates that was due to heterogeneity.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias, was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [40].

RESULTS

Search for Systematic Reviews

A total of 101 systematic reviews were identified by the literature search. Following a title and abstract screen, which excluded systematic reviews which were either irrelevant or not truly systematic, 51 systematic reviews underwent full-text review. A total of 15 systematic reviews were included in the evidence base. The remaining 36 studies were excluded during full-text review based on: including a narrative synthesis (n=8), not reporting on any outcomes of interest (n=6), having a search that was greater than five years old (n=6), and including the same primary literature as a more complete systematic review (n=16). When multiple systematic reviews reported on the same outcome, only the most complete systematic review was retained. Appendix 3 includes a list of all RCTs that were included in the systematic reviews

chosen for inclusion in the evidence base. Quality assessment of the 15 included systematic reviews is summarized in Appendix 4.

Search for Primary Literature

The included systematic reviews were organized by which systemic therapy was evaluated and then by the outcomes reported. All primary literature that evaluated therapies or outcomes not covered by the 15 included systematic reviews were considered. For systemic therapy outcomes that were evaluated by a systematic review, only primary literature published following the publication search date cut-off of that systematic review were considered.

Literature Search Results

Following study selection, 59 studies were identified as meeting the inclusion criteria (Appendix 5). Quality assessment of the included RCTs is included in Appendix 6.

Studies were organized by therapy type and then by specific regimen or biological agent. Based on the current and expected continued unavailability of S-1 chemotherapy in Canada, studies evaluating this chemotherapy have been described under a separate heading. Table 4-1 summarizes the number of systematic reviews and primary literature studies that evaluated each systemic therapy regimen under consideration by this systematic review.

Table 4-1. Identified Systematic Reviews and Primary Literature by Systemic Therapy Type

Therapy Type	Regimen	Included Studies [ref]
Chemotherapy		
First-line	Doublet and triplet chemotherapy regimens	4 SR [1,2,41,42] 5 RCT [43-47]
	Fluoropyrimidine monotherapy	1 SR [48]
Second-line or Later	Doublet and triplet chemotherapy regimens	1 SR [49] 1 RCT [43]
	Taxane monotherapy	2 SR [16,17] 2 RCT [50,51]
	Fluoropyrimidine monotherapy	1 RCT [52]
	Irinotecan monotherapy	2 SR [16,17]
	Trifluride plus tipiracil regimen	2 RCT [18,53]
Targeted Therapies		
First-line	HER2 targeted	2 RCT [54,55]
	VEGFR2 targeted	1 SR [6] 2 RCT [56,57]
	MET inhibitor	2 RCT [3,5]
Second-line or Later	HER2 targeted	3 RCT [58-60]
	VEGFR2 targeted	1 SR [6] 4 RCT [14,15,61,62]
	mTOR and Akt targeted	2 RCT [4,63]
	PARP inhibitor	1 RCT [64]
Mixed Line (first- and second-line or later)	HER2 targeted	3 SR [6,65,66]
	VEGFR2 targeted	2 SR [6,67] 1 RCT [68]
	MET inhibitor	3 SR [6,65,66]
Immune Checkpoint Inhibitors		
First-line	PD-1/PD-L1 targeted	3 RCT [7-9]
Second-line or Later	PD-1/PD-L1 targeted	1 SR [23] 5 RCT [20,22,69-71]
	CTLA-4 targeted	1 RCT [72]

Chemotherapy Regimens not Available in Canada		
S-1 Chemotherapy	Monotherapy	1 SR [73] 1 RCT [74]
	Double and triple regimens containing S-1	1 SR [75] 9 RCT [76-84]

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HER2, human epidermal growth receptor 2; mTOR, mechanistic target of rapamycin; PARP, Poly (ADP-ribose) polymerase; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RCT, randomized controlled trial; SR, systematic review; VEGFR2, vascular endothelial growth factor receptor 2

Certainty of the Evidence

The certainty of evidence by outcome for each considered systemic therapy is included at the end of each narrative summary for that therapy. Appendix 7 provides complete details of this assessment for each outcome.

Outcomes

Survival outcomes and adverse event outcomes were defined as critical for this systematic review. Treatment response outcomes were defined as important. Although all three sets of outcomes were extracted and are contained in the complete data tables within Appendix 8, only the critical outcomes are included in text, unless included studies only reported on important outcomes. In the sections below, studies reporting on the critical outcomes are organized and summarized as detailed in Table 4-1. For systemic therapies with many identified studies or complex studies, in-line tables are used to complement the text summary. Even in these situations, all complete data tables are included in Appendix 8 to maintain this appendix as a complete resource. When studies evaluate multiple systemic therapies, only details appropriate for the specific therapy are included in text under that therapy heading.

First-line Chemotherapy

Doublet and Triplet Chemotherapy Regimens

Four systematic reviews [1,2,41,42] and five RCTs [44-47,85] reported on survival outcomes, treatment response outcomes, or adverse events in patients being treated using doublet or triple chemotherapies in a first-line setting. Additionally, the FLOT4 trial compared triplet regimens in a perioperative setting [43].

Table 4-2. Survival Outcomes and Adverse Events for Doublet and Triple Chemotherapy Regimens in the First Line

Study [ref]	Treatment Regimen	Sample Size	Survival Outcomes	Adverse Events Outcomes
Systematic Reviews				
Huang et al, 2016 [2]	Oxaliplatin-based doublet/triplet regimen vs. cisplatin-based doublet/triplet regimen	• N=5 • n=2046 • Doublet regimens, N=2 • Triplet regimens, N=4 HER2 status NR	Overall Survival • Oxa-based vs. cis-based: HR, 0.91; 95% CI, 0.82-1.01; p=0.07 Progression-free survival • Oxa-based vs. cis-based: HR, 0.92; 95% CI, 0.84-1.01; p=0.09	Oxaliplatin-based regimen resulted in decreased risk when compared with cisplatin-based • Neutropenia: OR, 0.63; 95% CI, 0.40-0.99; p=0.04 • Anemia: OR, 0.50; 95% CI, 0.41-0.61; p<0.0001 • Nausea: OR, 0.65; 95% CI, 0.50-0.86; p=0.003 • Stomatitis: OR, 0.79; 95% CI, 0.66-0.96; p=0.02

Study [ref]	Treatment Regimen	Sample Size	Survival Outcomes	Adverse Events Outcomes
				• Thromboembolism: OR, 0.42; 95% CI, 0.28-0.64; p<0.0001 Oxaliplatin-based regimen resulted in increased risk when compared with cisplatin-based • Neurosensory toxicity: OR, 8.68; 95% CI, 5.28-14.27; p<0.0001 • Thrombocytopenia: OR, 1.29; 95% CI, 1.04-1.61; p=0.02
ter Veer et al, 2016 [1]	Compared fluoro-pyrimidine (F), platinum (cisplatin [C] and oxaliplatin [Ox]), taxane (T), anthracycline (A), irinotecan (I), and methotrexate (M) regimens	• N=65 • n=13,356 • Network meta-analysis, N=53 HER2 status NR	Overall Survival • FI vs. CF: HR, 0.85; 95% CI, 0.71-0.99 • FOx vs. CF: HR, 0.83; 95% CI, 0.71-0.98 Progression-free Survival • FOx vs. CF: HR, 0.82; 95% CI, 0.66-0.99 A-triplets and TCF triplets showed no benefit over F-doublets FOxT triplet showed increased PFS over F-doublets • FOxT vs. FT: HR, 0.61; 95% CI, 0.38-0.99 • FOxT vs. FI: HR, 0.62; 95% CI, 0.38-0.99 • FOxT vs. FOx: HR, 0.67; 95% CI, 0.44-0.99	Increased grade 3/4 toxicity for: • CF vs. F-doublets • ACF vs. FI • TCF vs. CF • FOxT vs. FOx
Xu et al, 2015 [42]	Capecitabine + oxaliplatin (XELOX) vs. 5-FU /leucovorin + oxaliplatin (FOLFOX)	• N=26 • n=1585 HER2 status NR	No outcomes reported	Significantly lower risk of following adverse events with XELOX when compared with FOLFOX • Alopecia: OR, 0.50; 95% CI, 0.31-0.83; p=0.008 Significantly higher risk of following adverse events with XELOX when compared with FOLFOX • Hand-foot syndrome: OR, 2.84; 95% CI, 2.19-3.69; p<0.001
Petrioli et al, 2016 [41]	Docetaxel-based regimens vs.	• N=7 • n=553	No outcomes reported	No significant differences in toxicities

Study [ref]	Treatment Regimen	Sample Size	Survival Outcomes	Adverse Events Outcomes
	epirubicin-based regimens • Docetaxel-based: docetaxel (D) + 5FU; docetaxel (D) + cisplatin (C) + 5FU; docetaxel (D) + oxaliplatin (Ox) + 5FU • Epirubicin-based: epirubicin (E) + cisplatin (C) + 5FU; epirubicin (E) + cisplatin (C) + capecitabine (Cb); epirubicin (E) + oxaliplatin (Ox) + capecitabine (Cb)	• E+C+5FU, N=5 • E+C+Cp, N=1 • E+Oxa+Cp, N=1 • D+5FU, N=2 • D+C+5FU, N=4 • D+Oxa+5FU, N=1 HER2 status NR		Events with non-sig decreased risk with E-based • Neutropenia • Anemia • Fatigue • Asthenia • Diarrhea • Paresthesia Events with non-sig decreased risk with D-based • Leukopenia • Thrombocytopenia • Anorexia • Nausea • Stomatitis • Hand and foot syndrome • Neutropenic fever
Randomized Controlled Trials				
Chen et al, 2018 [44] ML17032 trial	Capecitabine + cisplatin (XP) vs. 5-FU + cisplatin (FP)	• Phase III • XP, n=62 • FP, n=64 • F/U: NR HER2 status: NR	Progression-free Survival • XP: median PFS, 7.2m; 95% CI, 5.2-9.5m • FP: median PFS, 4.5m; 95% CI, 3.5-6.8m • p=0.0339 • HR, 0.52; 95% CI, 0.32-0.83; p=0.0063	No significant difference in rate of adverse events
Lu et al, 2018 [45]	Paclitaxel + capecitabine + capecitabine maintenance (PACX) vs. cisplatin + capecitabine (XP)	• Phase III • PACX, n=160 • XP, n=160 • F/U: median 31.4months HER2 status: not tested	Overall Survival • PACX: median OS, 12.5m; 95% CI, 11.5-14.5m • XP: median OS, 11.8m; 95% CI, 10.0-13.7m • HR, 0.878; 95% CI, 0.685-1.125; p=0.30 Progression-free Survival • PACX: median PFS, 5.0m; 95% CI, 4.3-6.3m • XP: median PFS, 5.3m; 95% CI, 4.7-5.8 • HR, 0.906; 95% CI, 0.706-1.164; p=0.44	No significant difference in rate of reported grade 3/4 adverse event • PACX: 34.2% • XP: 40.1% • p=0.28 Significantly lower rate of following grade 3/4 events in PACX vs. XP • Anemia: 1.9% vs. 6.8%; p=0.03 • Thrombocytopenia: 0.6% vs. 4.8%; p=0.02 • GI disorders: 5.1% vs. 12.2%; p=0.03 • Nausea: 1.9% vs. 8.2%; p=0.01 • Vomiting: 2.5% vs. 9.5%; p=0.01
Van Cutsem et al, 2015 [46]	Docetaxel + oxaliplatin (TE)	• Phase II • TE, n=64	Overall Survival	Frequency of grade 3/4 adverse events

Study [ref]	Treatment Regimen	Sample Size	Survival Outcomes	Adverse Events Outcomes
	vs. TE + infused 5-FU (TEF) vs. docetaxel + oxaliplatin + capecitabine (TEX)	• TEF, n=79 • TEX, n=63 • F/U: NR HER2 status: NR	• TEF: median OS, 14.59m; 95% CI, 11.70-21.78m • TE: median OS, 8.97m; 95% CI, 7.79-10.87m • TEX: median OS, 11.30m; 95% CI, 8.08-14.03m • p>0.05 Progression-free Survival • TEF: median PFS, 7.66m; 95% CI, 6.97-9.40m • TE: median PFS, 4.50m; 95% CI, 3.68-5.32 • TEX: median PFS, 5.55m; 95% CI, 4.30-6.37m • p>0.05	• TEF: 61% • TE: 77% • TEX: 67%
Nakajima et al, 2020 [47] JCOG1108/ WJOG7312G trial	5-FU + leucovorin + paclitaxel (FLTAX) vs. 5-FU + leucovorin (5-FU/LV)	• Phase II/III • FLTAX, n=50 • 5-FU/LV, n=51 HER2 status: NR	Progression-free Survival • FLTAX: median PFS, 5.4m; 95% CI, 2.6-6.9m • 5-FU/LV: median PFS, 1.9m; 95% CI, 1.5-3.5 • HR, 0.64; 95% CI, 0.43-0.96; p=0.029	Frequency of grade 3/4 adverse events • FLTAX: 77.1% • 5-FU/LV: 78.4%
Al-Batran et al, 2019 [43] FLOT4 trial	Epirubicin + cisplatin + fluorouracil /capectabine (ECF/ECX) vs. fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT)	• Phase 2/3 • ECF/ECX, n=326 • FLOT, n=320 • F/U: 6 years HER2 status: NR	Overall Survival • ECF/ECX: median OS, 35m; 95% CI, 27.35-46.26m • FLOT: median OS, 50m; 95% CI, 38.33 – not reached • HR, 0.77; 95% CI, 0.63-0.94; p=0.012	Significantly higher risk of following grade 3/4 events in ECF/ECX group vs. FLOT group • Diarrhea: 4% vs. 10%; p=0.0016 • Vomiting: 8% vs. 2%; p<0.001 • Nausea: 16% vs. 7%; p<0.001 • Anemia: 6% vs. 3%; p=0.036 Significantly lower risk of following grade 3/4 events in ECF/ECX group vs. FLOT group • Neutropenia: 39% vs. 51%; p=0.0017 • Peripheral neuropathy: 2% vs. 7%; p=0.0018 • Infections: 9% vs. 18%; p<0.001
Ni et al, 2021 [85]	• First line	• Phase 2 • XELOX, n=39	Overall Survival	No significant difference in rates of adverse events

Study [ref]	Treatment Regimen	Sample Size	Survival Outcomes	Adverse Events Outcomes
	Capecitabine + oxaliplatin (XELOX) vs. capecitabine + docetaxel (DX)	• DX, n=44 • Median F/U: 10.2m • HER2 status NR	• XELOX: median OS, 8.8m • DX: median OS, 9.0m • HR, 0.99; 95% CI, 0.60-1.65; p=0.973 Progression Free Survival • XELOX: median PFS, 6.1m • DX: median PFS, 4.1m • HR, 0.78; 95% CI, 0.46-1.31; p=0.346	Grade 3/4 adverse events in XELOX vs. DX Anemia: 7.7% vs. 9.1% Leukopenia: 0% vs. 2.3% Neutropenia: 0% vs. 4.5% Thrombocytopenia: 5.1% vs. 0% Peripheral neuropathy: 10.3% vs. 0% Liver function damage: 2.6% vs. 2.3%

Abbreviations: 5FU, 5-fluorouracil; CI, confidence interval; F/U, follow-up; HER2, human epidermal growth receptor 2; HR, hazard ratio; m, months; NR, not reported; OR, odds ratio.

Survival Outcomes

In a first-line setting, a systematic review that included five studies comparing oxaliplatin-based regimens with cisplatin-based regimens, reported no significant difference in overall survival (p=0.07) or progression-free survival (p=0.09) [2]. A second systematic review, which included a network meta-analysis using 53 studies, compared doublet and triplet regimens involving fluoropyrimidine, platinum chemotherapy, taxanes, anthracycline, irinotecan, and methotrexate [1]. Overall, fluoropyrimidine doublets showed increased efficacy over cisplatin doublets when assessing both overall survival and progression-free survival. Of note, the meta-analysis defined fluoropyrimidine-cisplatin as a cisplatin doublet and not as a fluoropyrimidine doublet (see Table 4-2 for further details on doublet regimen composition). Fluoropyrimidine-oxaliplatin demonstrated significantly improved overall survival when compared with fluoropyrimidine-cisplatin (HR, 0.83; 95% CI, 0.71 to 0.98), as did fluoropyrimidine-irinotecan (HR, 0.85; 95% CI, 0.71 to 0.99) [1]. Additionally, fluoropyrimidine-oxaliplatin-taxane triple regimen resulted in significantly increased overall survival when compared with fluoropyrimidine-cisplatin (HR, 0.64; 95% CI, 0.42 to 0.97) and cisplatin-taxane (HR, 0.64; 95% CI, 0.42 to 0.99) [1]. Two RCTs compared cisplatin-capecitabine (XP) with another doublet regimen. The first compared XP with cisplatin-5-fluorouracil (5FU) and reported significantly improved progression-free survival with XP (HR, 0.52; 95% CI, 0.32 to 0.83; p=0.0063) [44]. The second compared XP with paclitaxel-capecitabine plus capecitabine maintenance and reported no significant difference for overall survival (p=0.30) or progression-free survival (p=0.44) [45]. A recent RCT compared capecitabine plus oxaliplatin with capecitabine plus docetaxel and found no significant difference in overall survival rates during the median follow-up of 10 months [85]. An additional RCT reported on survival outcomes in a first-line setting comparing three regimens all containing docetaxel plus oxaliplatin [46]. The regimens were docetaxel-oxaliplatin (TE), docetaxel-oxaliplatin-5FU (TEF), and docetaxel-oxaliplatin-capecitabine (TEX). Although the study reported that TEF demonstrated improved overall survival and progression-free survival, the difference between the three treatments was not significant. The RCT that compared 5-FU plus leucovorin with 5-FU plus leucovorin and paclitaxel reported significantly improved progression-free survival in patients receiving the triplet regimen [47]. Finally, the FLOT4 trial compared FLOT4 (fluorouracil-leucovorin-oxaliplatin-docetaxel) with epirubicin-cisplatin-fluorouracil/capecitabine (ECF/ECX) in a first-line perioperative setting [43]. The study reported significantly improved overall survival with FLOT4 (HR, 0.77; 95% CI, 0.63 to 0.94; p=0.012; median overall survival: FLOT, 50 months; 95%CI, 38.33 months to not reached vs. ECF/ECX, 35 months; 95%CI, 27.35-46.26 months).

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

When compared with cisplatin-based regimens, oxaliplatin-based regimens demonstrated a decreased risk for neutropenia, anemia, nausea, stomatitis, and thromboembolism, and an increased risk for neurosensory toxicity, and thrombocytopenia [2]. Another systematic review, which compared capecitabine-oxaliplatin (XELOX) with 5FU/leucovorin-oxaliplatin (FOLFOX) reported a significantly lower risk of alopecia and a significantly higher risk of hand-foot syndrome with XELOX [42]. The network meta-analysis reported that fluoropyrimidine-oxaliplatin-taxane (FOXT) was associated with increased neutropenia, leukopenia, and nausea when compared with FOX [1]. In the FLOT4 trial [43], there was a significantly higher risk for diarrhea, vomiting, nausea, and anemia in patients treated with ECF/ECX when compared with FLOT4, but also a significantly reduced risk for neutropenia, peripheral neuropathy, and infections. The final study that evaluated an oxaliplatin-based regimen reported a 77% frequency of grade 3/4 adverse events for TE, 61% for TEF, and 67% for TEX [46].

The aforementioned network meta-analysis also reported that toxicity was generally more frequent with taxane-cisplatin-fluoropyrimidine (TCF) triplets when compared with anthracycline-CF, CF, and CT [1]. Although the RCT that compared XP with paclitaxel-capecitabine plus capecitabine maintenance reported no overall significant difference in the rate of reported grade 3/4 adverse events, paclitaxel-capecitabine demonstrated lower rate of anemia, thrombocytopenia, GI disorders, nausea, and vomiting [45].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Fluoropyrimidine Monotherapy

Survival Outcomes

An identified systematic review included 12 studies and compared 5FU with S-1 and capecitabine in a first-line setting [48]. When compared with 5FU, improved overall survival was reported with both capecitabine (HR, 0.85; 95% CI, 0.78 to 0.94; p=0.002) and S-1 (HR, 0.89; 95% CI, 0.80 to 0.98; p=0.02); however, there was no difference when overall survival using capecitabine was compared with S-1 therapy. The systematic review also reported no significant difference in overall response rate across the three therapies [48].

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Adverse Events

The systematic review [48] reported no significant difference in rates of grade 3 and 4 adverse events when comparing 5FU with capecitabine or S-1.

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Second- and Third-line Chemotherapy

Doublet and Triplet Chemotherapy Regimens

Survival Outcomes

In a second-line setting, a systematic review compared irinotecan doublet with irinotecan monotherapy [49]. Based on pooling from seven studies containing 905 patients, the systematic review demonstrated improved progression-free survival with irinotecan doublet therapy (HR, 0.82; 95% CI, 0.70 to 0.95) but no difference in overall survival.

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Adverse Events

The systematic review reported significantly increased grade 3 or higher neutropenia and anemia with doublet therapy when compared with monotherapy [49].

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Taxane Monotherapy

Survival Outcomes

Two systematic reviews [16,17] and two RCTs [50,51] reported on overall survival in patients treated with taxane monotherapy. In a second-line setting, based on inclusion of three studies, docetaxel plus best supportive care resulted in significantly improved overall survival when compared with best supportive care alone (HR, 0.71; 95% CI, 0.56 to 0.89; p=0.003) [16]. The second systematic review included 28 studies and compared chemotherapy monotherapy with best supportive care, other chemotherapy monotherapies, and chemotherapy plus targeted agents in a second- or third-line setting [17]. Monotherapy taxane showed increased survival when compared with best supportive care (HR, 0.71; 95% CI, 0.56 to 0.90) but there was no significant difference in overall survival when a taxane was compared with irinotecan (HR, 0.94; 95% CI, 0.78 to 1.13) or a doublet chemotherapy regimen (HR, 1.00; 95% CI, 0.90 to 1.12). Additionally, when compared with taxane plus ramucirumab (a vascular endothelial growth factor receptor [VEGFR] targeted therapy), monotherapy taxane was associated with reduced overall survival (HR, 0.81; 95% CI, 0.68 to 0.96; monotherapy set as the reference [HR, 1] in this comparison). The DREAM trial compared oral paclitaxel with intravenous paclitaxel in the second line and reported no difference in overall survival or progression-free survival between the groups [51]. Similarly, an RCT compared paclitaxel with paclitaxel plus valproic acid and reported no significant difference in overall survival or progression-free survival [50].

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

Adverse Events

One of the systematic reviews [17] and both RCTs [50,51] also reported on the rate of adverse events following treatment using taxane monotherapy. The meta-analysis indicated increased risk of grade 3-4 neutropenia, diarrhea and anorexia with irinotecan-based chemotherapy when compared with taxane monotherapy treatment [17]. No additional significant adverse events were reported when compared taxane monotherapy with any of the other included regimens. Neither of the RCTs reported difference between paclitaxel groups for adverse events; however, the DREAM trial reported grade 3-4 adverse events in 68.8% of patients on oral paclitaxel and in 83.9% of patients on intravenous [51]. The other RCT reported

on rate of at least grade 2 adverse events and reported a much lower rate of 9.5% across both patients receiving paclitaxel and patients receiving paclitaxel plus valproic acid [50].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Fluoropyrimidine Monotherapy

Survival Outcomes

An identified RCT compared 5FU with paclitaxel in a second-line setting [52]. This phase II trial reported no difference in median survival time (HR, 0.89; 95% CI, 0.57 to 1.38; median overall survival duration: 5FU, 7.7 months vs. paclitaxel, 7.7 months) or progression-free survival (HR, 0.58; 95% CI, 0.38 to 0.88; median progression-free survival duration: 5FU, 2.4 months vs. paclitaxel, 3.7 months) when the two patient groups were compared.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

The RCT reported a 6.1% rate of serious adverse events in patients treated with 5FU, and a 2.0% rate in patients treated with paclitaxel [52]. The study did not define a grade for serious adverse events and did not conduct a statistical analysis to compare rates.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Irinotecan Monotherapy

The same two systematic reviews described in the taxane monotherapy section also evaluated irinotecan monotherapy [16,17].

Survival Outcomes

The first study compared irinotecan plus best supportive care with best supportive care alone in a second-line setting and reported a significant improvement in overall survival for irinotecan (HR, 0.49; 95% CI, 0.36 to 0.67; $p<0.0001$) [16]. The second systematic review compared second- and third-line regimens of chemotherapy monotherapy, chemotherapy doublets and chemotherapy plus targeted agents [17]. When compared with best supportive care, overall survival was improved with irinotecan therapy (HR, 0.55; 95% CI, 0.40 to 0.77); however, there was no survival difference when irinotecan was compared with a taxane.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

Only the second systematic review reported on grade 3 and 4 adverse events [17]. The meta-analysis indicated increased risk of grade 3-4 neutropenia, diarrhea and anorexia with irinotecan-based chemotherapy when compared with taxane monotherapy treatment [17].

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Trifluridine plus Tipiracil

Survival Outcomes

The TAGS trial was a phase III study that randomized patients to either trifluride-tipiracil or placebo in a two to one ratio (trifluride-tipiracil , n=337; placebo, n=170) [18]. Among these patients, 67 (20%) in the trifluride-tipiracil group and 27 (16%) in the control arm, were positive for HER2. The study reported improved overall survival (HR, 0.69; 95% CI, 0.56 to 0.85; p=0.0058; median duration: trifluride-tipiracil, 5.7 months vs. placebo, 3.6 months) and improved progression-free survival (HR, 0.57; 95% CI, 0.47 to 0.70; p<0.0001; median progression-free survival duration: trifluride-tipiracil, 2.0 months vs. placebo, 1.8 months) in patients treated with trifluride-tipiracil. The study also reported a significant association between HER2 positivity and improved overall survival (p=0.016). A more recent pos-hoc analysis of the TAGS trial reported on outcomes specific for subgroup patient population with gastric carcinoma (n=360) and those with GEJ carcinoma (n=145) [53]. Among patients with gastric carcinoma, both overall survival (HR, 0.67; 95% CI, 0.52 to 0.87; p<0.05; median overall survival duration: trifluride-tipiracil, 6.0 months vs. placebo, 3.6 months) and progressive free survival (HR, 0.59; 95%CI, 0.46 to 0.75; p<0.05; median progression-free survival duration: trifluride-tipiracil, 2.1 months vs. placebo, 1.8 months) were significantly improved with trifluride-tipiracil therapy. In comparison, patients with GEJ experienced significantly improved progression free survival with trifluride-tipiracil therapy (HR, 0.60; 95% CI, 0.41 to 0.88; p<0.05; median progression-free survival duration: trifluride-tipiracil, 1.9 months vs. placebo, 1.8 months), but overall survival rates were different for trifluride-tipiracil and placebo (HR, 0.75; 95% CI, 0.50 to 1.11; median overall survival duration: trifluride-tipiracil, 4.8 months vs. placebo, 3.5 months).

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

Although the TAGS trial did not conduct statistical analysis on the frequency of grade 3/4 adverse events, the study did report a 80% frequency in the trifluride-tipiracil arm and a 58% frequency in the placebo arm [18]. In the post-hoc analysis, the frequency of at least grade 3 adverse events following trifluride-tipiracil therapy was 81% for patients with gastric carcinoma and 77% for patients with GEJ carcinoma [53]. The frequency in patients with gastric carcinoma receiving placebo was 58% and 59% for patients with GEJ carcinoma.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Targeted Agents

All Targeted Therapies

Adverse Events

Three systematic review that combined targeted therapies reported on adverse events. In two reviews, targeted agents were associated with increased risk of diarrhea [6,65], rash [6], fatigue [65], and neutropenia [65]. The third systematic review focused on the risk of adverse events with targeted therapies and reported a 72.5% (95% CI, 66.4 to 77.8%) rate of severe adverse events with targeted therapies [66]. When compared with control therapies, targeted

therapies carried a significantly higher risk of severe adverse events (p=0.02), but not a higher risk for fatal adverse events (p=0.88). None of the identified systematic reviews provided subgroup analysis for any specific targeted agent.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

HER2 Targeted Agents in the First Line

Survival Outcomes

The systematic search identified a systematic review that compared anti-angiogenic agents, HER2 targeted agents, anti-epidermal growth factor receptor (EGFR) agents, MET inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, and hedgehog inhibitors with conventional treatment in first, second-, and third-line settings [6]. When evaluating HER2 targeted therapies in a first- and second-line setting, overall survival was significantly improved with targeted therapy (HR, 0.82; 95% CI, 0.72 to 0.94; p=0.004) [6]. However, subgroup analyses for first- and second-line therapies did not show a significant benefit for HER2 targeted therapies. This pooling included the ToGA trial, which administered trastuzumab, and the LOGiC and TYTAN trials that evaluated the efficacy of lapatinib [6].

The JACOB trial, which was published after the study inclusion dates of the aforementioned meta-analysis, compared trastuzumab plus pertuzumab and chemotherapy with trastuzumab plus placebo plus chemotherapy in a first-line setting [54]. Although both arms contain trastuzumab, the study was designed to evaluate pertuzumab, which is not approved by Health Canada. This phase III trial reported improved progression-free survival in patients treated with the pertuzumab containing regimen (HR, 0.73; 95% CI, 0.62 to 0.95; p=0.0001; median progression-free survival duration: pertuzumab-based, 8.5 months vs. placebo, 7.0 months); however, there was no reported difference for overall survival (p=0.057). A planned post-hoc analysis of Japanese patients within the JACOB trial reported a similar trend of improved progression-free survival in this patient subgroup [55].

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

Adverse Events

Although the JACOB trial did not perform statistical comparison of the frequencies of adverse events, the study reported a 45% frequency of serious adverse events in the pertuzumab-containing arm and 39% in the placebo arm [54]. The frequency of all grade 3 through 5 adverse events was 80% in the pertuzumab-containing arm and 73% in the placebo arm. In the Japanese patient subgroup analysis, the frequency of at least grade 3 adverse events was 95.0% in the pertuzumab-containing arm and 75.0% in the placebo arm [55].

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

HER2 Targeted Agents in the Second Line and Beyond

Survival Outcomes

As previously mentioned, when evaluating HER2 targeted therapies in a first- and second-line setting, an identified meta-analysis demonstrated significantly improved overall survival following targeted therapy (HR, 0.82; 95% CI, 0.72 to 0.94; p=0.004) [6]. However, subgroup analyses for first- and second-line therapies did not show a significant benefit for

HER2 targeted therapies. The HER2 targeted therapy pooling included the ToGA trial, which administered trastuzumab, and the LOGiC and TYTAN trials that evaluated the efficacy of lapatinib [6].

In a second-line setting, the GATSBY trial compared trastuzumab with taxane in HER2 overexpressing advanced gastric cancer patients [58]. In the first stage of this small phase II/III study, 70 patients received trastuzumab emtansine every three weeks, 75 received trastuzumab weekly, and 37 received taxane. After a month, the committee chose weekly trastuzumab as the dose for stage 2 of the study and 153 patients were additionally randomized to trastuzumab and 80 to taxane chemotherapy. The study reported no significant difference in overall survival between the trastuzumab group and the taxane chemotherapy group. The recently published T-ACT study randomized patients with cancer refractory to first-line chemotherapy to either paclitaxel or paclitaxel plus trastuzumab [59]. Enrolled patients had positive HER2 status and had progressed following first-line therapy with trastuzumab plus fluoropyrimidine and platinum chemotherapy. The study reported no significant difference in overall survival or progression-free survival when the study arms were compared [59].

In a third-line setting, the DESTINY-Gastric01 Study compared trastuzumab deruxtecan with chemotherapy in previously treated HER2 overexpressing patients [60]. Patients had cancer that was refractory to two previous regimens of fluoropyrimidine, a platinum agent, and trastuzumab or an approved biosimilar agent. In the phase II trial, patients randomized to the chemotherapy arm received either irinotecan or paclitaxel at the physician's discretion. Both overall survival and progression-free survival were significantly improved in patients receiving trastuzumab deruxtecan [60].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

In the GATSBY trial, the frequency of grade 3/4 adverse events was reported as 60% in the trastuzumab group and 70% in the taxane group [58]. In the T-ACT study, although there was a trend toward higher incidence rates of at least grade 3 leukopenia, neutropenia, and anemia in the patients receiving paclitaxel plus trastuzumab [59], no statistical analysis was conducted. Finally, in the DESTINY study [60], grade 3 neutrophil count decrease, decreased appetite, anemia, platelet count decrease, and white cell count decrease appeared to be experienced at a higher rate in patients in the trastuzumab deruxtecan arm, but again, statistical analysis was not conducted.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

HER2 Targeted Agents in All Lines

Survival Outcomes

An identified network meta-analysis of 24 HER2 targeted trials did not specific therapy line [65]. When compared with placebo, trastuzumab demonstrated improved both one-year and two-year overall survival, while only trastuzumab demonstrated improved three-year overall survival.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

VEGFR2 Targeted Agents in the First Line

Survival Outcomes

An identified meta-analysis pooled nine studies evaluating anti-angiogenesis agents and demonstrated improved overall survival across all lines of therapy (HR, 0.76; 95% CI, 0.66 to 0.89; p<0.001) [6]. A subgroup analysis of first-line trials including AVAGAST, which administered bevacizumab, and two unnamed trials that administered ramucirumab and TSU-68, demonstrated no overall survival benefit for VEGF and VEGFR inhibitors [6].

Two RCTs have been published after the included search dates within the Ciliberto 2015 systematic review [6]. A phase II RCT compared FOLFOX6 plus ramucirumab with FOLFOX6 plus placebo [56]. This study reported no difference in overall survival, progression-free survival, or objective response rate when the two groups were compared. A first-line randomized trial that did not report phase of the trial, compared patients with advanced gastric cancer treated with apatinib and patients treated with apatinib plus tegafur [57]. The study reported improved progression-free survival in patients treated with both apatinib and tegafur (median 8.1 months vs. 5.0 months, p<0.05).

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

The trial that compared apatinib therapy alone with apatinib plus tegafur, reported significantly higher incidence rates of nausea (p<0.001), vomiting (p<0.001), hemoglobin decrease (p=0.002), hypertension (p<0.001), leukopenia (p=0.013), and proteinuria (p<0.001) in patients treated with the doublet therapy [57]. The phase II RCT reported no difference in frequency of grade 3 or higher adverse events when comparing patients on FOLFOX6-ramucirumab and FOLFOX6-placebo [56].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

VEGFR2 Targeted Agents in the Second Line and Beyond

Survival Outcomes

The aforementioned meta-analysis that pooled nine studies evaluating anti-angiogenesis agents and demonstrated improved overall survival across all lines of therapy (HR, 0.76; 95% CI, 0.66 to 0.89; p<0.001) also included subgroup analyses for second-line and beyond second-line studies [6]. Two studies in the second-line were pooled and demonstrated improved overall survival for therapy with VEGF inhibitors (HR, 0.81; 95% CI, 0.69 to 0.95; p=0.011) [6]. The two trials included the RAINBOW trial of ramucirumab and an unnamed trial that administered sunitinib. Another subgroup analysis that pooled four studies in the third-line and beyond, which evaluated apatinib, sunitinib, and ramucirumab (REGARD trial), demonstrated improved overall survival (HR, 0.63; 95% CI, 0.47 to 0.85; p=0.002) [6].

Although abstracts for both RAINBOW and the second-line sunitinib trial were included in the Ciliberto meta-analysis [6], full publication have since been released. The RAINBOW phase III trial randomized second-line patients to either ramucirumab plus paclitaxel or placebo plus paclitaxel [14]. The study reported improved overall survival (HR, 0.807; 95% CI, 0.678 to 0.962; p=0.017; median overall survival duration: ramucirumab, 9.6 months vs. placebo, 7.4 months), progression-free survival (HR, 0.635; 95% CI, 0.536 to 0.752; p<0.001; median progression-free survival duration: ramucirumab, 4.4 months vs. placebo, 2.9 months), objective response rate (28% vs. 16%; p<0.0001), and disease control rate (80% vs. 64%; p<0.0001) in patients receiving ramucirumab [14]. The study that compared FOLFIRI plus

sunitinib with FOLFIRI plus placebo did not report any significant difference in overall survival, progression-free survival, objective response rate, or disease control rate [61]. Sunitinib is also not yet approved by Health Canada for therapy in patients with gastric or GEJ carcinoma.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

Although the RAINBOW trial did not conduct statistical analysis when comparing adverse events, the rate of grade 3 and grade 4 adverse events appear to be higher in the ramucirumab plus paclitaxel arm (47% vs. 39% and 27% vs. 8%) [14]. An additional publication of the RAINBOW trial reported on quality of life based on the EORTC QLQ-C30 scale [15]. In the paclitaxel-ramucirumab group of patients, the study reported a longer time to worsening of emotional functioning and nausea and vomiting domains, but also a shorter time to worsening of diarrhea. A more recent RAINBOW publication reported on the quality of life in only the Japanese patient cohort [62]. Using the EORTC QLQ-C30 again, the analysis found no significant difference in the time to deterioration on quality of life scales when comparing treatment arms. The FOLFIRI plus sunitinib trial did not report on statistical significance, but reported a 56% rate of neutropenia, a 27% rate of leukopenia, and 2% rate of diarrhea in patients treated with FOLFIRI-sunitinib [61].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

VEGFR2 Targeted Agents in Any Line

Survival Outcomes

In the INTEGRATE phase II trial regorafenib plus best supportive care was compared with placebo plus best support care [68]. Although the study reported no difference in overall survival (HR, 0.74; 95% CI, 0.51 to 1.08; p=0.147), regorafenib plus best supportive care demonstrated a significant improvement in progression-free survival (HR, 0.40; 95% CI, 0.28 to 0.59; p<0.001; median progression-free survival duration: regorafenib, 2.6 months vs. placebo, 0.9 months).

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

Adverse Events

The INTEGRATE trial did not perform statistical analysis to compare adverse events between the groups. However, the frequency of grade 3 through 5 adverse events in patients receiving regorafenib-best supportive care was 67% and 52% in those receiving placebo-best supportive care [68].

An identified systematic review that evaluated therapy with apatinib compared with placebo in a first- and second-line setting reported significantly higher rates of leukopenia, neutropenia, thrombocytopenia, diarrhea, hypertension, proteinuria, hand-foot syndrome, and fatigue in apatinib-treated patients when compared with those on a placebo [67].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

MET Inhibitors in the First Line

Both the RILOMET-1 phase III trial that evaluated rilotumumab [3] and the METGastric phase III trial that evaluated onartuzumab [5] were stopped early. The RILOMET-1 trial was stopped based a higher number of deaths in the rilotumumab arm, while the METGastric trial was stopped based on a lack of efficacy in a simultaneous ongoing phase II trial. Results for both can be found in Appendix 8 but for the sake of brevity, a narrative synthesis has not been included. Neither of these agents have been approved by Health Canada.

MET Inhibitors in a Mixed First-line through Third-line Setting

Survival Outcomes

The aforementioned Ciliberto et al. systematic review included MET inhibitors in the overall meta-analysis that demonstrated improved overall survival with targeted therapy when compared with conventional therapy alone (HR, 0.82; 95% CI, 0.74 to 0.91; p<0.001) [6]. Although included in the large meta-analyses, the Ciliberto systematic review only identified one trial evaluating a MET inhibitor, so no subgroup analysis for MET inhibitors was conducted. The single identified trial evaluated rilotumumab and reported no significant overall survival benefit (HR, 0.73; 95% CI, 0.53 to 1.01) [6].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

mTOR and Akt Targeted Agents in the Second Line and Beyond

Survival Outcomes

Peer-reviewed full-text results from the phase III RADPAC trial have been recently published [63]. The study compared paclitaxel monotherapy with paclitaxel plus everolimus (RAD001), a P13K-Akt-mTOR pathway inhibitor, in a second- or third-line setting. Overall survival, progression-free survival, treatment response rates, and disease control rates were not different between groups.

A phase II trial that compared ipatasertib plus FOLFOX6 with FOLFOX6 plus placebo reported no significant difference in overall survival, progression-free survival, or overall response rate between the groups [4]. Ipatasertib is a small-molecule inhibitor of Akt.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

In the RADPAC trial incidence rates for at least grade 3 adverse events were 69.4% in the paclitaxel monotherapy arm and 78.3% in the paclitaxel plus everolimus arm [63].

The FOLFOX plus ipatasertib study reported a 67% rate of grade 3-5 adverse events in the ipatasertib arm and 61% in the placebo arm [4]. Additionally, the study reported adverse events resulting in death in 7% of patients treated with FOLFOX6-ipatasertib and only 2% in the FOLFOX6-placebo arm. Statistical significance was not reported for either comparison.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

PARP Inhibitors in the Second Line and Beyond

Survival Outcomes

The phase III GOLD trial compared paclitaxel plus olaparib with paclitaxel plus placebo in a second-line setting [64]. The study reported no significant difference in overall survival

for patients in the paclitaxel plus olaparib arm (HR, 0.79; 97.5% CI, 0.63 to 1.00; p=0.026; median overall survival duration: olaparib, 8.8 months vs. placebo, 6.9 months).

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Adverse Events

Although the GOLD trial did not conduct statistical analysis comparing the frequency of adverse events, the study reported a 35% frequency of serious adverse events experienced by patients treated with olaparib-paclitaxel and 25% by those in the paclitaxel-placebo arm [64].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Immune Checkpoint Inhibitors

PD-L1 Targeted Therapies in the First-line

Survival Outcomes

KEYNOTE-062 randomized untreated PD-L1 positive patients to pembrolizumab, pembrolizumab plus chemotherapy, or to chemotherapy [9]. In this study outcomes were reported by patients' tumour's CPS, where CPS is assessed as the total number of PD-L1 stained cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100. Based on a median follow-up of 29.4m, in the subset of patients with a CPS ≥1% (primary endpoint), the study reported no significant difference in overall survival for patients receiving pembrolizumab monotherapy (median overall survival, 10.6 months), or pembrolizumab plus chemotherapy (median overall survival, 12.5 months), when compared with chemotherapy (median overall survival, 11.1 months). Patients with a CPS ≥10% were also selected as a primary endpoint with a reported overall survival HR of 0.69 (95%CI, 0.49 to 0.97) indicating benefit with pembrolizumab over chemotherapy; however, based on the statistical plan of the study, the difference was not tested as it did not meet the criteria for superiority. The JAVELIN Gastric 100 trial randomized patients who had not progressed after 12 weeks of first-line chemotherapy to avelumab maintenance or continued chemotherapy [8]. The primary endpoint was overall survival in patients both unselected patients and in patients with a tumour positive score (TPS) of ≥1%. When considering all patients, the study reported no significant difference in median overall survival (HR, 0.91; 95% CI, 0.74 to 1.11; p=0.1779). Enrolled patients were a mix of those with TPS ≥1%, TPS <1%, and those with tumours where PD-L1 status was either not evaluated or unavailable. Among patients with TPS ≥1%, the overall survival was not significantly different for avelumab therapy (median overall survival, 16.2 months) when compared with chemotherapy (median overall survival, 17.7 months; p=0.6352). An exploratory subgroup analysis of patients with the more common CPS≥1% threshold also found no significant difference in overall survival (HR, 0.72; 95%CI, 0.49 to 1.05). The CheckMate 649 trial randomized unselected patients to either nivolumab plus chemotherapy, nivolumab plus ipilimumab, or to chemotherapy alone [7]. During patient enrollment, the primary endpoint population was amended to include only patients with tumours expressing PD-L1 at a CPS of 5% or greater. Published results reported only the nivolumab plus chemotherapy (n=789) and chemotherapy arms (n=792). The median follow-up for overall survival in this study was 13.1 months in the combination therapy arm and 11.1 months in the chemotherapy arm. In the primary endpoint population of CPS ≥5%, overall survival was significantly improved (HR, 0.71; 95%CI, 0.59 to 0.86; p<0.0001) in patients who received nivolumab plus chemotherapy (median overall survival, 14.4 months) when compared with those who received chemotherapy alone (median overall survival, 11.1 months). However, in the subgroup of patients with 0-5% CPS

score (n=606), nivolumab plus chemotherapy did not demonstrate a benefit over chemotherapy alone (HR, 0.94; 95%CI, 0.78 to 1.13; p not reported). Additionally, in all randomly assigned patients, the median overall survival was 13.8 months for patients treated with nivolumab plus chemotherapy and 11.6 months for patients treated with chemotherapy alone (HR, 0.80; 95%CI, 0.68-0.94; p=0.0002).

A meta-analysis that pooled findings from PD-L1 positive patient subgroups in these three RCTs demonstrated a significant overall survival benefit for PD-L1 positive patients receiving ICIs (HR, 0.77; 95%CI, 0.67 to 0.89; p=0.0006; Figure 4-1). Pooling of both RCTs in the first-line and later lines of therapy maintained this overall benefit (HR, 0.79; 95%CI, 0.68 to 0.93); however, as shown in Figure 4-1, the benefit was only statistically significant for the first line trials. Table 4-3 summarizes the immune checkpoint inhibitor agent, PD-L1 testing method, PD-L1 expression cut-off, chemotherapy comparator, primary endpoints, overall survival results for all relevant patient groups, and text denoting which subgroup was used in the pooled analysis. In all included studies reporting on first-line therapy, there appears to be a positive association between study-defined PD-L1 CPS positivity and the overall survival benefit.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Figure 4-1. Overall Survival in Patients Treated with Immune Checkpoint Inhibitors or Standard of Care

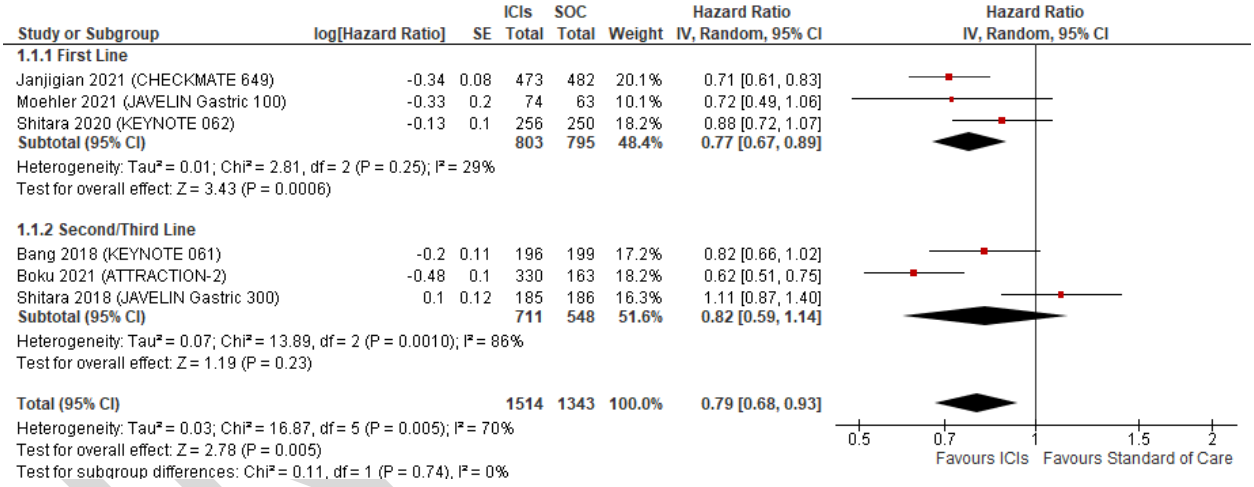

Table 4-3. Immune Checkpoint Inhibitor Overall Survival Benefit in RCTs

Study	ICI Agent	Standard of Care Comparison	PD-L1 IHC Clone	Primary Endpoint	PD-L1 Status	Overall Survival
First-line Therapy						
CheckMate 649 [7]	Nivolumab plus chemotherapy All patients, n=789 CPS ≥5%, n=473	XELOX or FOLFOX chemotherapy All patients, n=792	28-8	OS and PFS CPS ≥5%	Unselected	HR, 0.80; 99.3% CI, 0.68-0.94; p=0.0002
					CPS <1%	HR, 0.92; 95% CI, 0.70-1.23[A]
					CPS ≥1%	HR, 0.77; 99.3% CI, 0.64-0.92; p<0.0001
					CPS <5%	HR, 0.94; 95% CI, 0.78-1.13

		CPS ≥5%, n=482			CPS ≥5%	HR, 0.71; 98.4% CI, 0.59-0.86; p<0.0001 (included in Figure 4-1)
JAVELIN Gastric 100 [8]	Avelumab All patients, n=249 CPS ≥1%, n=74	Oxaliplatin + leucovorin + FU or oxaliplatin + capecitabine All patients, n=250 CPS ≥ 1%, n=63	22C3	OS Unselected and TPS ≥1%	Unselected	HR, 0.91; 95% CI, 0.74-1.11
					CPS ≥1%	HR, 0.72; 95% CI, 0.49-1.05 (included in Figure 4-1)
					TPS ≥1%	HR, 1.13; 95% CI, 0.57-2.23
KEYNOTE 062 [9]	Pembrolizumab CPS ≥1%, n=256 CPS ≥10%, n=92 (RCT also included a pembrolizumab plus chemotherapy arm)	Fluorouracil + capecitabine or cisplatin CPS ≥1%, n=250 CPS ≥10%, n=90	NR	OS and PFS CPS ≥1%/10%	CPS ≥1%	HR, 0.91; 99.2% CI, 0.69-1.18 (included in Fig 4-1)
					CPS ≥10%	HR, 0.69; 95% CI, 0.49-0.97
Second-Line Therapy						
KEYNOTE 061 [19]	Pembrolizumab, n=196	Paclitaxel, n=199	22C3	OS and PFS CPS ≥1%	CPS ≥1%	HR, 0.82; 95% CI, 0.66-1.03
Third-Line Therapy						
ATTRACTION-2 [20]	Nivolumab, n=330	Placebo, n=163	NA	OS	Unselected	HR, 0.62; 95% CI, 0.50-0.75; p<0.0001
JAVELIN Gastric 300 [21]	Avelumab, n=185	Paclitaxel or irinotecan or best supportive care, n=186	NA	OS	Unselected	HR, 1.1; 95% CI, 0.9-1.4

Abbreviations: CI, confidence interval; CPS, combined positive score; FU, fluorouracil; HR, hazard ratio; IHC, immunohistochemistry; NA, not applicable; NR, not reported; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; RCT, randomized controlled trial; TPS, tumour cell positive score.

Footnotes:

A. Reported unstratified hazard ratio.

Adverse Events

Although the KEYNOTE-062 publication did not include a statistical analysis for adverse event prevalence, only 16.9% of patients who received pembrolizumab monotherapy experienced grade 3 or higher adverse events, while 69.3% of patients receiving chemotherapy and 73.2% of combination therapy patients experienced high grade adverse events [9]. In the JAVELIN Gastric 100 trial [8], 12.8% of patients in the avelumab arm experienced grade 3 or higher treatment-related adverse events, while 32.8% of patients experienced the events in the continued chemotherapy arm. And finally, in CHECKMATE-649 [7], 59% of patients in the nivolumab plus chemotherapy group experienced grade 3 or 4 treatment-related adverse events, while 44% of patients in the chemotherapy arm experienced the events. Treatment-related deaths were reported in 16 patients (2.0%) in the nivolumab plus chemotherapy arm and four patients (0.5%) in the chemotherapy arm.

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

PD-L1 Targeted Therapies in the Second-line and Beyond

Survival Outcomes

One RCT in a second-line setting [19] and two in a third-line setting [20-22,71] were identified. In the second-line setting, KEYNOTE 061 randomized 196 patients to pembrolizumab and 199 to paclitaxel [19]. All enrolled patients had tumours that expressed PD-L1 of at least 1% CPS and the overall survival between treatment arms was not significantly different (HR, 0.82; 95%CI, 0.66 to 1.03). In the third-line setting, ATTRACTION-2 [20] randomized unselected patients to nivolumab or placebo, and JAVEIN Gastric 300 [21] randomized unselected patients to either avelumab or a control arm. Three publications [20,22,71] reporting on follow-up for the ATTRACTION-2 study were identified. The most recent publication using the entire study cohort reported on just over three years of follow-up (38.5 months) and demonstrated a survival benefit with nivolumab (overall survival HR, 0.62; 95% CI, 0.50 to 0.75; p<0.0001; progression-free survival HR, 0.60; 95% CI, 0.49 to 0.75; p<0.0001) [20]. An additional study was a pre-planned subgroup analysis of patients who received trastuzumab as one of their previous two lines of therapy [71]. In patients who received prior trastuzumab, treatment with nivolumab lead to improved overall survival (HR, 0.38; 95% CI, 0.22 to 0.66; p=0.0006) and progression-free survival (HR, 0.71; 95% CI, 0.57 to 0.88; p=0.0022) when compared with placebo. The JAVELIN Gastric 300 RCT [21] allowed for either chemotherapy or best supportive care in the control arm and reported no significant difference in overall survival when compared with patients who received avelumab (HR, 1.1; 95%CI, 0.9 to 1.4).

A meta-analysis that pooled findings from these three RCTs demonstrated no significant difference for overall survival benefit for patients receiving ICIs in a second or third-line setting (HR, 0.82; 95%CI, 0.59-1.14; Figure 4-1). Table 4-3 summarizes the ICI agent, PD-L1 testing method, PD-L1 expression cut-off, chemotherapy comparator, and overall survival for the included studies.

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

Adverse Events

An identified systematic review compared multiple anti-PD-1, anti-PD-L1, and anti-CTLA-4 agents with placebo, paclitaxel, irinotecan and best supportive care for advanced gastric or gastroesophageal junction cancer patients in a second- and third-line setting [23]. The systematic review included KEYNOTE 012, 059, and 061, as well as CHECKMATE 032, ATTRACTION-2, and JAVELIN Gastric 300 trials. Patient populations across the nine included studies were unselected for PD-L1 expression. Additionally, the systematic review was limited in that both RCT data and cohort study data were combined. The systematic review reported a significantly increased risk for all grades of adverse events using immunotherapies when compared with chemotherapy [23]. In a report on two-year follow-up of ATTRACTION-2, serious treatment-related adverse events were experienced by 11.5% of patients in the nivolumab arm and 5.0% of patients in the placebo arm [22].

Strength of Evidence

The strength of evidence underpinning this outcome is moderate (Appendix 7).

Chemotherapies Not Available in Canada for the Treatment of Gastric or GEJ Carcinoma

S-1 Monotherapy

Survival Outcomes

One systematic review evaluated survival outcomes in patients treated with S-1 monotherapy compared with 5FU chemotherapy in a first-line setting [73]. Based on pooling of seven studies that included 2443 patients, the systematic review reported no difference in overall survival (p=0.07) or progression-free survival (p=0.35) when the monotherapy regimens were compared.

Strength of Evidence

The strength of evidence underpinning this outcome is high (Appendix 7).

Adverse Events

One RCT that compared elderly patients who were receiving S-1 monotherapy and capecitabine in a first-line setting was identified [74]. The study reported a significantly increased frequency of grade 3 anorexia in patients on S-1 therapy when compared with capecitabine (21% vs. 8%). Alternatively, patients undergoing S-1 monotherapy demonstrated a significantly reduced frequency of grade 3 hand-foot syndrome (0% vs. 21%), as well as all grades of hand-foot syndrome (25% vs. 58%).

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

S-1-Containing Regimens

One systematic review [75] and nine RCTs [76-84] that evaluated S-1-containing doublet and triplet regimens in a first-line setting were identified.

Survival Outcomes

The systematic review included 11 studies and compared S-1 monotherapy and S-1 combination therapies with other regimens [75]. When compared with S-1 monotherapy, S-1 combination therapies demonstrated improved overall survival (HR, 0.76; 95% CI, 0.65 to 0.89; p<0.001) and progression-free survival (HR, 0.68; 95% CI, 0.56 to 0.82; p<0.001). Seven RCTs compared S-1 plus cisplatin (S-1C) with other combination regimens. When compared with cisplatin alone, S-1C was associated with improved overall survival (p=0.039) and progression-free survival (p=0.047) [80]. However, when compared with S-1 plus leucovorin [76], capecitabine plus cisplatin [77,79], S-1 plus docetaxel [78], and S-1 plus oxaliplatin [81], S-1C demonstrated no significant difference for overall survival or progression-free survival. Two studies compared S-1C with S-1 plus leucovorin and oxaliplatin (S-1LOx) with one reporting significantly improved overall survival and progression-free survival following S-1LOx [82] and one reporting no difference [76].

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

Adverse Events

Two of the RCTs reported on significant differences in adverse events between regimens [79,81], while five RCTs only reported on frequency of most common adverse events. The XParTS II trial, which compared S-1C with capecitabine plus cisplatin, reported a significant increase in grade 3 through 5 diarrhea in patients on S-1C (p=0.0118) [79]. The other RCT

compared S-1C with S-1 plus oxaliplatin and reported significantly higher rates of leukopenia, neutropenia, anemia, febrile neutropenia, and hyponatremia in patients on the S-1C regimen [81]. The frequency of sensory neuropathy was significantly reduced in these patients when compared with those on the S-1 plus oxaliplatin regimen [81]. Across the other five RCTs, common adverse events with S-1 regimens included neutropenia [76,80], decreased appetite [76], anorexia [80], anemia [76,77,83], hyponatremia [76], nausea [80], leukopenia [80], and decreased platelet counts [77,83].

Strength of Evidence

The strength of evidence underpinning this outcome is low (Appendix 7).

DISCUSSION

Chemotherapy

The goal of therapy for patients with advanced gastric and GEJ carcinoma is to prolong survival and improve quality of life. Several cytotoxic agents have demonstrated activity in gastric cancers. These agents include fluoropyrimidines, platinum agents, taxanes, irinotecan, and S-1. Despite the large body of evidence from RCTs supporting the use of these agents, there is no globally accepted standard first-line chemotherapy.

The recommendations from the previous iteration (2010) of this guideline endorsed a platinum-based combination therapy regimen as first-line treatment [35]. A comprehensive network meta-analysis of 65 randomized trials in the first-line setting published in 2016 [1] demonstrated that both the fluoropyrimidine-oxaliplatin and fluoropyrimidine-irinotecan doublet demonstrated superior overall survival when compared with fluoropyrimidine-cisplatin. Additionally, use of a fluoropyrimidine-oxaliplatin-taxane triple regimen resulted in significantly increased overall survival when compared with fluoropyrimidine-cisplatin and cisplatin-taxane doublet regimens [1]. Pairwise comparisons in the network meta-analysis demonstrated increased toxicity with fluoropyrimidine-cisplatin when compared with fluoropyrimidine-oxaliplatin and fluoropyrimidine-irinotecan doublets [1]. Although not a direct comparison of fluoropyrimidine doublets, a second meta-analysis provided a more in-depth assessment of adverse events for oxaliplatin- and cisplatin-based regimens and reported decreased neutropenia, anemia, nausea, and thromboembolism with oxaliplatin-based therapy [2]. In comparison, the oxaliplatin-based regimens increased neurosensory toxicity and thrombocytopenia [2]. Based on improved efficacy and reduced toxicity observed in the network meta-analysis, fluoropyrimidine paired with oxaliplatin or irinotecan are the preferred first-line regimens. As an alternative to a doublet regimen in selected patients, fluoropyrimidine-oxaliplatin-taxane may be offered based on improved efficacy; however, this must be weighed against the increased toxicity with the triplet regimen [1]. When deciding which chemotherapy regimen to offer to first-line patients, clinicians must carefully weigh the relative efficacy, quality of life improvements, and expected tolerance in the specific patient, against the toxicity and complexity of administration of therapy.

Individualized treatment recommendations need to be based on informed discussions of regimen benefits and toxicities, patient characteristics, and patient preferences. In the second-line setting, although paclitaxel plus ramucirumab is the recommended combination therapy, meta-analyses have demonstrated improved survival when patients undergo treatment with either irinotecan or taxane monotherapy [16,17]. Primary studies within these analyses reported median overall survival improvements of 1.4-1.6 months for taxane, and 1.6-2.7 months for irinotecan when compared with best supportive care [17]. In the third-line setting, the TAGS trial randomized patients with advanced gastric and GEJ adenocarcinoma to trifluride-tipiracil or placebo and reported a median overall survival improvement of 2.1 months [18]. Although the TAGS trial did not conduct statistical analysis on the frequency of

grade 3/4 adverse events, the study did report an 80% frequency in the trifluride-tipiracil arm and a 58% frequency in the placebo arm [18]. Medical oncologists can use the available data on efficacy, toxicity and quality of life as part of an informed decision-making process about the use of trifluride-tipiracil. When making recommendations for treatment as part of an informed decision-making process with individual patients in a second- and third-line setting, medical oncologists should consider patient preferences, their symptoms, performance status and co-morbidities when discussing potential risks and benefits of therapy.

Targeted Therapies

In patients with HER2 overexpressing gastric and GEJ adenocarcinoma, trastuzumab should be added to the first-line chemotherapy doublet regimen. The ToGA trial, which compared trastuzumab plus chemotherapy with chemotherapy alone in HER2 overexpressing gastric or GEJ patients, reported improved overall survival in the combination treatment arm [12]. The 2010 iteration of this guideline issued a provisional recommendation on the routine addition of trastuzumab to the then recommended first-line chemotherapy regimen for HER2 overexpressing patients [35]. The provisional recommendation was based on an interim analysis of ToGA trial data. In 2014, based upon the final analysis of the ToGA trial [12], the GI DSG endorsed the original recommendation. Although the chemotherapy regimens in the ToGA trial were capecitabine-cisplatin or fluorouracil-cisplatin [12], a meta-analysis of three observational studies that added trastuzumab to fluorouracil/cisplatin-oxaliplatin demonstrated that compared with the ToGA regimen, trastuzumab plus the oxaliplatin doublet significantly improved overall survival. Based on this evidence and an understanding of the biological pathways being targeted by the therapy, the Working Group members extrapolated the benefits of the ToGA trial to any of the recommended fluoropyrimidine regimens. The benefits observed in the randomized phase II DESTINY [60] study of pre-treated patients with HER2 overexpressing tumours needs to be confirmed in a phase III study to better define the role of trastuzumab deruxtecan in managing patients with HER2 overexpressing tumours. Initial findings from the KEYNOTE-811 RCT identified an improved overall response with the addition of pembrolizumab to chemotherapy and trastuzumab. Mature results of this study are required to determine whether this combination therapy improves the more clinically relevant outcomes of survival and quality of life.

In patients with adenocarcinoma who progress following first-line therapy, both ramucirumab monotherapy [87] and ramucirumab plus paclitaxel [14,15] has been shown to improve overall survival and quality of life . In the monotherapy trial, patients who received ramucirumab experienced a median overall survival of 5.2 months, up from 3.8 months in the placebo groups [87], while in the combination therapy trial, a median overall survival duration of 9.6 months was reported for ramucirumab therapy compared with 7.4 months for patients on placebo [14]. This modest survival benefit needs to be weighed against the higher rates of all grade 3 and grade 4 adverse events in the ramucirumab plus paclitaxel arm (47% vs. 39% and 27% vs. 8%) when compared with placebo plus paclitaxel [14]. Medical oncologists may prescribe paclitaxel plus ramucirumab to patients who are refractory to fluoropyrimidine doublet chemotherapy after careful discussion of these benefits and risks.

Apart from ramucirumab, the benefits of targeted therapy have not been demonstrated. In fact, studies report higher risk of adverse events with targeted therapies [3,66] and no significant effect on survival or treatment response rates in a first-line setting [3-6].

Immune Checkpoint Inhibitors

Three large randomized trials of ICIs for the first-line treatment of advanced gastric and GEJ carcinoma [7-9] have been published since 2020. RCTs randomized patients to nivolumab [7], avelumab [8], or pembrolizumab [9] and compared these ICI treatments alone or with

chemotherapy to chemotherapy in the first-line setting. Our meta-analysis of these three RCTs demonstrated a significant overall survival benefit for PD-L1-positive patients receiving ICIs. However, when considering each study as a stand-alone, only CheckMate-649demonstrated a survival benefit [7]. Published results from CheckMate-649 demonstrated an overall survival benefit with nivolumab for both patients with a CPS ≥1 and for patients with CPS ≥5 [7]. However, the benefit was not demonstrated for patients with CPS <1 or CPS <5, and the publication does not include subgroup analysis of patients with CPS of 1-4. Since more than 75% of patients included in the CPS ≥1 subgroup did in fact express CPS ≥5, it is likely that the benefit for patients with CPS ≥1 was driven by patients with a CPS ≥5. In an effort to further determine the effect of CPS threshold on survival, a secondary analysis sought to reconstruct unreported survival curves from CheckMate-649 [10]. The analysis demonstrated no difference in overall survival for patients with a CPS of 1-4 when comparing patients treated with nivolumab plus chemotherapy and patients treated with chemotherapy alone (HR, 0.950; 95%CI, 0.747 to 1.209; p=0.678) [10]. Additionally, although rates of grade 3 and 4 adverse events were similar in both arms for all three RCTs [7-9], in CheckMate-649, there were 16 treatment-related deaths (2.0%) in the nivolumab plus chemotherapy group and four deaths (0.5%) in the chemotherapy group [7]. Based on the overall survival benefit using ICIs and a similar rate of grade 3 and 4 treatment-related adverse events, it is recommended that medical oncologists prescribe the addition of an ICI to any fluoropyrimidine chemotherapy regimen in patients with recurrent or metastatic gastric and GEJ carcinoma in the first-line setting. However, given the higher number of treatment-related deaths with the ICI therapy in CheckMate-649 and survival benefit being confined to patients with CPS ≥5, we suggest that medical oncologists obtain the CPS and confine treatment to patients with CPS ≥5.

In both second and third lines of therapy, the survival benefits of ICIs have yet to be elucidated, while the potential for toxicity is still present. In the second-line setting, KEYNOTE-061 randomized patients to pembrolizumab or paclitaxel and no difference in overall survival between treatment arms was detected [19]. In the third-line setting, ATTRACTION-2 [20] randomized unselected patients to nivolumab or placebo, and JAVEIN Gastric 300 [21] randomized unselected patients to either avelumab or a control arm. The most recent publication for ATTRACTION-2 reported on just over three years of follow-up and demonstrated a survival benefit with nivolumab [20]. The JAVELIN Gastric 300 RCT [21] allowed for either chemotherapy or best supportive care in the control arm and reported no significant difference in overall survival when compared with patients who received avelumab (HR, 1.1; 95%CI, 0.9-1.4). Although our meta-analysis of all RCTs evaluating ICIs demonstrated an overall survival benefit for patients receiving ICI therapy, the subgroup analysis for second and third-line setting studies revealed no significant difference in overall survival for patients treated with ICI or chemotherapy alone. In patients with gastric or GEJ carcinoma undergoing later lines of therapy, medical oncologists should not prescribe ICIs.

CONCLUSIONS

In patients with locally advanced, recurrent, or metastatic gastric and GEJ carcinoma, a fluoropyrimidine-oxaliplatin or fluoropyrimidine-irinotecan doublet chemotherapy regimen is the preferred first-line therapy. Medical oncologists should individualize treatment based on patient characteristics, regimen toxicity profiles, and patient preferences when choosing the appropriate therapy for their patients. Medical oncologists should also obtain the tumour PD-L1 CPS score in these patients and prescribe nivolumab in patients with a CPS ≥5. In patients with HER2 overexpressing carcinoma, trastuzumab should be prescribed in addition to the doublet chemotherapy regimen. However, no biological agent has yet to demonstrate benefit in HER2 non-overexpressing patients and none has been recommended in this patient population. In patients who demonstrate disease progression on or after treatment with

fluoropyrimidine doublet chemotherapy, medical oncologists may prescribe paclitaxel plus ramucirumab based on a modest improvement in overall survival and quality of life with this therapy. If patients previously treated with at least two prior lines of chemotherapy experience disease progression, medical oncologists may prescribe trifluride-tipiracil monotherapy. This recommendation is based on a single trial with a modest overall survival benefit and is associated with increased toxicity, both of which providers should discuss with prospective patients.

Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the seven members of the GDG Expert Panel, six members voted and one abstained, for a total of 85.7% response in November 2020 through February 2021. Of those who voted, six approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. I would like to ask the authors why AVAGAST was not one of the studies included?	The AVAGAST RCT was included within the Ciliberto et al. systematic review. The Targeted Agent section of the current systematic review was rewritten to include greater detail on which RCTs and which targeted agents were included in the Ciliberto meta-analyses. Additionally, an appendix (Appendix 3) was added that lists every RCT included within systematic reviews used as evidence base.

RAP Review and Approval

Three RAP members reviewed this document in November 2020. The RAP approved the document. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Recommendation 2 - Is there a chance that Herceptin was making up for inferior chemotherapy given statement 1 that oxaliplatin or irinotecan doublet generally felt to be better than cisplatin? I doubt it. Maybe an extra statement on why extrapolation is ok? Makes biological sense, using a unique pathway and no evidence of harm with doublet agent proposed.	The Working Group has added data from a systematic review on the efficacy of adding trastuzumab to a fluoropyrimidine-oxaliplatin regimen in the Justification Section of Recommendation 2 to support the extrapolation.
2. Recommendation 2 and 4 – RAP reviewer asked for data to support added benefit of therapy.	The Working Group redrafted the Key Evidence sections for both Recommendation 2 and 4 to better highlight reported survival rates.
3. Recommendation 5 - Herceptin and ramucirumab are immunotherapies. Maybe	The language for Recommendation 5 was altered to include "immune checkpoint inhibitors" instead of "immunotherapy".

be more explicit about PD-1, PD-L1 and CTLA-4 directed immunotherapies.	
4. Recommendation 5, Key Evidence - What is the difference between placebo and best supportive care?	Definitions for these terms were added to the Key Evidence section.
5. Page 13 – is there more that can be said about S-1 chemotherapy?	Although the Working Group members appreciate this comment, based on the current and expected continued unavailability of S-1 chemotherapy in Canada, the Working Group believes that devoting a larger section to explanation of this therapy would be of little benefit to the guideline's target user.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

One targeted peer reviewer from Ontario and one targeted peer reviewer from Quebec, who were considered to be clinical experts on the topic were identified by the Working Group. Both agreed to be the reviewers (Appendix 1). Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (n=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					2
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.					2
4. Rate the completeness of reporting.					2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?					2
6. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	1
8. I would recommend this guideline for use in practice.				1	1
9. What are the barriers or enablers to the implementation of this guideline report?	**1.** I recommend to update rapidly the guidelines knowing that new data will emerge, especially an imminent publication of the trial Checkmate 209-649				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	**Responses**

1. My only comment relates to Recommendation 5. The role of ICIs is evolving rapidly. Physicians and importantly patients may demand the use of these biologic agents. Although I agree with the evidence presented and the recommnedation, it is possible that this recommendation will be outdated by the time the guidelines are published.	Following full publication of CheckMate-649, the literature search was updated and a new recommendation for ICIs in the first-line setting was developed.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All oncologists with an interest in gastrointestinal carcinoma in the PEBC database were contacted by email to inform them of the survey. Additionally, all members of the Lung DSG were contacted by email. One hundred forty-six professionals, all practicing in Ontario, were contacted. Fifteen (10.3%) responses were received. The results of the feedback survey from 15 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1 (6.7%)	8 (53.3%)	6 (40.0%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (6.7%)	9 (60.0%)	5 (33.3%)
3. I would recommend this guideline for use in practice.			1 (6.7%)	8 (53.3%)	6 (40.0%)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers 1. Challenges in optimizing therapy may relate to patients' abilities to gauge the risks and benefits of each regimen; a dedicated, topic-specific Question Prompt List might provide patients with the means to understand and discuss the options better. 2. Prejudice against guidelines as opposed to "feelings" about best treatment for an individual patient. Not something that can be overcome by any guideline. 3. Toxicity still seems too high Enablers 4. Requirement by OH (CCO) that treatments recommended at Tumour Boards be declared conformal/non-conformal with				

	approved guidelines, and reported to CCO, would help acceptance. 5. Get to the multidisciplinary teams of centres that treat esophageal ca, usually Thoracic team rather than the GI team.

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Clearly written, although I would prefer to see actual median times for overall survival etc as well as HR/overall survival in all sections (currently patchy) - the information can be found in the detailed summaries of the clinical trials but would add little to the length of the introductory summary.	Text has been modified to include both median durations and hazard or odds ratios when reported.
2. Given the newer trials that are ongoing related to ICI options and potential for benefit with these newer agents, current guideline may need to be reviewed and revised in the not too distant future. I believe this item has been addressed in the current guideline.	Following full publication of CheckMate-649, the literature search was updated and a new recommendation for ICIs in the first-line setting was developed.
3. The release of both abstract and fully published data after the search date for this guideline, dealing with the immunotherapy question, is unfortunate but understandable. It may mean that this topic needs to be refreshed yet again in a short period of time (i.e. one year or two years maximum).	Following full publication of CheckMate-649, the literature search was updated and a new recommendation for ICIs in the first-line setting was developed.
4. Vague recommendation about HER2 partner chemotherapy should state 5-fluorouracil/oxaliplatin doublet is recommended as partner despite not being in ToGA trials. May help fund this treatment as it is what is used in most jurisdictions.	The recommendation intentionally states that trastuzumab can be added to a fluoropyrimidine doublet as multiple chemotherapy doublet regimens are allowable.
5. As immunotherapy in gastric/GEJ and esophageal are evolving monthly, a separate guideline just to deal with their role is likely appropriate over the next year as Recommendation #5 is really of little value as written.	Following full publication of CheckMate-649, the literature search was updated and a new recommendation for ICIs in the first-line setting was developed.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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junction (G/GEJ) cancer: Initial findings of the global phase 3 KEYNOTE-811 study. J Clin Oncol. 2021;39(15_suppl):4013-.
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Appendix 1: Affiliations and Conflict of Interest Declarations

Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG Working Group		
Name	Affiliation	Conflict of Interest
Tim Asmis	Ottawa Hospital	Local principal investigator of an Eli Lilly-funded study gastric cancer; director of medical oncology fellowship program funded by several industry sources. Advisory board member for several pharmaceutical entities.
Scott Berry	Kingston Health Sciences Centre	Serves on the advisory board for Merck and BMS and as a consultant for Oncology Education.
Kristopher Dennis	Ottawa Hospital	None declared
Tarek Elfiki	Windsor Regional Cancer Centre	None declared
Julie Hallet	Sunnybrook Hospital	Speaking honoraria for Ipsen and Novartis for rounds concerning a different form of cancer. Received an unrestricted educational grant from Ipsen.
Chika Agbassi	PEBC, Ontario Health	None declared
Lesley Souter	PEBC, Ontario Health	None declared

Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG Expert Panel		
Name	Affiliation	Conflict of Interest
Mala Bahl	Trillium Health Partners	None declared
Jim Biagi	Kingston Health Sciences Centre	None declared
Valerie Francescutti	Hamilton Health Sciences Centre	Acted as a consultant for Novartis for immunotherapy on a different form of cancer
Maria Kalyvas	Kingston Health Sciences Centre	None declared
Aamer Mahmud	Kingston Health Sciences Centre	None declared
Rebecca Wong	Princess Margaret Cancer Centre	None declared
Rachel Goodwin	Ottawa Hospital	Advisory board member for several pharmaceutical entities

Management of Advanced Gastric and Gastro-Esophageal Carcinoma GDG Report Approval Panel		
Name	Affiliation	Conflict of Interest
Bill Evans	Hamilton Health Sciences Centre	None declared
Donna Maziak	Ottawa Hospital	None declared
Jonathan Sussman	Juravinski Cancer Centre	None declared

Appendix 2: Literature Search Strategy

SEARCH STRATEGY: OVID MEDLINE EPUB AHEAD OR PRINT, IN-PROCESS & OTHER NON-INDEXED CITATIONS, OVID MEDLINE(R) DAILY AND OVID MEDLINE(R) <1946 TO JULY 2021>

Search Term	Search Term Description
1. exp meta analysis/ or exp systematic review/	Included study types
2. (meta analy$ or metaanaly$).tw.	
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.	
4. (systematic adj (review$ or overview?)).tw.	
5. exp review/ or review.pt.	
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.	
7. (study adj selection).ab.	
8. 5 and (6 or 7)	
9. or/1-4,8	
10. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/	
11. randomization/ or single blind procedure/ or double blind procedure/	
12. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.	
13. or/10-12	
14. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/	
15. 14 and random$.tw.	
16. (clinic$ adj trial$1).tw.	
17. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.	
18. placebo/	
19. (placebo? or random allocation or randomly allocated or allocated randomly).tw.	
20. (allocated adj2 random).tw.	
21. or/16-20	
22. 9 or 13 or 15 or 21	
23. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/	Study type exclusions and limits
24. 22 not 23	
25. limit 24 to english	
26. limit 25 to human	
27. (stomach adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	Disease terms
28. (gastric adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	
29. (gastro?esophageal adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	
30. 27 or 28 or 29	
31. (recurrent or advanced or metasta$).ti.	
32. 30 and 31	
33. 26 and 32	Combining of terms
34. limit 33 to yr="2013 – 2021"	

SEARCH STRATEGY: EMBASE <1996 TO 2021 WEEK 31>

Search Term	Search Term Description
1. exp meta analysis/ or exp systematic review/	Included study types
2. (meta analy$ or metaanaly$).tw.	
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.	
4. (systematic adj (review$ or overview?)).tw.	
5. exp review/ or review.pt.	
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.	
7. (study adj selection).ab.	
8. 5 and (6 or 7)	
9. or/1-4,8	
10. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/	
11. randomization/ or single blind procedure/ or double blind procedure/	
12. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.	
13. or/10-12	
14. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/	
15. 14 and random$.tw.	
16. (clinic$ adj trial$1).tw.	
17. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.	
18. placebo/	
19. (placebo? or random allocation or randomly allocated or allocated randomly).tw.	
20. (allocated adj2 random).tw.	
21. or/16-20	
22. 9 or 13 or 15 or 21	
23. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/	Study type exclusions and limits
24. 22 not 23	
25. limit 24 to english	
26. limit 25 to human	
27. (stomach adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	Disease terms
28. (gastric adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	
29. (gastro?esophageal adj5 (neoplas$ or carcin$ or cancer$ or tumo$ or metasta$ or malig$)).tw.	
30. 27 or 28 or 29	
31. (recurrent or advanced or metasta$).ti.	
32. 30 and 31	Combining of terms
33. limit 32 to yr="2013 - 2021"	

Appendix 3: List of RCTs Included in Identified Systematic Reviews

Systematic Review [reference]	Intervention of Interest	Included RCTs
Huang et al, 2016 [2]	Oxaliplatin-based vs. cisplatin-based chemotherapy	1. Yamada. Ann Oncol. 2015; 26: 141-148 2. Kim. Cancer Chemother Pharmacol. 2014; 73:163-169 3. Al-Batran. J Clin Oncol. 2008; 26:1435-1442 4. Cunningham. N Engl J Med. 2008; 358:36-46 5. Popov. Journal of BUON. 2008; 13:505-511
Petrioli et al, 2016 [41]	Epirubicin-based vs. docetaxel-based chemotherapy	1. Roth. J Clin Oncol. 2007; 25:3217-3223 2. Teker. Asian Pac J Cancer Prev. 2014; 15: 6727-6732 3. Thuss-Patience. J Clin Oncol. 2005; 23:494-501 4. Yao. J Chemother. 2014; 26:117-121
ter Veer et al, 2016 [1]	Multiple first-line chemotherapy regimens	1. Cunningham. N Engl J Med. 2008; 358:36–46 2. Boku. Lancet Oncol. 2009; 10:1063–1069 3. Jin. J Clin Oncol. 2008; 26 4. Scheithauer. Ann Hematol. 1996; 73:A181 5. Murad. Cancer. 1993; 72:37–41 6. Pyrhonen. Br J Cancer. 1995; 71:587–591 7. Coombes. Ann Oncol. 1994; 5:33–36 8. Loehrer. Invest New Drugs. 1994; 12:57–63 9. Colucci. Am J Clin Oncol. 1995; 18:519–524 10. Cullinan. JAMA. 1985; 253:2061–2067 11. Hironaka. Lancet Oncol. 2016; 17:99–108 12. Kim. Cancer. 1993; 71:3813–3818 13. Koizumi. Lancet Oncol. 2008; 9:215–221 14. Lutz. J Clin Oncol. 2007; 25:2580–2585 15. Ohtsu. J Clin Oncol. 2003; 21:54–59 16. Bouche. J Clin Oncol. 2004; 22:4319–4328 17. Komatsu. JFMC31-0301 Trial. Anticancer Drugs. 2011; 22:576–583 18. Narahara. Study GC0301/TOP-002. Gastric Cancer. 2011; 14:72–80 19. Koizumi. Cancer Res Clin Oncol. 2014; 140:319-328 20. Wang. Clin Transl Oncol. 2013; 15:836–842 21. Hwang. J Clin Oncol. 2014; 32:158 22. Lu. J Chemother. 2014; 26:159–164 23. Yamamura. Gan To Kagaku Ryoho. 1998; 25:1543–1548 24. Ridwelski. J Clin Oncol. 2008; ASCO Annual Meeting Proceedings 25. Pozzo. Ann Oncol. 2004; 15:1773–1781 26. Tesselaar. J Clin Oncol. 2008; ASCO annual meeting proceedings 27. Dank. Ann Oncol. 2008; 19:1450–1457 28. Moehler. Ann Oncol. 2010; 21:71–77 29. Ikeda. J Clin Oncol. 2009; 27:4595 30. Mochiki. Br J Cancer. 2012; 107:31–36 31. Al-Batran. J Clin Oncol. 2008; 26:1435–1442 32. Popov. Journal of B U On. 2008; 13:505–511 33. Yamada. Ann Oncol. 2015; 26:141–148

		34. Jeung. Cancer. 2011; 117:2050–2057 35. Kim. Cancer Chemother Pharmacol. 2014; 73:163–169 36. Sugimoto. OGSG0402 Trial. Anticancer Res. 2014; 34:851–857 37. Roy. Br J Cancer. 2012; 107:435–441 38. Roth. Tumouri. 1999; 85 :234–238 39. Vanhoefer. J Clin Oncol. 2000; 18:2648–2657 40. Kim. Eur J Cancer. 2001;37 41. KRGCGC. Anticancer Res. 1992; 12:1983–1988 42. Yun. Eur J Cancer. 2010; 46:885–891 43. Van Cutsem. J Clin Oncol. 2006; 24:4991–4997 44. Wang. Gastric Cancer. 2016; 19:234-244 45. Roth. J Clin Oncol. 2007; 25:3217–3223 46. Ajani. J Clin Oncol. 2005; 23:5660–5667 47. Guimbaud. J Clin Oncol. 2014; 32:3520–3526 48. Thuss-Patience. J Clin Oncol. 2005; 23:494–501 49. Li. World J Gastroenterol. 2011; 17:1082–1087 50. Al-Batran. FLOT65þ Trial. Eur J Cancer. 2013; 49:835–842 51. Cutsem. Ann Oncol. 2015; 26:149–156 52. Cocconi. Ann Oncol. 2003; 14:1258–1263 53. Waters. Br J Cancer. 1999; 80(1-2):269–272
Xu et al, 2015 [42]	XELOX vs. FOLFOXs	1. Sun. Cancer Res Prev Treat. 2005; 32:729–730 2. Cai. J Clin Exp Med. 2007; 16:45–46 3. Chen. China Oncol. 2007; 17:483–486 4. Qu. Fujian Med J. 2007; 29:41–43 5. Xue. Fujian Med J. 2008; 30:114–116 6. Shi. J South Med Univ. 2008; 28:1490–1491 7. Gao. Mod Med J China. 2008; 10:35–37 8. Wang. Eval Anal Drug-Use Hosp China. 2009; 9:856–857 9. Hu. China Pract Med. 2009; 4:25–26 10. Zhao. Chin J Clin Oncol. 2009; 36:1044–1046 11. Lei. Med J Natl Defending Forces N China. 2009; 21:10–12 12. Cui. Chin J Curr Adv Gen Surg.2009; 12:869–871 13. Wang. Mod Oncol. 2010; 18:947–950 14. Du. Inn Mong Med J. 2010; 42:260–263 15. Liu. Chin J Curr Adv Gen Surg. 2010; 13:960–963 16. Liu. J Clin Med Pract. 2010; 14:50–51 17. Wu. Chin J Clin Gastroenterol. 2011; 23:330–331 18. Lu. J Clin Med Pract. 2011; 15:112–113 19. Wang. Anhui Med Pharm J. 2011; 15:329–330 20. Yang J. Pract J Card Cereb Pneumal Vasc Dis. 2011; 19:369–370 21. Jiang. Guide China Med. 2012; 10:118–119 22. Zhou. Chin Foreign Med Res. 2012; 10:11–12 23. Wang. China Med Her. 2012; 9:58–59 24. Hu. Chongqing Med. 2013; 42:156–159 25. Fan. Pract J Cancer. 2013; 28:396–398 26. Zhang. Chin J Med Guid. 2014; 16:129–130
Yang et al, 2018 [49]	Irinotecan doublet vs. irinotecan monotherapy	1. Higuchi. TCOG GI-0801/BIRIP Trial. Eur J Cancer. 2014; 50:1437–45 2. Nishikawa. Eur J Cancer. 2015; 51:808–16

		3. Satoh. Gastric Cancer. 2015; 18:824–32 4. Sym. Cancer Chemother Pharmacol. 2013; 71:481–8 5. Tanabe. JACCROGC-05 Trial. Ann Oncol. 2015; 26:1916–22 6. Ueda. Anticancer Res. 2013; 33:5107–11 7. Oba. Oncol Lett. 2011; 2:241–5
Janowitz et al, 2016 [16]	Chemotherapy vs. supportive care	1. Ford. Lancet Oncol. 2014; 15:78-86 2. Kang. J Clin Oncol. 2012; 30:1513-1518 3. Thuss-Patience. Eur J Cancer. 2011; 47:2306-2314
ter Veer et al, 2016 [17]	Multiple second and third-line systemic therapies	1. Fuchs. REGARD Trial. Lancet. 2014; 383:31–39 2. Wilke. RAINBOW Trial. Lancet Oncol. 2014 15:1224–1235 3. Satoh. Gastric Cancer. 2015; 18:824–832 4. Yi. Br J Cancer. 2012; 106:1469–1474 5. Ohtsu. GRANITE-1 study. J Clin Oncol. 2013; 31:3935–3943 6. Li. J Clin Oncol. 2013; 31:3219–3225 7. Li. J Clin Oncol. 2016; 34:1448-1454 8. Ford. Lancet Oncol. 2014; 15:78–86 9. Thuss-Patience. Eur J Cancer. 2011; 47:2306–2314 10. Kang. J Clin Oncol. 2012; 30:1513–1518 11. Hironaka. WJOG 4007 Trial. J Clin Oncol. 2013; 31:4438–4444 12. Nishikawa. OGSG0701 Trial. J Clin Oncol. 2015; 33 13. 22. Roy. Br Journal Cancer. 2012; 107:435–441 14. 23. Higuchi. TCOG GI-0801/BIRIP Trial. Eur J Cancer. 2014; 50:1437–1445 15. Nishikawa. TRICS Trial. Eur J Cancer. 2015; 51:808–816 16. Kim. Eur J Cancer. 2015; 51:S432 17. Kim. Anticancer Res. 2015; 35:3531–3536 18. Nakanishi. CCOG0701 Trial. Int J Clin Oncol. 2015; 21:557-565 19. Tanabe. JACCRO GC-05 Trial. Ann Oncol. 2015; 26:1916–1922 20. Sym. Cancer Chemother Pharmacol. 2013; 71:481–488 21. Maruta. Med Oncol. 2007; 24:71–75 22. Nishina. JCOG0407 Trial. Gastric Cancer. 2016; 19:902-910 23. Pavlakis. INTEGRATE Trial. J Clin Oncol. 2015; 33:9 24. Bang. J Clin Oncol. 2015; 33:3858–3865 25. Moehler. Onkologie. 2013; 36:73–74 26. Bang. SHINE Study. J Clin Oncol. 2015; 33 27. Satoh. TyTAN Trial. J Clin Oncol. 2014; 32:2039–2049 28. Lorenzen. Eur J Cancer. 2015; 51:569–576
Zhu et al, 2016 [48]	Fluoropyrimidine-based chemotherapy	1. Cunningham. N Engl J Med. 2008; 358:36–46 2. Ajani. FLAGS Trial. J Clin Oncol. 2010; 28:1547–1553

		3. Boku. Lancet Oncol. 2009; 10:1063–1069 4. Jin. SC-101 Study. J Clin Oncol. 2008; 26:4533 5. Kang. Ann Oncol. 2009; 20:666–673 6. Lee. Br J Cancer. 2008; 99:584–590 7. Kim. Eur J Cancer. 2012; 48:518–526 8. Xu. J Clin Oncol. 2013; 31 9. Huang. Eur J Cancer. 2013; 49:2995–3002 10. Ocvirk. Am J Clin Oncol. 2012; 35(3):237–241 11. Nishikawa. Gastric Cancer. 2012; 15:363–369 12. Sanofi. ClinicalTrialsgov:NCT00382720. 2011
Ciliberto et al, 2015 [6]	Multiple targeted therapies	1. Bang. ToGA Trial. Lancet 2010; 376:687-97 2. Ohtsu. AVAGAST Trial. J Clin Oncol. 2011; 29:3968-76 3. Kim. J Clin Oncol. 2011; 29:87 4. Ohtsu. J Clin Oncol. 2013; 31:3935-43 5. Lordick. EXPAND Trial. Lancet Oncol. 2013; 14:490-9 6. Yi. Br J Cancer 2012; 106:1469-74 7. Rao. Ann Oncol. 2010; 21:2213-9 8. Eatock. Ann Oncol. 2013; 24:710-8 9. Li. J Clin Oncol. 2013; 31:3219-25 10. Fuchs. REGARD Trial. Lancet. 2014; 383:31-9 11. Hecht. LOGiC Trial. ASCO Meet Abstr. 2013 12. Wilke. RAINBOW Trial. ASCO Meet Abstr. 2014 13. Waddell. REAL-3 Trial. Lancet Oncol. 2013; 14:481-9 14. Richards. Eur J Cancer. 2013; 49:2823-31 15. Koizumi. Br J Cancer. 2013; 109:2079-86 16. Bang. Tytan Study. ASCO Meet Abstr. 2013; 31:11 17. Cohen. ASCO Meet Abstr. 2013; 31:4011 18. Bang. TYTAN Trial. ASCO Meet Abstr. 2013; 31:4013 19. Moehler. ASCO Meet Abstr. 2010; 28 20. Yoon. ASCO Meet Abstr. 2014; 32:4004 21. Qin. ASCO Meet Abstr. 2014; 32:4003 22. Iveson. Lancet Oncol. 2014; 15:1007-18
Wang et al, 2017 [66]	Multiple molecular targets Focus on adverse events	1. Fuchs. Lancet. 2014; 383:31-39 2. Wilke. RAINBOW trial. Lancet Oncol. 2014; 15:1224-1235 3. Shen. AVATAR study. Gastric Cancer. 2015; 18:168-176 4. Satoh. TyTAN trial. J Clin Oncol. 2014; 32:2039-2049 5. Waddell. REAL3 trial. Lancet Oncol. 2013; 14:481-489 6. Ohtsu. GRANITE-1 study. J Clin Oncol. 2013; 31:3935-3473 7. Lordick. EXPAND trial. Lancet Oncol. 2013; 14:490-499 8. Ohtsu. J Clin Oncol. 2011; 29:3968-3976 9. Bang. ToGA trial. Lancet. 2010; 376:687-697
Xie et al, 2017 [65]	Multiple targeted agents plus chemotherapy	1. Bang. Lancet. 2010; 376:687–697 2. Rao. Ann Oncol. 2010; 21:2213–2219 3. Ohtsu. J Clin Oncol. 2011; 29:3968–3976

		4. Van Cutsem. J Clin Oncol. 2012; 30:2119–2127 5. Yi. Br J Cancer. 2012; 106:1469–1474 6. Lordick. Lancet Oncol. 2013; 14:490–499 7. Ohtsu. J Clin Oncol. 2013; 31:3935–3943 8. Richards. Eur J Cancer. 2013; 49:2823–2831 9. Shen. Zhonghua zhong liu za zhi. 2013; 35:295–300 [article in Chinese] 10. Xu. OncoTargets Ther. 2013; 6:925–929 11. Fuchs. Lancet. 2014; 383:31–39 12. Satoh. J Clin Oncol. 2014; 32:2039–2049 13. Wilke. RAINBOW Trial. Lancet Oncol. 2014; 15:1224–1235 14. Xu. Asian Pac J Cancer Prev. 2014; 15:10273–10276. 15. Casak. Clin Cancer Res. 2015; 21:3372–3376. 16. Du. Medicine. 2015; 94:e958. 17. Satoh. Gastric Cancer. 2015; 18:824–832 18. Shen. AVATAR Study. Gastric Cancer. 2015; 18:168–176. 19. Hecht. TRIO- 013/LOGiC Trial. J Clin Oncol. 2016; 34:443–451 20. Muro. RAINBOW Trial. J Gastroenterol Hepatol. 2016; 31:581–589 21. Shah. Oncologist. 2016; 21:1085–90 22. Shitara. RAINBOW Trial. Gastric Cancer. 2016; 19:927 938 23. Tebbutt. Br J Cancer. 2016; 114:505–509
Chen et al, 2018 [67]	Apatinib	1. Li. J Clin Oncol. 2016;34(13):1448–1454 2. Li. J Clin Oncol. 2013;31(26):3219–3225 3. Zhu. Chin J Surg Oncol. 2016;8(6):394–396 4. Gao. Clin J Med Offic. 2017;45(1):9–12 5. Gao. Clin Album. 2016;12(6):624–625 6. Wen. Clin Study. 2017;33(7):589–591 7. Chen. Chin J Clin Ratl Drug Use. 2017;10(6A):79–80 8. Ding. Pract J Cancer. 2017;32(6):996–998 9. Fan. Chin J Med Front. 2017;9(2):63–67 10. Wang. World Latest Med Inf. 2016;16(87):130–131 11. Wang. J Taishan Med Coll. 2016;37(8):919–920 12. Xue. Contemp Med Symp. 2016;14(22):126–127
Chen et al, 2019 [23]	Immune checkpoint inhibitors	1. Fashoyin-Aje. Oncologist. 2019; 24:103–109 2. Janjigian. CheckMate-032 study. J Clin Oncol. 2018; 36:2836-2844 3. Kang. ATTRACTION-2 Trial. Lancet. 2017; 390:2461–2471 4. Shitara. KEYNOTE-061 Trial. Lancet. 2018; 392(10142):123–133 5. Cs. KEYNOTE-059 Trial. JAMA Oncol. 2018; 4:e180013 6. Kim. Nat Med. 2018; 24:1449–1458 7. Muro. KEYNOTE-012 Trial. Lancet Oncol. 2016; 17:717–726 8. Bang. JAVELIN Gastric 300 Trial. Ann Oncol. 2018; 29(10):2052–2060

		9. Bang. Clin Cancer Res. 2017; 23:5671–5678

Appendix 4: Quality Assessment of Included Systematic Reviews

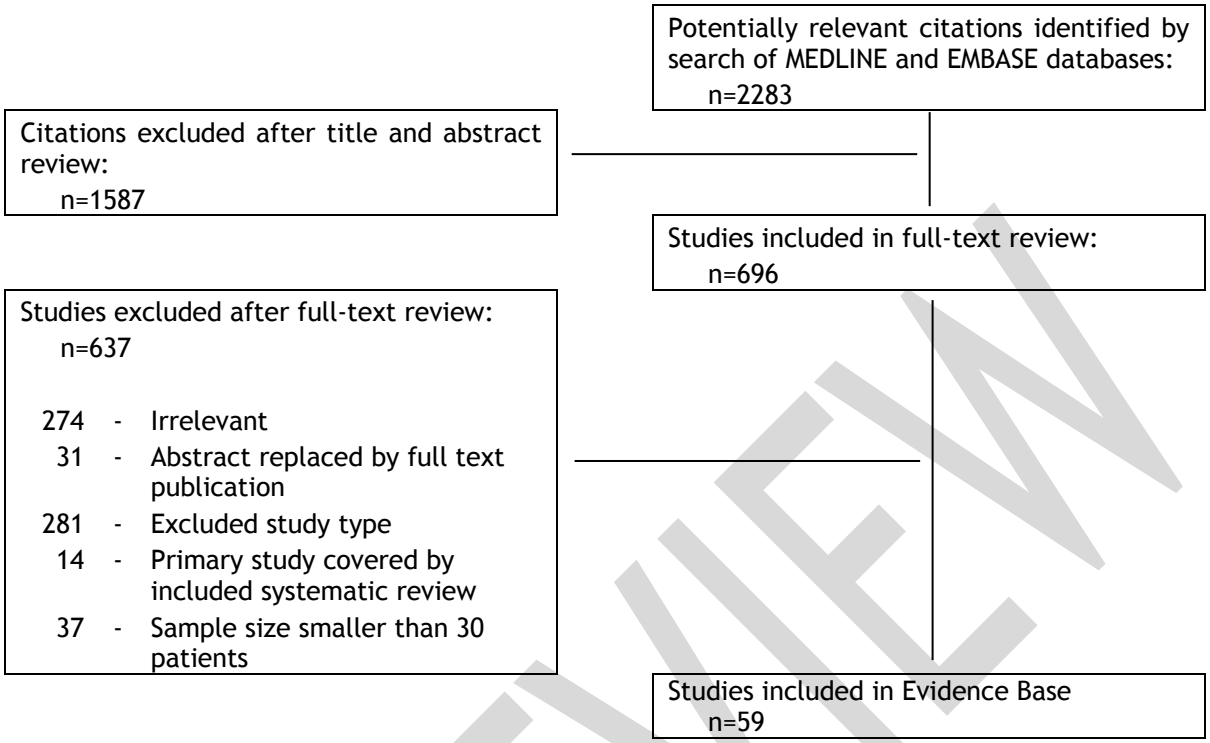
Study		Chen et al, 2016 [73]	Chen et al, 2018 [67]	Chen et al, 2019 [23]	Ciliberto et al, 2015 [6]	Huang et al, 2016 [2]	Janowitz et al, 2016 [16]	Petriolo et al, 2016 [41]	ter Veer et al, 2016 [17]
AMSTAR Assessment	A priori design	Y	Y	Y	Y	Y	Y	Y	Y
	Duplicate study selection and data extraction	Y	N	Y	Y	Y	N	Y	Y
	Comprehensive literature search	Y	Y	Y	Y	Y	Y	Y	Y
	Publication status as inclusion criterion	N	N	N	Y	N	N	Y	Y
	List of included and excluded studies	Y	Y	Y	Y	Y	N	Y	Y
	Characteristics of included studies	Y	Y	Y	Y	Y	Y	Y	Y
	Study quality assessment conducted	Y	N	Y	Y	Y	Y	Y	Y
	Quality assessment used in formulating conclusions	N	N	N	Y	N	N	N	N
	Appropriate methods to combine findings	Y	Y	Y	Y	Y	Y	Y	Y
	Publication bias assessment	Y	Y	Y	Y	N	N	N	N
	Conflict of interest reported	N	Y	Y	Y	Y	Y	Y	Y
Reported funding sources		Y	N	Y	Y	Y	Y	N	Y

Abbreviations: Int, Intermediate; N, no; Y, yes.

Study		ter Veer et al, 2016 [1]	ter Veer et al, 2016 [75]	Wang et al, 2017 [66]	Xie et al, 2017 [65]	Xu et al, 2015 [42]	Yang et al, 2018 [49]	Zhu et al, 2016 [48]
AMSTAR Assessment	A priori design	Y	Y	Y	Y	Y	Y	Y
	Duplicate study selection and data extraction	Y	Y	Y	Y	Y	N	Y
	Comprehensive literature search	Y	Y	Y	Y	Y	Y	Y
	Publication status as inclusion criterion	Y	Y	N	N	N	N	N
	List of included and excluded studies	Y	N	Y	Y	Y	Y	Y
	Characteristics of included studies	Y	Y	Y	N	Y	Y	Y
	Study quality assessment conducted	Y	Y	Y	Y	Y	Y	Y
	Quality assessment used in formulating conclusions	Y	Y	N	Y	Y	N	N
	Appropriate methods to combine findings	Y	Y	Y	N	Y	Y	Y
	Publication bias assessment	N	Y	Y	N	Y	Y	N
	Conflict of interest reported	Y	Y	Y	Y	Y	Y	Y
Reported funding sources		Y	Y	N	Y	N	Y	Y

Abbreviations: Int, Intermediate; N, no; Y, yes.

Appendix 5. PRISMA Flow Diagram



Appendix 6: Quality Assessment of Included Randomized Controlled Trials

Study		Al-Batran et al, 2016 [15]	Al-Batran et al, 2019 [43]	Bang et al, 2017 [64]	Bang et al, 2019 [4]	Boku et al, 2021 [20]	Catenacci et al, 2017 [3]	Chen et al, 2018 [44]	Chen et al, 2020 [22]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	LR	LR	UR	UR	LR	LR	UR
	Allocation concealment	LR	HR	LR	UR	LR	LR	HR	LR
	Blinding – patients and conductors	LR	HR	LR	UR	LR	LR	HR	LR
	Blinding – outcome assessors	LR	HR	LR	UR	LR	LR	HR	LR
	Complete outcome data	HR	HR	HR	HR	LR	HR	HR	LR
	Selective outcome reporting	LR	LR	LR	LR	LR	LR	HR	LR
Adequately powered		Y	Y	Y	N	Y	N	Y	Y
Reported funding sources		Y	Y	Y	Y	Y	Y	Y	Y
Industry funded		Y	N	Y	Y	Y	Y	Y	Y

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear: UR, unclear risk; Y, yes.

Study		Fushida et al, 2016 [50]	Hironaka et al, 2016 [76]	Janjigian et al, 2021[7]	Kang et al, 2018 [51]	Kang et al, 2020 [82]	Kawakami et al, 2018 [77]	Kim et al, 2018 [74]	Lee et al, 2021 [83]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	LR	LR	UC	LR	UR	LR	LR
	Allocation concealment	HR	HR	HR	HR	UR	HR	UR	HR
	Blinding – patients and conductors	HR	HR	LR	HR	HR	HR	UR	HR
	Blinding – outcome assessors	HR	HR	LR	HR	LR	HR	UR	HR
	Complete outcome data	LR	HR	HR	LR	LR	UR	LR	LR
	Selective outcome reporting	LR	LR	LR	LR	LR	HR	LR	LR
Adequately powered		N	N	Y	Y	Y	Y	Y	Y
Reported funding sources		N	Y	Y	Y	Y	Y	Y	Y
Industry funded		U	Y	Y	Y	Y	Y	N	Y

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear: UR, unclear risk; Y, yes.

Study		Li et al, 2020 [57]	Lorenzen et al, 2020 [63]	Lu et al, 2018 [45]	Lu et al, 2019 [78]	Makiyama et al, 2020 [59]	Mansoor et al, 2021 [53]	Moehler et al, 2016 [61]	Moehler et al, 2021 [8]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	UR	LR	UR	UR	LR	UR	HR
	Allocation concealment	UR	UR	HR	HR	UR	LR	UR	HR
	Blinding – patients and conductors	UR	LR	HR	HR	UR	LR	LR	HR
	Blinding – outcome assessors	HR	LR	HR	HR	UR	LR	LR	HR
	Complete outcome data	LR	LR	LR	UR	LR	HR	LR	LR
	Selective outcome reporting	LR	LR	HR	UR	LR	LR	LR	LR
Adequately powered		N	Y	Y	Y	Y	Y	Y	Y
Reported funding sources		Y	Y	Y	N	Y	Y	Y	Y
Industry funded		N	U	Y	U	N	Y	N	Y

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear; Y, yes.

Study		Nakajima et al, 2020 [47]	Ni et al, 2021 [85]	Nishikawa et al, 2018 [79]	Nishina et al, 2016 [52]	Pavlakis et al, 2016 [68]	Satoh et al, 2020 [71]	Shah et al, 2017 [5]	Shitara et al, 2020 [60]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	HR	LR	LR	LR	UR	LR	LR
	Allocation concealment	LR	HR	HR	HR	LR	LR	UR	UR
	Blinding – patients and conductors	HR	HR	HR	HR	LR	LR	LR	UR
	Blinding – outcome assessors	LR	HR	HR	HR	LR	LR	LR	UR
	Complete outcome data	LR	LR	LR	LR	HR	LR	HR	LR
	Selective outcome reporting	HR	LR	LR	LR	LR	LR	LR	LR
Adequately powered		Y	Y	Y	Y	Y	N	N*	Y
Reported funding sources		Y	Y	Y	Y	Y	Y	Y	N
Industry funded		N	N	N	N	Y	Y	Y	U

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear; Y, yes.

Study		Shitara et al, 2020 [55]	Shitara et al, 2018 [18]	Shitara et al, 2020 [9]	Tabernero et al, 2018 [54]	Thuss-Patience et al, 2017 [58]	Van Cutsem et al, 2015 [46]	Wilke et al, 2014 [14]	Wu et al, 2015 [80]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	LR	LR	LR	LR	UR	LR	LR
	Allocation concealment	LR	LR	LR	LR	UR	HR	LR	LR
	Blinding – patients and conductors	LR	LR	HR	LR	HR	HR	LR	UR
	Blinding – outcome assessors	LR	LR	HR	LR	HR	HR	LR	UR
	Complete outcome data	HR	HR	HR	HR	HR	HR	LR	HR
	Selective outcome reporting	LR	LR	LR	LR	LR	LR	LR	HR
Adequately powered		N	Y	Y	Y	N	Y	Y	N
Reported funding sources		Y	Y	Y	Y	Y	Y	Y	N
Industry funded		Y	Y	Y	Y	Y	Y	Y	U

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear; Y, yes.
* Study was stopped early based on lack of efficacy

Study		Yamada et al, 2015 [81]	Yamaguchi et al, 2021 [62]	Yoon et al, 2016 [56]	Zhang et al, 2021 [84]
Cochrane Risk of Bias Tool Assessment	Random sequence generation	LR	LR	UR	LR
	Allocation concealment	HR	LR	UR	LR
	Blinding – patients and conductors	HR	LR	LR	HR
	Blinding – outcome assessors	HR	LR	LR	HR
	Complete outcome data	HR	HR	HR	LR
	Selective outcome reporting	LR	LR	LR	HR
Adequately powered		Y	Y	N	Y
Reported funding sources		Y	Y	Y	Y
Industry funded		Y	Y	Y	Y

Abbreviations: HR, high risk; Int, intermediate; LR, low risk; N, no; U, unclear; Y, yes.

Appendix 7: Strength of Evidence Assessment

Number of Studies and Design	Aggregate Risk of Bias	Inconsistency	Indirectness	Imprecision	Other[£]	SOE Grade
First line - Doublet/Triplet Chemotherapy, Survival						
4 SR, 5 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
First line - Doublet/Triplet Chemotherapy, Adverse Events						
3 SR, 3 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
First line – Fluoropyrimidine, Survival						
1 SR[€]	Not serious	NA	NA	NA	NA	High
First line – Fluoropyrimidine, Adverse Events						
1 SR[€]	Not serious	NA	NA	NA	NA	High
Second plus line – Doublet/Triplet Chemotherapy, Survival						
1 SR[€]	Not serious	NA	NA	NA	NA	High
Second plus line – Doublet/Triplet Chemotherapy, Adverse Events						
1 SR[€]	Not serious	NA	NA	NA	NA	High
Second plus line – Taxane monotherapy, Survival						
2 SR, 2 RCT	Serious	Serious	Not serious	Not serious	None	Low
Second plus line – Taxane monotherapy, Adverse Events						
1 SR, 2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – Fluoropyrimidine Monotherapy, Survival						
1 RCT[€]	Serious	NA	NA	NA	NA	Moderate
Second plus line – Fluoropyrimidine Monotherapy, Adverse Events						
1 RCT[€]	Serious	NA	NA	NA	NA	Moderate
Second plus line – Irinotecan Monotherapy, Survival						
2 SR	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – Irinotecan Monotherapy, Adverse Events						
1 SR[€]	Not serious	NA	NA	NA	NA	High
Second plus line – Trifluride + tipiracil, Survival						
2 RCT	Not serious	NA	NA	NA	Confounding[§]	Moderate
Second plus line – Trifluride + tipiracil, Adverse Events						
2 RCT	Not serious	NA	NA	NA	Confounding[§]	Moderate
First line – HER2 targeted, Survival						
2 RCT	Serious	Not serious	Not serious	Not serious	Confounding[§]	Low
First line – HER2 targeted, Adverse Events						
2 RCT	Serious	Not serious	Not serious	Not serious	Confounding[§]	Low
Second plus line – HER2 targeted, Survival						
3 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – HER2 targeted, Adverse Events						
3 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Mixed Line – HER2 targeted, Survival						
2 SR	Not serious	Not serious	Serious	Not serious	None	Moderate
Mixed Line – HER2 targeted, Adverse Events						
3 SR	Not serious	Not serious	Serious	Not serious	None	Moderate
First line – VEGFR2 Targeted, Survival						
1 SR, 2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
First line – VEGFR2 Targeted, Adverse Events						
2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – VEGFR2 Targeted, Survival						
1 SR, 2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – VEGFR2 Targeted, Adverse Events						
3 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Mixed Line – VEGFR2 Targeted, Survival						
1 RCT[€]	Serious	NA	NA	NA	None	Moderate
Mixed Line – VEGFR2 Targeted, Adverse Events						
4 SR, 1 RCT	Serious	Not serious	Serious	Not serious	None	Low
Mixed Line – MET Inhibitor, Survival						

Number of Studies and Design	Aggregate Risk of Bias	Inconsistency	Indirectness	Imprecision	Other[£]	SOE Grade
1 SR[€]	Not serious	NA	NA	NA	NA	Moderate
Mixed Line – MET Inhibitor, Adverse Events						
3 SR	Not serious	Not serious	Serious	Not serious	None	Moderate
Second plus line – mTOR and Akt Targeted, Survival						
2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – mTOR and Akt Targeted, Adverse Events						
2 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line – PARP Inhibitor, Survival						
1 RCT[€]	Serious	NA	NA	NA	NA	Moderate
Second plus line – PARP Inhibitor, Adverse Events						
1 RCT[€]	Serious	NA	NA	NA	NA	Moderate
First line – PD-L1 Targeted, Survival						
3 RCT	Serious	Not serious	Not serious	Not serious	None	Moderate
First line – PD-L1 Targeted, Adverse Events						
3 RCT	Not serious	Not serious	Not serious	Not serious	None	Moderate
Second plus line - PD-L1 Targeted, Survival						
1 SR, 3 RCT	Serious	Not serious	Not serious	Not serious	Confounding[Ω]	Low
Second plus line - PD-L1 Targeted, Adverse Events						
1 SR, 3 RCT	Not serious	Not serious	Not serious	Not serious	Confounding[Ω]	Moderate
S-1 Monotherapy, Survival						
1 SR[€]	Not serious	NA	NA	NA	NA	High
S-1 Monotherapy, Adverse Events						
1 RCT[€]	Very Serious	NA	NA	NA	NA	Low
S-1 Regimens, Survival						
1 SR, 8 RCT	Serious	Serious	Not serious	Not serious	None	Low
S-1 Regimens, Adverse Events						
8 RCT	Very serious	Not serious	Not serious	Not serious	None	Low

Abbreviations: NA, not applicable; RCT, randomized controlled trial; SOE, strength of evidence; SR, systematic review.

£ Other category includes assessment for detection of publication bias, large effect, and confounding.

€ Strength of evidence based on 1 study, SOE is based solely on quality assessment of study.

§ Downgraded for confounding as the planned post-hoc analysis included a subgroup of the original patient cohort.

Ω Downgraded for confounding as the identified SR included short-term results of the ATTRACTION-2 trial with longer follow-up data reported in the primary literature. This leads to a potential for an overestimate of effect.

Appendix 8: Data Tables of included Systematic Reviews and Primary Literature

FIRST-LINE CHEMOTHERAPY

Doublet and Triplet Chemotherapy Regimens

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Huang et al, 2016 [2]	• First line • Oxaliplatin-based regimen vs. cisplatin-based regimen	• N=5 • n=2046 • Doublet regimens, N=2 • Triplet regimens, N=4 • HER2 status NR	April 2016	Overall Survival • Oxa-based vs. cis-based: HR, 0.91; 95% CI, 0.82-1.01; p=0.07 Progression-free survival • Oxa-based vs. cis-based: HR, 0.92; 95% CI, 0.84-1.01; p=0.09	Overall Response Rate • Oxa-based vs. cis-based: OR, 1.17; 95% CI, 0.98-1.40; p=0.08	Oxaliplatin-based regimen resulted in decreased risk of • Neutropenia: OR, 0.63; 95% CI, 0.40-0.99; p=0.04 • Anemia: OR, 0.50; 95% CI, 0.41-0.61; p<0.0001 • Nausea: OR, 0.65; 95% CI, 0.50-0.86; p=0.003 • Stomatitis: OR, 0.79; 95% CI, 0.66-0.96; p=0.02 • Thromboembolism: OR, 0.42; 95% CI, 0.28-0.64; p<0.0001 Oxaliplatin-based regimen resulted in increased risk of • Neurosensory toxicity: OR, 8.68; 95% CI, 5.28-14.27; p<0.0001 • Thrombocytopenia: OR, 1.29; 95% CI, 1.04-1.61; p=0.02

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Petrioli et al, 2016 [41]	• First line • Docetaxel-based regimens vs. epirubicin-based regimens • Docetaxel-based: docetaxel (D) + 5FU; docetaxel (D) + cisplatin (C) + 5FU; docetaxel (D) + oxaliplatin (Ox) + 5FU • Epirubicin-based: epirubicin (E) + cisplatin (C) + 5FU; epirubicin (E) + cisplatin (C) + capecitabine (Cb); epirubicin (E) + oxaliplatin (Ox) + capecitabine (Cb)	• N=7 • n=553 • E+C+5FU, N=5 • E+C+Cp, N=1 • E+Oxa+Cp, N=1 • D+5FU, N=2 • D+C+5FU, N=4 • D+Oxa+5FU, N=1 • HER2 status NR	Feb 2016		Response Rate • EPI vs. D: RR, 1.08; 95% CI, 0.85-1.37; p=0.52 Disease Control Rate • EPI vs. D: RR, 0.90; 95% CI, 0.75-1.08; p=0.27	• No significant differences in toxicities Events with non-sig decreased risk with E-based • Neutropenia • Anemia • Fatigue • Asthenia • Diarrhea • Paresthesia Events with non-sig decreased risk with D-based • Leukopenia • Thrombocytopenia • Anorexia • Nausea • Stomatitis • Hand and foot syndrome • Neutropenic fever
ter Veer et al, 2016 [1]	• First line • Compared fluoropyrimidine (F), platinum (cisplatin [C] and oxaliplatin [Ox]), taxane (T), anthracycline (A), irinotecan (I), and methotrexate (M) regimens	• N=65 • n=13356 • Network meta-analysis, N=53 • HER2 status NR	June 2015	F-doublets show increased efficacy over C-doublets Overall Survival • FI vs. CF: HR, 0.85; 95% CI, 0.71-0.99 • FOx vs. CF: HR, 0.83; 95% CI, 0.71-0.98 Progression-free survival		Increased grade 3/4 toxicity for: • CF vs. F-doublets • ACF vs. FI • TCF vs. CF • FOxT vs. FOx

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
				• FOx vs. CF: HR, 0.82; 95% CI, 0.66-0.99 A-triplets and TCF triplets showed no benefit over F-doublets FOxT triplet showed increased PFS over F-doublets • FOxT vs. FT: HR, 0.61; 95% CI, 0.38-0.99 • FOxT vs. FI: HR, 0.62; 95% CI, 0.38-0.99 • FOxT vs. FOx: HR, 0.67; 95% CI, 0.44-0.99		
Xu et al, 2015 [42]	• First line • Capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil/leucovorin + oxaliplatin (FOLFOX)	• N=26 • n=1585 • HER2 status NR	June 2014		Overall Response Rate XELOX vs. FOLFOXs: OR, 1.18; 95% CI, 1.00-1.41; p=0.057	Significantly lower risk of following adverse events with XELOX when compared with FOLFOX • Alopecia: OR, 0.50; 95% CI, 0.31-0.83; p=0.008 Significantly higher risk of following adverse events with XELOX when compared with FOLFOX • Hand-foot syndrome: OR, 2.84; 95% CI, 2.19-3.69; p<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Chen et al, 2018 [44] ML17032 trial	• First line • Capecitabine + cisplatin (XP) vs. 5-FU + cisplatin (FP)	• Phase III • XP, n=62 • FP, n=64 • F/U: NR • HER2 status: NR	Progression-free survival • XP: median PFS, 7.2m; 95% CI, 5.2-9.5m • FP: median PFS, 4.5m; 95% CI, 3.5-6.8m • p=0.0339 • HR, 0.52; 95% CI, 0.32-0.83; p=0.0063	Time to Treatment Failure • XP: median TTF, 4.0m; 95% CI, 3.1-4.4m • FP: median TTF, 2.7m; 95% CI, 2.3-3.2m • p=0.0136 • HR, 0.54; 95% CI, 0.35-0.84; p=0.0061	No significant difference in rate of adverse events
Lu et al, 2018 [45]	• First line • Paclitaxel + capecitabine + capecitabine maintenance (PACX) vs. cisplatin + capecitabine (XP)	• Phase III • PACX, n=160 • XP, n=160 • F/U: median 31.4 months • HER2 status: not tested	Overall Survival • PACX: median OS, 12.5m; 95% CI, 11.5-14.5m • XP: median OS, 11.8m; 95% CI, 10.0-13.7m • HR, 0.878; 95% CI, 0.685-1.125; p=0.30 Progression-free survival • PACX: median PFS, 5.0m; 95% CI, 4.3-6.3m • XP: median PFS, 5.3m; 95% CI, 4.7-5.8	Overall Response Rate • PACX: 43.1% • XP: 28.8% • p=0.012 • OR, 1.9; 95% CI, 1.2-3.3; p=0.01	No significant difference in rate of reported grade 3/4 adverse event • PACX: 34.2% • XP: 40.1% • p=0.28 Significantly lower rate of following grade 3/4 events in PACX vs. XP • Anemia: 1.9% vs. 6.8%; p=0.03 • Thrombocytopenia: 0.6% vs. 4.8%; p=0.02 • GI disorders: 5.1% vs. 12.2%; p=0.03 • Nausea: 1.9% vs. 8.2%; p=0.01 • Vomiting: 2.5% vs. 9.5%; p=0.01

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
			• HR, 0.906; 95% CI, 0.706-1.164; p=0.44		
Van Cutsem et al, 2015 [46]	• First line • Docetaxel + oxaliplatin (TE) vs. TE + infused 5-FU (TEF) vs. docetaxel + oxaliplatin + capecitabine (TEX)	• Phase II • TE, n=64 • TEF, n=79 • TEX, n=63 • F/U: NR • HER2 status: NR	Overall Survival • TEF: median OS, 14.59m; 95% CI, 11.70-21.78m • TE: median OS, 8.97m; 95% CI, 7.79-10.87m • TEX: median OS, 11.30m; 95% CI, 8.08-14.03m • p>0.05 Progression-free survival • TEF: median PFS, 7.66m; 95% CI, 6.97-9.40m • TE: median PFS, 4.50m; 95% CI, 3.68-5.32 • TEX: median PFS, 5.55m; 95% CI, 4.30-6.37m • p>0.05	Overall Response Rate • TEF: 46.6%; 95% CI, 35.9-57.5% • TE: 23.1%; 95% CI, 14.3-34.0% • TEX: 25.6%; 95% CI, 16.6-36.4%	Frequency of grade 3/4 adverse events • TEF: 61% • TE: 77% • TEX: 67%
Nakajima et al, 2020 [47] JCOG1108/ WJOG7312G trial	• First line • 5-FU + leucovorin + paclitaxel (FLTAX) vs. 5-FU + leucovorin (5-FU/LV)	• Phase II/III • FLTAX, n=50 • 5-FU/LV, n=51 • F/U: median 6.4m • HER2 status: NR	Progression-free survival • FLTAX: median PFS, 5.4m; 95% CI, 2.6-6.9m • 5-FU/LV: median PFS, 1.9m; 95% CI, 1.5-3.5		Frequency of grade 3/4 adverse events • FLTAX: 77.1% • 5-FU/LV: 78.4%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
			• HR, 0.64; 95% CI, 0.43-0.96; p=0.029		
Ni et al, 2021 [85]	• First line • Capecitabine + oxaliplatin (XELOX) vs. capecitabine + docetaxel (DX)	• Phase 2 • XELOX, n=39 • DX, n=44 • Median F/U: 10.2m • HER2 status NR	Overall Survival • XELOX: median OS, 8.8m • DX: median OS, 9.0m • HR, 0.99; 95% CI, 0.60-1.65; p=0.973 Progression Free Survival • XELOX: median PFS, 6.1m • DX: median PFS, 4.1m HR, 0.78; 95% CI, 0.46-1.31; p=0.346	Complete Response • XELOX: 3.0% • DX: 0% • p=1.00 Partial Response • XELOX: 21.2% • DX: 24.2% • p=0.769 Stable Disease • XELOX: 66.7% • DX: 51.5% p=0.211	No significant difference in rates of adverse events Grade 3/4 adverse events in XELOX vs DX Anemia: 7.7% vs. 9.1% Leukopenia: 0% vs. 2.3% Neutropenia: 0% vs. 4.5% Thrombocytopenia: 5.1% vs. 0% Peripheral neuropathy: 10.3% vs. 0% Liver function damage: 2.6% vs. 2.3%

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio; m, month; NR, not reported; OR, odds ratio; PFS, progression-free survival; TTF, time to treatment failure

Fluoropyrimidine Monotherapy

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Zhu et al, 2016 [48]	• First line • 5FU vs. S-1 vs. capecitabine • HER2 status NR	• N=12 • n=4026 • 5FU vs. cap, N=4 • 5FU vs. S-1, N=6 • S-1 vs. cap, N=2	Not reported	Overall Survival • Improved OS for capecitabine and S-1 when compared with 5FU • S-1 vs. 5FU: HR, 0.89; 95% CI, 0.80-0.98; p=0.02	Overall Response Rate • No significant differences • S-1 vs. 5FU: OR, 1.58; 95% CI, 0.87-2.88; p=0.13 • Cap vs. 5FU: OR, 1.00; 95% CI, 0.57-1.77; p=0.99	No significant differences in rates of grade 3 or 4 adverse events

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
				• Cap vs. 5FU: HR, 0.85; 95% CI, 0.78-0.94; p=0.002 • S-1 vs. cap: HR, 1.09; 95% CI, 0.80-1.48; p=0.58	• S-1 vs. cap: OR, 0.92; 95% CI, 0.50-1.70; p=0.80	

Abbreviations: 5FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; NR, not reported; OR, odds ratio

SECOND- AND THIRD-LINE CHEMOTHERAPY

Doublet and Triplet Chemotherapy Regimens

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Yang et al, 2018 [49]	• Second line • Irinotecan doublet vs. irinotecan monotherapy	• N=7 • n=905 • HER2 status: NR	NR	• Irinotecan-containing doublet improved PFS compared with irinotecan monotherapy (HR, 0.82; 95% CI, 0.70-0.95)	• No difference in OS or overall response rate or disease control rates	• Increased ≥Grade 3 neutropenia (RR, 1.23; 95% CI, 1.01-1.51) and anemia with irinotecan-containing doublet (RR, 2.00; 95% CI, 1.37-2.91)

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, relative risk

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Al-Batran et al, 2019 [43] FLOT4 trial	• First and second line	• Phase 2/3 • ECF/ECX, n=326 • FLOT, n=320	Overall Survival		Significantly higher risk of following grade 3/4 events in ECF/ECX group vs. FLOT group

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
	• Epirubicin + cisplatin + fluorouracil/ capectabine (ECF/ECX) vs. fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT)	• F/U: 6 years • HER2 status: NR	• ECF/ECX: median OS, 35m; 95% CI, 27.35-46.26m • FLOT: median OS, 50m; 95% CI, 38.33 – not reached • HR, 0.77; 95% CI, 0.63-0.94; p=0.012		• Diarrhea: 4% vs. 10%; p=0.0016 • Vomiting: 8% vs. 2%; p<0.001 • Nausea: 16% vs. 7%; p<0.001 • Anemia: 6% vs. 3%; p=0.036 Significantly lower risk of following grade 3/4 events in ECF/ECX group vs. FLOT group • Neutropenia: 39% vs. 51%; p=0.0017 • Peripheral neuropathy: 2% vs. 7%; p=0.0018 • Infections: 9% vs. 18%; p<0.001

Abbreviation: CI, confidence interval; m, month; OS, overall survival

Taxane Monotherapy

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Janowitz et al, 2016 [16]	• Second line • Chemotherapy (CT; docetaxel and/or irinotecan) vs. best supportive care (BSC) • HER2 status NR	• N=3 • n=410	Aug 2015	Overall Survival • CT plus BSC vs. BSC: HR, 0.63; 95% CI, 0.51-0.77; p<0.0001 • Docetaxel + BSC vs. BSC: HR, 0.71; 95% CI, 0.56-0.89; p=0.003	
ter Veer et al, 2016 [17]	• Second and third line • Compared second and third line regimens of CT monotherapy and	• N=28 • n=4810 • HER2 status: positive in one	Jan 2016	Overall Survival • Taxane vs. BSC: HR, 0.71; 95% CI, 0.56-0.90 • Irinotecan vs. BSC: HR, 0.55; 95% CI, 0.40-0.77	Relative Risks for grade 3/4 adverse events showing significant difference between regimens • Neutropenia ○ Irinotecan vs. taxane: RR, 1.40; 95% CI, 1.04-1.88; p=0.03

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
	CT + targeted agents	lapatinib study		• Taxane vs. irinotecan: HR, 0.94; 95% CI, 0.78-1.13 • Doublet vs. monotherapy: HR, 1.00; 95% CI, 0.90-1.12 • Ramucirumab vs. BSC: HR, 0.78; 95% CI, 0.61-1.00 • Ram+Taxane vs. taxane mono: HR, 0.81; 95% CI, 0.68-0.96	• Diarrhea ○ Irinotecan vs. taxane: RR, 5.06; 95% CI, 1.85-13.87; p=0.002 • Neuropathy ○ Irinotecan vs. taxane: RR, 0.06; 95% CI, 0.00-0.99; p=0.05

Abbreviations: CI, confidence interval; HR, hazard ratio

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Fushida et al, 2016 [50]	• Second or third line • Paclitaxel (PTX) vs. paclitaxel + valproic acid (VPA) • HER2 status NR	• Phase II • PTX, n=33 • PTX + VPA, n=33 • F/U not reported	Overall Survival • PTX: median OS, 9.8m • PTX + VPA: median OS, 8.7m • HR, 1.19; 95% CI, 0.702-2.026; p=0.51 Progression-free survival • PTX: median PFS, 4.5m • PTX + VPA: median PFS, 3.0m • HR, 1.29; 95% CI, 0.753-2.211; p=0.35		Overall >grade 2 adverse events: • n=6, 9.5% PTX • Neutropenia: n=1 • Pneumonia: n=1 • Liver injury: n=1 • Brain infarction: n=1 • Ruptures abdominal aortic aneurysm: n=1 PTX + VPA • Pneumonia: n=1
Kang et al, 2018 [51] DREAM trial	• Second line • Oral paclitaxel (DHP107) vs. iv paclitaxel • HER2 status NR	• Phase III • DHP107, n=118 • IV PTX, n=118	Overall Survival • DHP107: median OS, 9.7m; 95% CI, 7.1-11.5m	Overall Response Rate • DHP107: 17.8% • PTX: 25.4% • p=0.824	Serious Adverse Events • DHP107: 39% • PTX: 41% • p>0.05

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
		• F/U: 27m	• PTX: median 8.9m; 95% CI, 7.1-12.2m • HR, 1.04; 95% CI, 0.76-1.41; p=0.824 Progression-free survival • DHP107: median PFS, 3.0m; 95% CI, 1.7-4.0m • PTX: median PFS, 2.6m; 95% CI, 1.8-2.8m • HR, 0.85; 95% CI, 0.64-1.13		Grade 3/4 Adverse Events • DHP107: 68.6% • PTX: 83.9%

Abbreviations: CI, confidence interval; HR, hazard ratio m, month; OS, overall survival

Fluoropyrimidine Monotherapy

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Nishina et al, 2016 [52]	• Second line • Paclitaxel (PTX) vs. 5-fluorouracil (5FU) • HER2 status NR	• Phase II • PTX, n=51 • 5FU, n=49 • F/U: NR	Median Survival Time • 5FU: 7.7m; 95% CI, 6.7-9.0m • PTX: 7.7m; 95% CI, 6.0-9.7m • HR, 0.89; 95% CI, 0.57-1.38 Progression-free survival • 5FU: median PFS, 2.4m; 95% CI, 1.7-3.6m • PTX: median PFS, 3.7m; 95% CI, 2.6-5.3m • HR, 0.58; 95% CI, 0.38-0.88	Serious Adverse Events • 5FU: 6.1% • PTX: 2.0% • p not reported

Abbreviations: CI, confidence interval; HR, hazard ratio m, month; PFS, progression-free survival

Irinotecan Monotherapy

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Janowitz et al, 2016 [16]	• Second line • Chemotherapy (CT; docetaxel and/or irinotecan) vs. best supportive care (BSC) • HER2 status NR	• N=3 • n=410	Aug 2015	Overall Survival • CT plus BSC vs. BSC: HR, 0.63; 95% CI, 0.51-0.77; p<0.0001 • Irinotecan + BSC vs. BSC: HR, 0.49; 95% CI, 0.36-0.67; p<0.001	
ter Veer et al, 2016 [17]	• Second and third line • Compared second- and third-line regimens of CT monotherapy and CT + targeted agents	• N=28 • n=4810 • HER2 status: positive in one lapatinib study	Jan 2016	Overall Survival • Taxane vs. BSC: HR, 0.71; 95% CI, 0.56-0.90 • Irinotecan vs. BSC: HR, 0.55; 95% CI, 0.40-0.77 • Taxane vs. irinotecan: HR, 0.94; 95% CI, 0.78-1.13 • Doublet vs. monotherapy: HR, 1.00; 95% CI, 0.90-1.12 • Ramucirumab vs. BSC: HR, 0.78; 95% CI, 0.61-1.00 • Ramucirumab+Taxane vs. taxane monotherapy: HR, 0.81; 95% CI, 0.68-0.96	Relative Risks for grade 3/4 adverse events showing significant difference between regimens • Neutropenia ○ Irinotecan vs. taxane: RR, 1.40; 95% CI, 1.04-1.88; p=0.03 • Diarrhea ○ Irinotecan vs. taxane: RR, 5.06; 95% CI, 1.85-13.87; p=0.002 • Neuropathy ○ Irinotecan vs. taxane: RR, 0.06; 95% CI, 0.00-0.99; p=0.05

Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported; RR, relative risk

Trifluridine plus Tipiracil Regimen

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Shitara et al, 2018 [18]	• Third line	• Phase III • trifluride-tipiracil, n=337	Overall Survival	Objective Response Rate • trifluride-tipiracil : 4%; 95% CI, 2-8%	Frequency of grade 3/4 adverse events

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
TAGS trial	• Trifluride + tipiracil vs. placebo	• Placebo, n=170 • F/U: median 10.7m • HER2 status: • TT, n=67 (20%) pos • Placebo, n=27 (16%) pos	• trifluride-tipiracil : median OS, 5.7m; 95% CI, 4.8-6.2m • Placebo: median OS, 3.6m; 95% CI, 3.1-4.1 • HR, 0.69; 95% CI, 0.56-0.85; p=0.0006 Factors predicting OS • HER2 status, p=0.016 Progression-free survival • trifluride-tipiracil : median PFS, 2.0m; 95% CI, 1.9-2.3m • Placebo: median PFS, 1.8m; 95% CI, 1.7-1.9m • HR, 0.57; 95% CI, 0.47-0.70; p<0.0001	• Placebo: 2%; 95% CI, 1-6% • p=0.28 Disease Control Rate • trifluride-tipiracil : 44%; 95% CI, 38-50% • Placebo: 14%; 95% CI, 9-21% • p<0.0001	• trifluride-tipiracil : 80% • Placebo: 58%
Mansoor et al, 2021 [53] TAGS trial	• Third line • Trifluride + tipiracil vs. placebo • Subgroup analysis for patients w/ gastric carcinoma (GC) and GEJ	• Phase III • GC, n=360 ○ trifluride-tipiracil , n=239 ○ Placebo, n=121 • GEJ, n=145 ○ trifluride-tipiracil , n=98 ○ Placebo, n=47 • F/U: median 10.7m • HER2 status: NR	Overall Survival GC • trifluride-tipiracil : median OS, 6.0m • Placebo: median OS, 3.6m • HR, 0.67; 95% CI, 0.52-0.87; p NR GEJ • trifluride-tipiracil : median OS, 4.8m • Placebo: median OS, 3.5m • HR, 0.75; 95% CI, 0.50-1.11; p NR		Frequency of Grade ≥3 Adverse Events GC • trifluride-tipiracil : 81% • Placebo: 58% GEJ • trifluride-tipiracil : 77% • Placebo: 59%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
			Progression Free Survival GC • trifluride-tipiracil : median PFS, 2.1m • Placebo: median PFS, 1.8m • HR, 0.59; 95% CI, 0.46-0.75; p NR GEJ • trifluride-tipiracil : median PFS, 1.9m • Placebo: median PFS, 1.8m • HR, 0.60; 95% CI, 0.41-0.88; p NR		

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio; m, month; NR, not reported; OS, overall survival; PFS, progression-free survival

TARGETED AGENTS

HER2 Targeted Agents in the First Line

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Tabernero et al, 2018 [54] JACOB trial	• First line • Pertuzumab + trastuzumab + CT (PTCT) vs. placebo + trastuzumab + CT (PBTCT)	• Phase III • PTCT, n=384 • PBTCT, n=389 • F/U: median 25m • HER2 status: positive	Overall Survival • PTCT: median OS, 17.5m; 95% CI, 16.2-19.3m • PBTCT: median OS, 14.2m; 95% CI, 12.9-15.5m • HR, 0.84; 95% CI, 0.71-1.00; p=0.057 Progression-free survival	Frequency of Adverse Events • Serious Adverse Events ○ PTCT: 45% ○ PBTCT: 39% • Grade 3-5 ○ PTCR: 80% ○ PBTCT: 73%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
			• PTCT: median PFS, 8.5m; 95% CI, 8.2-9.7m • PBTCT: median PFS, 7.0m; 95% CI, 6.4-8.2m • HR, 0.73; 95% CI, 0.62-0.86; p=0.0001	
Shitara et al, 2020 [55] JACOB Subgroup Analysis	• First line • Pertuzumab + trastuzumab + CT (PTCT) vs. placebo + trastuzumab + CT (PBTCT) • Japanese patients	• Phase III • PTCT, n=40 • PBTCT, n=40 • F/U: median 33m • HER2 status: positive	Overall Survival • PTCT: median OS, 22.0m; 95% CI, 13.8-not evaluable • PBTCT: median OS, 15.6m; 95% CI, 9.7-19.2 • HR, 0.64; 95% CI, 0.37-1.10 Progression-free survival • PTCT: median PFS, 12.4m; 95% CI, 6.1-14.1m • PBTCT: median PFS, 6.3m; 95% CI, 4.3-8.1m • HR, 0.50; 95% CI, 0.30-0.82	Frequency of Grade ≥3 Adverse Events • PTCT: 95.0% • PBTCT: 75.0%

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio; m, month; OS, overall survival

HER2 Targeted Agents in the Second Line and Beyond

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Thuss-Patience et al, 2017 [58] GATSBY trial	• Second line • Trastuzumab (T) vs. taxane	• Phase II/III • T weekly (Tw), n=228 • Taxane, n=117 • F/U: median 17.5m • HER2 status: positive	Overall Survival • Taxane: median OS, 8.6m; 95% CI, 7.1-11.2m • T: median OS, 7.9m; 95% CI, 6.7-9.5m • HR, 1.15; 95% CI, 0.87-1.51; p=0.86	Frequency of Grade 3/4 Adverse Events • Taxane: 70% • T: 60%
Makiyama et al, 2020 [59]	• Second line • Cancer refractory to first-line CT	• Phase II • Paclitaxel, n=46 • PT, n=45	Overall Survival • Paclitaxel: median OS, 10.0m; 95% CI, 7.6-13.1m	Incidence Rates of Grade ≥3 Adverse Events • Leukopenia

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
T-ACT Study	with trastuzumab + fluoropyrimidine and platinum CT • Paclitaxel vs. paclitaxel + trastuzumab (PT)	• F/U: median 10m • HER2 status: positive	• PT: median OS, 10.2m; 95% CI, 7.9-12.8m • HR, 1.23; 95% CI, 0.76-1.99; p=0.20 Progression-free survival • Paclitaxel: median PFS, 3.2m; 95% CI, 2.9-3.5m • PT: median PFS, 3.7m; 95% CI, 2.8-4.5m • HR, 0.91; 80%CI, 0.67-1.22; p=0.33	○ Paclitaxel: 17.8% ○ PT: 28.9% • Neutropenia ○ Paclitaxel: 26.7% ○ PT: 33.3% • Anemia ○ Paclitaxel: 24.4% ○ PT: 31.1%
Shitara et al, 2020 [60] DESTINY-Gastric01 Study	• Third line • Cancer refractory to 2 previous regimens, including fluoropyrimidine, platinum agent, and trastuzumab (or approved biosimilar agent) • Trastuzumab deruxtecan (TD) vs. CT (irinotecan or paclitaxel)	• Phase II • TD, n=125 • CT, n=62 • F/U: median for TD, 4.6m • HER2 status: positive	Overall Survival • TD: median OS, 12.5m • CT: median OS, 8.4m • HR, 0.59; 95% CI, 0.39-0.88; p=0.01 Progression-free survival • TD: median PFS, 5.6m; 95% CI, 4.3-6.9m • CT: median PFS, 3.5m; 95% CI, 2.0-4.3m • HR, 0.47; 95% CI, 0.31-0.71; p NR	Frequency of Grade 3 Adverse Events • Neutrophil count decrease ○ TD: 38% ○ CT: 16% • Decreased appetite ○ TD: 17% ○ CT: 13% • Anemia ○ TD: 38% ○ CT: 21% • Platelet count decrease ○ TD: 10% ○ CT: 2% • White cell count decrease ○ TD: 21% ○ CT: 8% Frequency of Grade 4 Adverse Events • Neutrophil count decrease ○ TD: 13% ○ CT: 8%

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio; m, month; OS, overall survival

HER2 Targeted Agents in a Mixed First through Third-Line Setting

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Ciliberto et al, 2015 [6]	• First, second, and third line • Targeted therapy (TT) vs. conventional treatment (C)	• N=22 • n=7022 • Anti-angiogenic agents (AA), N=10 • HER2 targeted agents, N=3 • Anti-EGFR agents, N=4 • MET inhibitor, N=1 • mTOR inhibitor, N=1 • PARP inhibitor, N=1 • Hedgehog inhibitor, N=1 • HER2 status: reported in 3 studies	2014	Overall Survival • TT+C vs. C: HR, 0.82; 95% CI, 0.74-0.91; p<0.001 • C+AA vs. C: HR, 0.76; 95% CI, 0.66-0.88; p=0.027 • C+anti-EGFR vs. C: HR, 1.08; 95% CI, 0.85-1.37; p=0.543 • C+anti-HER2 vs. C: HR, 0.82; 95% CI, 0.72-0.94; p=0.004 Progression-free survival • C+TT vs. C: HR, 0.76; 95% CI, 0.66-0.88; p<0.001 • C+AA vs. C: HR, 0.70; 95% CI, 0.57-0.85; p<0.001 • C+anti-EGFR vs. C: HR, 1.12; 95% CI, 0.98-1.27; p=0.639 • C+anti-HER2 vs. C: HR, 0.78; 95% CI, 0.65-0.94; p=0.009	Significantly increased risk of following grade 3/4 events in TT vs. C groups • Diarrhea: OR, 1.622; 95% CI, 1.062-2.477; p=0.025 • Rash: OR, 3.455; 95% CI, 1.449-8.234; p=0.005
Wang et al, 2017 [66]	• First and second line • Risk of adverse events with targeted therapies	• N=9 • n=4934 • HER2 status: NR	Dec 2015		Incidence Rates • Severe AE: 72.5%; 95% CI, 66.4-77.8% • Fatal AE: 2.2%; 95% CI, 1.6-2.9% Relative Risk • Targeted therapy vs. control • Severe AE: RR, 1.12; 95% CI, 1.02-1.24; p=0.02

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
					• Fatal AE: RR, 0.97; 95% CI, 0.65-1.45; p=0.88
Xie et al, 2017 [65]	• Line not specified • Targeted agents (TA) plus CT vs. placebo or other TA+CT	• N=23 • n=8405	Oct 2016	1y Overall Survival • Placebo vs. trastuzumab: HR, 1.30; 95% CI, 1.01-1.67 • Placebo vs. ramucirumab: HR, 1.36; 95% CI, 1.21-1.53 2y Overall Survival (NB: TA and control order flipped based on comparison) • Bevacizumab vs. placebo: HR, 0.85; 95% CI, 0.77-0.95 • Placebo vs. ramucirumab: HR, 1.26; 95% CI, 1.15-1.37 • Placebo vs. trastuzumab: HR, 1.32; 95% CI, 1.15-1.52 3y Overall Survival • Placebo vs. trastuzumab: HR, 1.36; 95% CI, 1.11-1.65	Adverse Events with significant difference between regimens • Fatigue ○ Ramucirumab vs. placebo: OR, 1.90; 95% CI, 1.02-2.94 • Neutropenia ○ Ramucirumab vs. placebo: OR, 2.89; 95% CI, 2.08-4.22 ○ Ramucirumab vs. bevacizumab: OR, 3.10; 95% CI, 1.60-6.75 ○ Ramucirumab vs. trastuzumab: OR, 2.92; 95% CI, 1.31-5.93 • Diarrhea ○ Ramucirumab vs. placebo: OR, 2.39; 95% CI, 1.22-4.76 ○ Trastuzumab vs. placebo: OR, 2.64; 95% CI, 1.02-7.24

Abbreviations: AE, adverse events; CI, confidence interval; HR, hazard ratio

VEGFR2 Targeted Agents in the First-Line

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Yoon et al, 2016 [56]	• First line • FOLFOX6 + ramucirumab vs. FOLFOX6 + placebo	• Phase II • FOLFOX6+RAM, n=84 • FOLFOX6+PBO, n=84 • F/U: NR • HER2 status: NR	Overall Survival • FOLFOX6+RAM: median OS, 11.7m • FOLFOX6+PBO: median OS, 11.5m • HR, 1.08; 95% CI, 0.73-1.58; p=0.712	Objective Response Rate • FOLFOX+RAM: 45.2%; 95% CI, 34.3-56.5% • FOLFOX6+PBO: 46.4%; 95% CI, 35.5-57.6%	No significant difference in grade 3 or higher adverse events

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
			Progression-free survival • FOLFOX6+RAM: median PFS, 6.4m • FOLFOX6+PBO: median PFS, 6.7m • HR, 0.98; 95% CI, 0.69-1.37; p=0.886	• p=0.830	
Li et al, 2020 [57]	• First line • Tegafur + apatinib vs. apatinib	• Phase NR • Tegafur + apatinib, n=31 • Apatinib, n=31 • F/U: 1y	Progression-free survival • Tegafur + apatinib: median PFS, 8.1m • Apatinib: median PFS, 5.0m • p<0.05	Disease Control Rate • Tegafur + apatinib: 93.5% • Apatinib: 67.7% • p<0.001	Reported adverse events with significant rate difference • Nausea: TA, 83.9%; A, 54.8%; p<0.001 • Vomiting: TA, 61.3%; A, 29.0%; p<0.001 • Hemoglobin decrease: TA, 58.1%; A, 35.5%; p=0.002 • Hypertension: TA, 51.6%; A, 9.7%; p<0.001 • Leukopenia: TA, 90.3%; A, 77.4%; p=0.013 • Proteinuria: TA, 35.4%; A, 9.7%; p<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio m, month; PFS, progression-free survival

VEGFR2 Targeted Agents in the Second-Line and Beyond

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Wilke et al, 2014 [14] RAINBOW trial	• Second line • Ramucirumab + paclitaxel vs. placebo + paclitaxel	• Phase III • RAM+PTX, n=330 • PBO+PTX, n=335 • F/U: 7.9m	Overall Survival • RAM+PTX: median OS, 9.6m; 95% CI, 8.5-10.8 • PBO+PTX: median OS,	Objective Response Rate • RAM+PTX: 28%; 95% CI, 23-33% • PBO+PTX: 16%; 95% CI, 13-20% • p=0.0001	Prevalence of Grade 3 Adverse Events • RAM+PTX: 47% • PBO+PTX: 39% Prevalence of Grade 4 Adverse Events • RAM+PTX: 22%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
		• HER2 status: NR	7.4m; 95% CI, 6.3-8.4 • HR, 0.807; 95% CI, 0.678-0.962; p=0.017 Progression-free survival • RAM+PTX: median PFS, 4.4m; 95% CI, 4.2-5.3 • PBO+PTX: median PFS, 2.9m; 95% CI, 2.8-3.0 • HR, 0.635; 95% CI, 0.536-0.752; p<0.0001	Disease Control Rate • RAM+PTX: 80%; 95% CI, 75-84% • PBO+PTX: 64%; 95% CI, 58-69% • p<0.0001	• PBO+PTX: 8%
Al-Batran et al, 2016 [15] RAINBOW trial	• Second line • Ramucirumab + paclitaxel vs. placebo + paclitaxel	• Phase III • RAM+PTX, n=330 • PBO+PTX, n=335 • F/U: NR • HER2 status: NR			Quality of Life, based on EORTC QLQ-C30 scales Longer time before worsening of symptoms on RAM+PTX vs. PBO+PTX • Emotional functioning: HR, 0.642; 95% CI, 0.491-0.840 • Nausea and vomiting: HR, 0.746; 95% CI, 0.574-0.969 Shorter time before worsening of symptoms on RAM+PTX vs. PBO+PTX • Diarrhea: HR, 1.333; 95% CI, 1.007-1.764 Similar time for both groups • Global health status, physical functioning, role functioning, cognitive functioning, social

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
					functioning, fatigue, pain, dyspnea, insomnia, appetite loss, constipation, financial difficulties
Yamaguchi et al, 2021 [62] RAINBOW	• Second line • Ramucirumab + paclitaxel vs. placebo + paclitaxel	• Phase III • Japanese subgroup analysis • RAM+PTX, n=68 • PBO+PTX, n=72 • F/U: NR • HER2 status: NR			Quality of Life, based on EORTC QLQ-C30 scales Longer time to deterioration for QoL scales on RMA+PTX vs PBO+PTX • NB: all CIs cross 1, indicating no significant difference. • Global QoL: HR, 0.944; 95% CI, 0.598-1.487 • Physical function: HR, 0.683; 95% CI, 0.414-1.25 • Emotional functioning: HR, 0.653; 95% CI, 0.354-1.205 • Cognitive functioning: HR, 0.871; 95% CI, 0.528-1.437
Moehler et al, 2016 [61]	• Second or third line • Sunitinib + FOLFIRI (SFOLFIRI) vs. placebo + FOLFIRI (PFOLFIRI) • Sunitinib is a TKI inhibitor	• Phase II • SFOLFIRI, n=45 • PFOLFIRI, n=45 • F/U: 1y • HER2 status: NR	Overall Survival • SFOLFIRI: median OS, 10.4m • PFOLFIRI: median OS, 8.9m • HR, 0.82; 95% CI, 0.50-1.34; p=0.42 Progression-free survival • SFOLFIRI: median PFS, 3.5m • PFOLFIRI: median PFS, 3.3m • HR, 1.11; 95% CI, 0.70-1.74; p=0.66	No reported outcomes	Frequency of Most Common Grade 3-5 Adverse Events • Neutropenia ○ SFOLFIRI: 56% ○ PFOLFIRI: 20% • Leucopenia ○ SFOLFIRI: 27% ○ PFOLFIRI: 16% • Diarrhea ○ SFOLFIRI: 2% ○ PFOLFIRI: 13%

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio m, month; OS, overall survival

VEGFR2 Targeted Agents in a Mixed First-Line through Third-Line Setting

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Chen et al, 2018 [67]	• First and second line • Apatinib (A) vs. placebo (PCB)	• N=13 • n=1069 • HER2 status: NR	July 2017	No outcomes reported	Adverse Events with Significant Difference in Rate for A vs. PCB • Leukopenia, any grade: OR, 5.73; 95% CI, 2.90-11.32; p<0.0001 • Neutropenia, any grade: OR, 3.38; 95% CI, 1.57-7.29; p=0.002 • Thrombocytopenia, any grade: OR, 2.25; 95% CI, 1.30-3.90; p=0.004 • Diarrhea, any grade: OR, 2.88; 95% CI, 1.46-5.68; p=0.002 • Hypertension, any grade: OR, 10.76; 95% CI, 5.94-17.49; p<0.00001 • Proteinuria, any grade: OR, 4.55; 95% CI, 2.78-7.44; p<0.00001 • Hand-foot syndrome, any grade: OR, 5.15; 95% CI, 2.91-9.11; p<0.0001 • Fatigue, any grade: OR, 1.67; 95% CI, 1.01-2.76; p=0.04

Abbreviations: CI, confidence interval; OR, odds ratio

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Pavlakis et al, 2016 [68] INTEGRATE trial	• Second line • Regorafenib + BSC vs. placebo + BSC	• Phase II • REG, n=97 • PBO, n=50 • F/U: median 17.1m • HER2 status: n=2 positive	Overall Survival • REG: median OS, 5.8m; 95% CI, 4.4-6.8 • PBO: median OS, 4.5m; 95% CI, 3.4-5.2m	Frequency of grade 3-5 adverse events • REG: 67% • PBO: 52% Most common grade 3-5 AE

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
			• HR, 0.74; 95% CI, 0.51-1.08; p=0.147 Progression-free survival • REG: median PFS, 2.6m; 95% CI, 1.8-3.1 • PBO: median PFS, 0.9m; 95% CI, 0.9-0.9 • HR, 0.40; 95% CI, 0.28-0.59; p<0.001	• GI disorders ○ REG: 11% ○ PBO: 0% • Infections ○ REG: 6% ○ PBO: 2%

Abbreviations: CI, confidence interval; F/U, follow-up; GI, gastrointestinal; HR, hazard ratio m, month; OS, overall survival

MET Inhibitors in the First-Line

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Catenacci et al, 2017 [3] RILOMET-1	• First line • Rilotumumab + epirubicin + cisplatin + capecitabine (RECC) vs. placebo + epirubicin + cisplatin + capecitabine (PECC) • Rilotumumab is a MET inhibitor	• Phase III • RECC, n=304 • PECC, n=305 • F/U: median 7.7m • HER2 status: negative • MET status: positive	Overall Survival • RECC: median OS, 8.8m; 95% CI, 7.7-10.2m • PECC: median OS, 10.7m; 95% CI, 9.6-12.4m • HR, 1.34; 95% CI, 1.10-1.63; p=0.003	Study stopped early due to higher number of deaths in RECC group
Shah et al, 2017 [5] METGastric trial	• First line • Onartuzumab + FOLFOX6 (OnaFOLFOX6) vs. placebo + FOLFOX6 (PFOLFOX6)	• Phase III • OnaFOLFOX6, n=279 • PFOLFOX6, n=283 • F/U: 1y • HER2 status: negative • MET status: positive	Overall Survival • PFOLFOX6: median OS, 11.3m • OnaFOLFOX6: median OS, 11.0m • HR, 0.82; 95% CI, 0.59-1.15; p=0.24 Progression-free survival	Frequency of Adverse Events (AE) • Serious AE ○ PFOLFOX6: 32.5% ○ OnaFOLFOX6: 35.8% • AE leading to withdrawal ○ PFOLFOX6: 21.8% ○ OnaFOLFOX6: 31.2%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
	• Onartuzumab is a MET inhibitor • Enrollment stopped early based on lack of efficacy in a phase II study		• PFOLFOX6: median PFS, 6.8m • OnaFOLFOX6: median PFS, 6.7m HR, 0.90; 95% CI, 0.71-1.16; p=0.43	• Grade 3-5 AE ○ PFOLFOX6: 66.8% ○ OnaFOLFOX6: 68.8%

Abbreviations: CI, confidence interval; F/U, follow-up; GI, gastrointestinal; HR, hazard ratio m, month; OS, overall survival

MET Inhibitors in a Mixed First-Line through Third-Line Setting

Systematic Review

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Ciliberto et al, 2015 [6]	• First, second, and third line • Targeted therapy (TT) vs. conventional treatment (C)	• N=22 • n=7022 • Anti-angiogenic agents (AA), N=10 • HER2 targeted agents, N=3 • Anti-EGFR agents, N=5 • MET inhibitor, N=1 • mTOR inhibitor, N=1 • PARP inhibitor, N=1 • Hedgehog inhibitor, N=1 • HER2 status: reported in 3 studies	2014	Overall Survival • TT+C vs. C: HR, 0.82; 95% CI, 0.74-0.91; p<0.001 • C+AA vs. C: HR, 0.76; 95% CI, 0.66-0.88; p=0.027 • C+anti-EGFR vs. C: HR, 1.08; 95% CI, 0.85-1.37; p=0.543 • C+anti-HER2 vs. C: HR, 0.82; 95% CI, 0.72-0.94; p=0.004 Progression-free survival • C+TT vs. C: HR, 0.76; 95% CI, 0.66-0.88; p<0.001 • C+AA vs. C: HE, 0.70; 95% CI, 0.57-0.85; p<0.001 • C+anti-EGFR vs. C: HR, 1.12; 95% CI, 0.98-1.27; p=0.639 • C+anti-HER2 vs. C: HR, 0.78; 95% CI, 0.65-0.94; p=0.009	Significantly increased risk of following grade 3/4 events in TT vs. C groups • Diarrhea: OR, 1.622; 95% CI, 1.062-2.477; p=0.025 • Rash: OR, 3.455; 95% CI, 1.449-8.234; p=0.005

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes
Wang et al, 2017 [66]	• First and second line • Risk of adverse events with targeted therapies	• N=9 • n=4934 • HER2 status: NR	Dec 2015	No outcomes reported	Incidence Rates • Severe AE: 72.5%; 95% CI, 66.4-77.8% • Fatal AE: 2.2%; 95% CI, 1.6-2.9% Relative Risk • Targeted therapy vs. control • Severe AE: RR, 1.12; 95% CI, 1.02-1.24; p=0.02 • Fatal AE: RR, 0.97; 95% CI, 0.65-1.15; p=0.88
Xie et al, 2017 [65]	• Line not specified • Targeted agents (TA) plus CT vs. placebo or other TA+CT	• N=23 • n=8405	Oct 2016	1y Overall Survival • Placebo vs. trastuzumab: HR, 1.30; 95% CI, 1.01-1.67 • Placebo vs. ramucirumab: HR, 1.36; 95% CI, 1.21-1.53 2y Overall Survival (NB: TA and control order flipped based on comparison) • Bevacizumab vs. placebo: HR, 0.85; 95% CI, 0.77-0.95 • Placebo vs. ramucirumab: HR, 1.26; 95% CI, 1.15-1.37 • Placebo vs. trastuzumab: HR, 1.32; 95% CI, 1.15-1.52 3y Overall Survival • Placebo vs. trastuzumab: HR, 1.36; 95% CI, 1.11-1.65	AE with significant difference between regimens • Fatigue ○ Ramucirumab vs. placebo: OR, 1.90; 95% CI, 1.02-2.94 • Neutropenia ○ Ramucirumab vs. placebo: OR, 2.89; 95% CI, 2.08-4.22 ○ Ramucirumab vs. bevacizumab: OR, 3.10; 95% CI, 1.60-6.75 ○ Ramucirumab vs. trastuzumab: OR, 2.92; 95% CI, 1.31-5.93 • Diarrhea ○ Ramucirumab vs. placebo: OR, 2.39; 95% CI, 1.22-4.76 ○ Trastuzumab vs. placebo: OR, 2.64; 95% CI, 1.02-7.24

Abbreviations: AE, adverse events; CI, confidence interval; F/U, follow-up; GI, gastrointestinal; HR, hazard ratio m, month; OS, overall survival

mTor and Akt Targeted Agents in the Second Line and Beyond

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Bang et al, 2019 [4]	• First line • Ipatasertib + mFOLFOX6 (IpaFOLFOX6) vs. placebo + mFOLFOX6 (FOLFOX6) • Ipatasertib is an Akt inhibitor	• Phase II • IpaFOLFOX6, n=71 • FOLFOX6, n=82 • F/U: NR • HER2 status: negative	Overall Survival • IpaFOLFOX6: median OS, 12.1m; 90%CI, 10.3-14.6m • FOLFOX6: median OS, 15.7m; 90%CI, 13.5-19.8 • HR, 1.85; 90%CI, 1.23-2.79; p NR Progression-free survival • IpaFOLFOX6: median PFS, 6.6m; 90%CI, 5.7-7.5m • FOLFOX6: median PFS, 7.5m; 90%CI, 6.2-8.1m HR, 1.12; 90%CI, 0.81-1.55; p=0.56	Frequency of Grade 3-5 • Adverse Events related to any study drug ○ IpaFOLFOX6: 67% ○ FOLFOX6: 61% • AE resulting in death ○ IpaFOLFOX6: 7% ○ FOLFOX6: 2%
Lorenzen et al, 2020 [63] RADPAC Trial	• Second or third line • Paclitaxel (PTX) vs. paclitaxel + everolimus (RAD001)	• Phase III • PTX, n=150 • PTX + RAD001, n=150 • F/U: median 6.2m	Overall Survival • PTX: median OS, 5.0; 95% CI, 4.4-6.4m • PTX + RAD001: median OS, 6.1; 95% CI, 4.2-6.6m • HR, 0.93; 95% CI, 0.73-1.18; p=0.544 Progression-free survival • PTX: median PFS, 2.07; 95% CI, 1.87-2.50m • PTX + RAD001: median PFS, 2.20; 95% CI, 2.07-2.76m • HR, 0.88; 95% CI, 0.70-1.11; p=0.273	Incidence of Grade ≥3 Adverse Events • PTX: 69.4% • PTX + RAD001: 78.3%

Abbreviations: CI, confidence interval; F/U, follow-up; GI, gastrointestinal; HR, hazard ratio m, month; NR, not reported; OS, overall survival

PARP Inhibitors in the Second Line and Beyond

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Bang et al, 2017 [64] GOLD trial	• Second line • Olaparib + paclitaxel (OP) vs. placebo + paclitaxel (PP) • Olaparib is a PARP inhibitor	• Phase III • OP, n=263 • PP, n=262 • F/U: median 11.1m • HER2 status: NR	Overall Survival • OP: median OS, 8.8m; 95% CI, 7.4-9.6m • PP: median OS, 6.9m; 95% CI, 6.3-7.9 • HR, 0.79; 97.5%CI, 0.63-1.00; p=0.026	Objective Response Rate • OP vs. PP: OR, 1.69; 95% CI, 0.92-3.17; p=0.055	Frequency of Adverse Events • Serious AE ○ OP: 35% ○ PP: 25%

Abbreviations: AE, adverse events; CI, confidence interval; F/U, follow-up; GI, gastrointestinal; HR, hazard ratio m, month; OS, overall survival

IMMUNE CHECKPOINT INHIBITORS

PD-L1 Targeted in the First Line

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Shitara et al, 2020 [9] KEYNOTE-062	• Pembrolizumab or pembrolizumab plus chemotherapy vs. chemotherapy • PD-L1 CPS ≥1%	• Phase III • Pembrolizumab, n=256 • Pembrolizumab + CT, n=257 • CT, n=250 • Median F/U: 29.4m • HER2 status: negative	Overall Survival, CPS ≥1% • Pembro: median OS, 10.6m; 95% CI, 7.7-13.8 • CT: median OS, 11.1m; 95% CI, 9.2-12.8 • Pembro + CT: median OS, 12.5m; 95% CI, 10.8-13.9 • Pembro vs. CT: HR, 0.91; 99.2%, 0.69-1.18 • Pembro + CT vs. CT: HR, 0.85; 95% CI, 0.70-1.03 Overall Survival, CPS ≥10% • Pembro: median OS, 17.4m; 95% CI, 9.1-23.1 • CT: median OS, 10.8m; 95% CI, 8.5-13.8	Any AE (all grades) • Pembro: 95.3% • Pembro + CT: 97.6% • CT: 98.4% Grade 3-5 AE • Pembro: 16.9% • Pembro + CT: 73.2% • CT: 69.3%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
			• Pembro + CT: median OS, 12.3m; 95% CI, 9.5-14.8 • Pembro vs. CT: HR, 0.69; 95% CI, 0.49-0.97 • Pembro + CT vs. CT: HR, 0.85; 95% CI, 0.62-1.17	
Moehler et al, 2021 [8] JAVELIN Gastric 100 Trial	• Avelumab maintenance vs. continued CT • PD-L1 status with 2 IHC assays ○ TPS using 73-10; approved companion diagnostic for avelumab. • CPS using 22C3; approved companion diagnostic for pembrolizumab.	• Phase III • Avelumab, n=249 • CT, n=250 • F/U: minimum 18m • TPS ≥1% (73-10) ○ Pos: avelumab, n=30; CT, n=24 ○ Neg: avelumab, n=194; CT, n=190 ○ Unavailable: avelumab, n=25; CT, n=36 • CPS ≥1% (22C3) ○ Pos: avelumab, n=74; CT, n=63 ○ Neg: avelumab, n=40; CT, n=36 ○ Unavailable: avelumab, n=135; CT, n=151	Overall Survival • Avelumab: median OS, 10.4m; 95% CI, 9.1-12.0 • CT: median OS, 10.9m; 95% CI, 9.6-12.4 • HR, 0.91; 95% CI, 0.74-1.11; p=0.1779 Overall Survival, PD-L1 positive subgroups TPS ≥1% • Avelumab: median OS, 16.2m; 95% CI, 8.2-NYR • CT: median OS, 17.7m; 95% CI, 9.6-NYR • HR, 1.13; 95% CI, 0.57-2.23; p=0.6352 CPS ≥1% • Avelumab: median OS, 14.9m; 95% CI, 8.7-17.3 • CT: median OS, 11.6m; 95% CI, 8.4-12.6 • HR, 0.72; 95% CI, 0.49-1.05	Frequency of Grade ≥3 Treated-Related Adverse Events • Avelumab: 12.8% • CT: 32.8%
Janjigian et al, 2021 [7] CheckMate 649	• Nivolumab plus CT vs. nivolumab plus ipilimumab vs. CT • PD-L1 ≥5%	• Phase III • Nivolumab plus CT, n=789 • CT, n=792 • CPS ≥5% ○ Nivolumab, n=473 ○ CT, n=482	Overall Survival • Nivolumab plus CT: median OS, 14.4m; 95%CI, 13.1-16.2 • CT: median OS, 11.1m; 95%CI, 10.0-12.1 • HR, 0.71; 98.4%CI, 0.59-0.86; p<0.0001	Frequency of Treatment-Related Adverse Events • Grade 1-2 ○ Nivo: 35% ○ CT:44% • Grade 3 ○ Nivo: 46% ○ CT: 37%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes

				• Grade 4
				  ○ Nivo: 13%
				  ○ CT: 7%
				• Grade 5
				  ○ Nivo: 1%
				  ○ CT: n=0

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio m, month; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand; OS, overall survival; RR, relative risk

PD-L1 Targeted in the Second Line and Beyond

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Adverse Events Outcomes

Chen et al, 2019 [23]	• Second and third line
	• Multiple anti-PD-1 and anti-PD-L1 agents vs. placebo or paclitaxel or irinotecan or BSC (control)
		• N=9
		• n=2003
		• HER2 status: NR
		• Unselected patients
			Sept 2018	Overall Survival
				• Anti PD-1 vs. control: 12m OS; RR, 1.79; 95% CI, 1.13-2.83; p=0.013
				• Anti PD-1 vs. control: 18month OS; RR, 2.20; 95% CI, 1.20-4.06; p=0.011
					Treatment Related Adverse Events
					• All grades
					  ○ Anti-PD-1/PD-L1 vs. CT: RR, 0.64; 95% CI, 0.58-0.71; p<0.001
					• Grade 3-5
					  ○ Anti PD-1/PD-L1 vs. CT: RR, 0.37; 95% CI, 0.28-0.48; p<0.001

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio m, month; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand; OS, overall survival; RR, relative risk

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
Chen et al, 2020 [22] ATTRACTION-2 Study	• Third line or later • Nivolumab vs. placebo	• Phase III • Nivolumab, n=330 • Placebo, n=163 • F/U: 2 year	Overall Survival • Nivolumab: median OS, 5.26m; 95% CI, 4.60-6.37 • Placebo: median OS, 4.14m; 95% CI, 3.42-4.86 • HR, 0.62; 95% CI, 0.51-0.76; p<0.0001	Frequency of Serious Treatment-Related Adverse Events • Nivolumab: 11.5% • Placebo: 5.0%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
			Progression-free survival • Nivolumab: median PFS, 1.61; 95% CI, 1.54-2.30 • Placebo: median PFS, 1.45m; 95% CI, 1.45-1.54 • HR, 0.60; 95% CI, 0.49-0.75; p<0.0001	
Boku et al, 2021 [20] ATTRACTION-2 Study	• Third line or later • Nivolumab vs. placebo	• Phase III • Nivolumab, n=330 • Placebo, n=163 • F/U: 38.5m	Overall Survival • Nivolumab: median OS, 5.26m; 95% CI, 4.60-6.37m • Placebo: median OS, 4.14m; 95% CI, 3.42-4.86m • HR, 0.62; 95% CI, 0.50-0.75; p<0.0001 Progression-free survival • Nivolumab: median PFS, 1.61m; 95% CI, 1.54-2.30m • Placebo: median PFS, 1.45m; 95% CI, 1.45-1.54m • HR, 0.60; 95% CI, 0.49-0.75; p<0.0001	No new reported AEs after the 2-year F/U (Chen et al, 2020 [22])

Satoh et al, 2020 [71]
 	
ATTRACTION-2 Study
	• Third line or later
	• Nivolumab vs. placebo
	• Subgroup analysis: patients with prior trastuzumab (T) treatment
		• Phase III, post-hoc
		• Nivolumab, n=330
		  ○ Tpos, n=59
		  ○ Tneg, n=271
		• Placebo, n=163
		  ○ Tpos, n=22
		  ○ Tneg, n=141
		• F/U: NR
			Overall Survival
			• Prior T
			  ○ Nivolumab: median OS, 8.3m; 95% CI, 5.3-12.9m
			  ○ Placebo: median OS, 3.1m; 95% CI, 1.9-5.3m
			  ○ HR, 0.38; 95% CI, 0.22-0.66; p=0.0006
			• No prior T
			  ○ Nivolumab: median OS, 4.8m; 95% CI, 4.1-6.0m
			  ○ Placebo: median OS, 4.2m; 95% CI, 3.6-4.9m
			  ○ HR, 0.71; 95% CI, 0.57-0.88; p=0.0022
			
			Progression-free survival
			• Prior T
				Frequency of Serious Nivolumab Treatment-Related Adverse Events
				• Prior T: 10.2%
				• No prior T: 10.7%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Adverse Events Outcomes
			○ Nivolumab: median PFS, 1.6m; 95% CI, 1.5-4.0m ○ Placebo: median PFS, 1.5m; 95% CI, 1.3-2.9m ○ HR, 0.49; 95% CI, 0.29-0.85; p=0.0111 • No prior T ○ Nivolumab: median PFS, 1.6m; 95% CI, 1.5-2.4m ○ Placebo: median PFS, 1.5m; 95% CI, 1.5-1.5m ○ HR, 0.64; 95% CI, 0.51-0.80; p=0.0001	

Abbreviations: CI, confidence interval; F/U, follow-up; HR, hazard ratio m, month; PFS, progression-free survival; OS, overall survival

CHEMOTHERAPY REGIMENS NOT AVAILABLE IN CANADA

S-1 Chemotherapy

Monotherapy

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes
Chen et al, 2016 [73]	• First line • S-1 vs. 5-FU	• N=7 • n=2443	Dec 2015	Overall Survival • S-1 vs. 5-FU: HR, 0.91; 95% CI, 0.83-1.01; p=0.07 Progression-free survival • S-1 vs. 5-FU: HR, 0.89; 95% CI, 0.70-1.13; p=0.35	Time to Treatment Failure • S-1 vs. 5-FU: HR, 0.74; 95% CI, 0.56-0.97; p=0.03 Objective Response Rate • S-1 vs. 5-FU: RR, 1.36; 95% CI, 0.95-1.96; p=0.10

Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; RR, relative risk

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Treatment Response Outcomes	Adverse Events Outcomes
Kim et al, 2018 [74]	• First line • Elderly patients • S-1 vs. capecitabine	• Phase II • S-1, n=53 • CAP, n=54 • F/U: NR • HER2 status: NR	Overall Response Rate • S-1: 26.4%; 95% CI, 14.5-38.3% • CAP: 24.1%; 95% CI, 12.7-35.5% • p=0.780 Disease Control Rate • S-1: 62.3%; 95% CI, 49.6-74.9% • CAP: 66.7%; 95% CI, 53.9-79.5% • p=0.787	Significantly increased frequency of following AEs with S-1 vs. CAP • Anorexia, grade 3: 21% vs. 8% Significantly reduced frequency of following AEs with S-1 vs. CAP • Hand-foot syndrome, grade 3: 0% vs. 21% • Hand-foot syndrome, all grades: 25% vs. 58%

Abbreviations: AE, adverse events; CI, confidence interval; F/U, follow-up; NR, not reported

S-1 Containing Regimens

Systematic Reviews

Study [ref]	Treatment Regimen	No. of studies (N) / No. of patients (n)	Search Cut-off Date	Survival Outcomes	Treatment Response Outcomes
ter Veer et al, 2016 [75]	• First line • S-1 vs. 5-FU, S-1 vs. capecitabine-based regimens, and S-1 monotherapy vs. S-1 combination therapies	• N=11 • n=3135 • HER2 status: NR	May 2015	Overall Survival • S-1 vs. 5-FU: HR, 0.92; 95% CI, 0.82-1.03; p=0.16 • S-1 vs. CAP: HR, 1.03; 95% CI, 0.79-1.35; p=0.81 • S-1 mono vs. S-1 combo: HR, 0.76; 95% CI, 0.65-0.89; p<0.001 Progression-free survival • S-1 vs. 5-FU: HR, 0.88; 95% CI, 0.73-1.08; p=0.22 • S-1 vs. CAP: 0.76; 95% CI, 0.50-1.16; p=0.2 • S-1 mono vs. S-1 combo: HR, 0.68; 95% CI, 0.56-0.82; p<0.001	Overall Response Rate • S-1 vs. 5-FU: RR, 1.43; 95% CI, 1.05-1.96; p=0.02 • S-1 vs. CAP: RR, 0.92; 95% CI, 0.67-1.27; p=0.61 • S-1 combo vs. S-1 mono (note the flip): RR, 1.51; 95% CI, 1.32-1.74; p<0.001

Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; NR, not reported; RR, relative risk

Primary Literature

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Hironaka et al, 2016 [76]	• First line • S-1 + leucovorin (S1L) vs. S-1 + leucovorin + oxaliplatin (S1LOxa) vs. S-1 + cisplatin (S1CAP)	• Phase II • S1L, n=47 • S1LOxa, n=47 • S1CAP, n=48 • F/U: median 25.9m • HER2 status: pos in 11% of S1L, 15% of S1LOxa, and 13% of S1CAP patients • Trastuzumab given to 71-83% of these patients post RCT	Overall Survival • S1L: median OS, 15.6m; 95% CI, 10.4-19.3m • S1LOxa: median OS, 18.4m; 95% CI, 14.5 - 22.8m • S1CAP: median OS, 12.6m; 95% CI, 10.1-16.7m • p NR Progression-free survival • S1L: median PFS, 4.2m; 95% CI, 4.1-5.7m • S1LOxa: median PFS, 8.3m; 95% CI, 6.8-12.5m • S1CAP: median PFS, 5.6m; 95% CI, 4.1-8.3 • p NR	Overall Response Rate • S1L: 43%; 95% CI, 28.3-57.8 • S1LOxa: 66%; 95% CI, 50.7-79.1% • S1CAP: 46%; 95% CI, 31.4-60.8 • S1L vs. S1CAP, p=0.84; S1LOxa vs. S1CAP, p=0.063; S1LOxa vs. S1L, p=0.038 Disease Control Rate • S1L: 74%; 95% CI, 59.7-86.1% • S1LOxa: 100%; 95% CI, 92.5 – 100% • S1CAP: 83%; 95% CI, 69.8-92.5% • p NR	Most Common Grade 3-4 Adverse Events • Neutropenia ○ S1L: 6% ○ S1LOxa: 26% ○ S1CAP: 35% • Decreased Appetite ○ S1L: 13% ○ S1LOxa: 30% ○ S1CAP: 24% • Anemia ○ S1L: 10% ○ S1LOxa: 15% ○ S1CAP: 27% • Hyponatraemia ○ S1L: 4% ○ S1LOxa: 4% ○ S1CAP: 18%
Kawakami et al, 2018 [77] HERBIS-4A trial	• First line • Capecitabine + cisplatin (CC) vs. S-1 + cisplatin (S1C)	• Phase II • S1C, n=41 • CC, n=43 • F/U: median 11.3m • HER2 status: negative	Overall Survival • S1C: median OS, 13.5m • CC: median OS, 10.0m • HR, 0.776; 95% CI, 0.485-1.244; p=0.290 Progression-free survival • S1C: median PFS, 5.9m • CC: median PFS, 4.1m • HR, 0.763; 95% CI, 0.462-1.259; p=0.284	Overall Response Rate • S1C: 51.2%; 95% CI, 35.1-67.1% • CC: 53.5%; 95% CI, 37.7-68.8% • p>0.999	Most Common Grade 3-5 Adverse Events • Anemia ○ S1C: 23% ○ CC: 28% • Neutrophil count decrease ○ S1C: 23% ○ CC: 35% • Platelet count decrease ○ S1C: 23% ○ CC: 18%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Lu et al, 2019 [78]	• First line • S-1 + docetaxel (S1D) vs. S-1 + cisplatin (s1C)	• Phase III • S1D, n=150 • S1C, n=150 • F/U: NR • HER2 status: NR	Overall Survival • S1D: median OS, 405d • S1C: median OS, 378d • p=0.5127 Progression-free survival • S1D: median PFS, 180d • S1C: median PFS, 171d • p>0.05		Frequency of all Adverse Events • S1D: 90.67% • S1C: 91.33% Frequency of Moderate and Severe AEs • S1D: 31.33% • S1C: 32.67%
Nishikawa et al, 2018 [79] XParTS II trial	• First line • Capecitabine + cisplatin (CC) vs. S-1 + cisplatin (S1C)	• Phase II • S1C, n=55 • CC, n=55 • F/U: 1.5y • HER2 status: negative	Overall Survival • S1C: median OS, 13.5m • CC: median OS, 12.6m • HR, 0.942; 95% CI, 0.624-1.423; p=0.7769 Progression-free survival • S1C: median PFS, 5.6m • CC: median PFS, 5.1m • HR, 1.126; 95% CI, 0.753-1.685; p=0.5626	Overall Response Rate • S1C: 42.4%; 95% CI, 25.5-60.8% • CC: 69.4%; 95% CI, 51.9-83.7% • p=0.0237 Disease Control Rate • S1C: 75.8%; 95% CI, 57.7-88.9% • CC: 80.6%; 95% CI, 64.0-91.8% • p=0.6293	Significant Difference in Rate of Grade 3-5 Adverse Events • Diarrhea ○ S1C: 11% ○ CC: 0% ○ p=0.0118
Wu et al, 2015 [80]	• First line • S-1 + cisplatin (S1C) vs. cisplatin (C)	• Phase NR • S1C, n=36 • C, n=36 • F/U: NR • HER2 status: NR	Overall Survival • S1C: median OS, 9.4m; 95% CI, 1.9-24.4m • C: median OS, 7.6m; 95% CI, 1.7-21.4m • p=0.039 Progression-free survival • S1C: median PFS, 7.7m; 95% CI, 1.8-19.4m • C: median PFS, 6.5m; 95% CI, 1.5-16.4m • p=0.047	Overall Response Rate • S1C: 51.5% • C: 42.3% • p<0.05	Most Common Grade 3/4 Adverse Events • Leukopenia ○ S1C: 19.0% ○ C: 19.4% • Neutropenia ○ S1C: 30.6% ○ C: 25.0% • Anorexia ○ S1C: 19.4% ○ C: 16.7% • Nausea ○ S1C: 11.1% ○ C: 8.3%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
Yamada et al, 2015 [81]	• First line • S-1 + oxaliplatin (S1Ox) vs S-1 + cisplatin (S1C)	• Phase III • S1Ox, n=318 • S1C, n=324 • F/U: median 25.9m • HER2 status: not tested NB: non-inferiority study	Overall Survival • S1Ox: median OS, 14.1m; 95% CI, 13.0-15.8m • S1C: median OS, 13.1m; 95% CI, 12.1-15.1 • HR, 0.969; 95% CI, 0.812-1.157 Progression-free survival • S1Ox: median PFS, 5.5m; 95% CI, 4.4-5.7m • S1C: median PFS, 5.4m; 95% CI, 4.2-5.7% • HR, 1.004; 95% CI, 0.840-1.199; p(NI)=0.0044	Response Rate • S1Ox: 55.7% • S1C: 52.2% Disease Control Rate • S1Ox: 85.2% • S1C: 81.8%	Significant Difference in Rate of Grade 3-5 Adverse Events • Leukopenia ○ S1Ox: 4.1% ○ S1C: 19.4% ○ p<0.0001 • Neutropenia ○ S1Ox: 19.5% ○ S1C: 41.8% ○ p<0.0001 • Anemia ○ S1Ox: 15.1% ○ S1C: 32.5% ○ p<0.0001 • Febrile neutropenia ○ S1Ox: 0.9% ○ S1C: 6.9% ○ p<0.0001 • Hyponatremia ○ S1Ox: 4.4% ○ S1C: 13.4% ○ p<0.0001 • Sensory Neuropathy ○ S1Ox: 4.7% ○ S1C: 0% ○ p<0.0001
Kang et al, 2020 [82] SOLAR	• First line • S-1 + leucovorin + (S1LOx) oxaliplatin vs. S-1 + cisplatin (S1C)	• Phase III • S1LOx, n=356 • S1C, n=355 • F/U: median 26.0m • HER2 status: negative	Overall Survival • S1LOx: median OS, 16.0m; 95% CI, 13.8-18.3m • S1C: median OS, 15.1m; 95% CI, 13.6-16.4m • HR, 0.83; 95% CI, 0.69-0.99; p=0.039	Overall Response Rate • S1LOx: 73%; 95% CI, 67.0-79.3% • S1C: 50%; 95% CI, 43.1-56.9% Disease Control Rate • S1LOx: 93%; 95% CI, 89.1-96.3%	

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
			Progression Free Survival • S1LOx: median PFS, 7.1m; 95% CI, 6.8-8.3m • S1C: median PFS, 6.4m; 95% CI, 5.6-6.9m • HR, 0.79; 95% CI, 0.66-0.93; p=0.0045	• S1C: 88%; 95% CI, 83.1-92.2	
Lee et al, 2021 [83] SOPP	• First line • S-1 + oxaliplatin (S1Ox) vs. S-1 plus cisplatin (S1C)	• Phase III • S1Ox, n=173 • S1C, n=164 • F/U: median 12m • HER2 status: NR NB: non-inferiority study	Overall Survival • S1Ox: median OS, 12.9m; 95% CI, 10.3-14.6m • S1C: median OS, 11.4m; 95% CI, 9.9-12.4m • HR, 0.86; 95% CI, 0.66-1.11; p=0.242 Progression Free Survival • S1Ox: median PFS, 5.6m; 95% CI, 4.4-6.9m • S1C: median PFS, 5.7m; 95% CI, 4.9-6.7m • HR, 0.85; 95% CI, 0.67-1.07		Most common Grade 3/4 Adverse Events • Anemia ○ S1Ox: 5.2% ○ S1C: 11.0% • Neutrophil count decrease ○ S1Ox: 16.2% ○ S1C: 39.6% • White blood cell decrease ○ S1Ox: 2.3% ○ S1C: 10.4% • Platelet count decrease ○ S1Ox: 7.5% ○ S1C: 4.9% • Fatigue ○ S1Ox: 6.4% ○ S1C: 8.5% • Anorexia ○ S1Ox: 8.7% ○ S1C: 6.7% • Peripheral sensory neuropathy ○ S1Ox: 8.7% ○ S1C: 3.7%
Zhang et al, 2021 [84] RESOLVE	• First line • S-1 + oxaliplatin (S1Ox) vs. S-1	• Phase III • Adjuvant S1C, n=364	Disease Free Survival • Adjuvant S1C: 51.06m; 95%CI, 45.54-56.31		Frequency of Adverse Events • Grade 1-2 ○ Adjuvant S1C: 45%

Study [ref]	Treatment Regimen	Study Design (phase, n, F/U)	Survival Outcomes	Treatment Response Outcomes	Adverse Events Outcomes
	plus cisplatin (S1C)	• Adjuvant S1Ox, n=365 • Perioperative S1Ox, n=365 • F/U: median 40.6m • HER2 status: NR	• Adjuvant S1Ox: 56.53m; 95%CI, 50.96-61.72 • Perioperative S1Ox: 59.43m; 95%CI, 53.83-64.57		○ Adjuvant S1Ox: 41% ○ Perioperative S1Ox: 48% • Grade 3 ○ Adjuvant S1C: 13% ○ Adjuvant S1Ox:14% ○ Perioperative S1Ox: 14% • Grade 4 ○ Adjuvant S1C: 4% ○ Adjuvant S1Ox:5% ○ Perioperative S1Ox: 6%

Abbreviations: CI, confidence interval; d, days; F/U, follow-up; HR, hazard ratio; m, month; NR, not reported; PFS, progression-free survival; RR, relative risk; OS, overall survival

Appendix 9: Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original 2010	2004 - 2009	Full Report	Web publication.	N.A.
Version 2 2014	2009 - 2013	New data added to original Full Report	Updated web publication.	2010 recommendations were Endorsed
Version 3 2020	2013 - 2020	New Full Report		